A framework to support the decision-making process for modelling of communicable diseases

by

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Declaration

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Abstract

Infectious disease outbreaks have the potential to disrupt and strain the global health care system, even more so when a localised disease outbreak propagates rapidly to a large area. Such a disease outbreak is referred to as a pandemic disease outbreak. Pandemic outbreaks often inspire global collaboration between researchers and modelling practitioners with a view to devise strategies, disease propagation models and actions on how to address the outbreak.

Modelling of infectious disease is a complex endeavour. The literature on the available modelling approaches and general application to disease modelling is well documented in the literature. What is, however, less evident, especially to a modelling practitioner with less rigorous modelling experience, is the selection and consideration of modelling considerations based on the specific context of the disease outbreak.

To address this challenge, a modelling support framework is designed in this research project, with a view to formalise the most salient universal modelling steps and assist novice modelling practitioners in the consideration and selection of appropriate approaches for modelling infectious diseases. The research consists of three phases, namely the design and execution of a structured literature review, analysis of the findings of the literature review, and the construction of a modelling support and guidance framework.

During the first phase of the research, the chain of infection is used as an overarching metaphor to guide the process in identifying relevant considerations, disease characteristics and contextual factors which may potentially affect disease propagation, and this is used as the basis for determining the scope of the structured literature review. The review is designed to construct a sufficiently detailed dataset which is well representative of the various modelling approaches as applied in literature. The 283 identified literature pieces are methodically analysed and the relevant modelling considerations, disease characteristics and contextual factors from each of the pieces are captured to the dataset.

During the second phase of the research the dataset is analysed. The modelling considerations are analysed in relation to the disease transmission mode, and the relationship between modelling considerations are also analysed. In general, the selection of modelling approaches and considerations were not reducible to a single factor. This suggests that numerous factors must be considered in the model decision making process, and additionally, it highlights the importance of contextualising the disease outbreak.

The third phase of the research consists of the framework construction. Both the first and the second phases of the research are used to inform and guide the framework construction. The framework is

constructed with two goals in mind, namely to inform modelling considerations from a holistic viewpoint and to aid in the selection of the relevant modelling considerations.

The framework use is verified with an illustrative case study and validated with semi-structured interviews that are conducted with external subject matter experts with a background in engineering and health care modelling.

Opsomming

Die uitbreek van ’n aansteeklike siekte het die potensiaal om die globale gesondheidsorgsisteem te ontwrig en onder geweldige druk te plaas, des te meer wanneer so ’n gelokaliseerde uitbreking spoedig na ’n groter area versprei. Sulke siekte-uitbrekings staan bekend as pandemiese siektes. Die ontstaan van pandemiese uitbrekings van siektes lei tipies tot wêreldwye samewerking tussen navorsers en modelleerders. Die doel van samewerking hou verband met die skep van strategieë, modelle wat siekte-oordrag modelleer en aksieplanne om die uitbreking te bestuur.

Die modellering van aansteeklike siektes is ’n komplekse onderneming. Beskikbare modelleringsbenaderings en die generiese gebruik daarvan om siektes te modelleer is goed opgeteken in die literatuur. Wat minder ooglopend is van hierdie benaderings, veral vir die modelleerder met elementêre modelleringskennis, is die oorweging en selektering van modelleringelemente gebaseer op die spesifieke kontekstuele omstandighede van die siekte-uitbreking.

Om hierdie uitdaging aan te pak word daar in hierdie navorsingsprojek ’n ondersteuningsraamwerk vir modellering geskep. Die doel hiervan is die formalisering van die belangrikste modelleringsstappe en om onervare modelleerders te ondersteun in die oorweging en selektering van toepaslike benaderings om aansteeklike siektes te modelleer. Die navorsing bestaan uit drie fases, naamlik die ontwerp en uitvoering van ’n gestruktureerde literatuuroorsig, ’n analise van die bevindinge van die literatuuroorsig, en die opstel van ’n raamwerk wat ondersteuning en raadgewing ten opsigte van modellering bied.

As deel van die eerste fase van die navorsing, word die ketting van infeksie as ’n oorhoofse metafoor gebruik. Hierdie metafoor word gebruik om relevante oorwegings, siekte-eienskappe en kontekstuele faktore te identifiseer wat die potensiaal het om die verspreiding van siektes te beïnvloed. Dit word ook as die basis gebruik om die bestek van die gestruktureerde literatuuroorsig te bepaal. Die gestruktureerde literatuuroorsig is ontwerp om ’n gedetailleerde datastel op te stel wat ’n goeie verteenwoordiging is van die verskeie modelleringsbenaderings soos dit in die literatuur toegepas is. Die geïdentifiseerde 283 literatuurstukke is stapsgewys geanaliseer en die relevante modelleringsbenaderings, siekte-eienskappe en kontekstuele faktore van die literatuurstukke is in die datastel opgeneem.

As deel van die tweede fase van die navorsing word die datastel geanaliseer. Die modelleringsoorwegings is geanaliseer met betrekking tot die siekte-oordragsmetode en die verhoudings tussen ander modelleringsoorwegings. Oor die algemeen is daar bevind dat die keuse van ’n modelleringsbenadering of -oorweging nie reduseerbaar is tot die oorweging van ’n enkele faktor nie. Die afleiding is dus dat verskeie faktore in ag geneem moet word in die seleksieproses

van ’n modelleringsbenadering, en dat die belangrikheid van die kontekstualisering van ’n siekte-uitbreking benadruk moet word.

As deel van die derde fase van die navorsing is die raamwerk opgestel. Beide die eerste en tweede fases van die navorsing is gebruik om die opstelproses van die raamwerk te lei en die opstelkeuses in te lig. Die raamwerk is opgestel met twee verwagte uitkomstes, naamlik om die modelleringsoorwegings vanuit ’n holistiese oogpunt in te lig, sowel as om die selektering van relevante modelleringsoorwegings te ondersteun.

Die gebruik van die raamwerk is geverifieer met behulp van ’n verduidelikende gevallestudie. Die validasie is voltooi met behulp van semi-gestruktureerde onderhoude met eksterne vakgebiedkenners met ’n agtergrond in die ingenieurswese en gesondheidssorg-modelleringsvelde.

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Nomenclature

General abbreviations and acronyms

CAT	Category
CD(s)	Communicable disease(s)
EPI	Expanded Programme on Immunisation
GIDEON	Global Infectious Diseases and Epidemiology Online Network
H1N1	A flu-strain responsible for the global flu-epidemic in 2009-2010
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
N/A	Not applicable
NCD(s)	Non-communicable disease(s)
REF	Reference
RI	Routine immunisation
SARS	Severe acute respiratory syndrome
SME(s)	Subject matter expert(s)
TB	Tuberculosis
WHO	World Health Organisation

Glossary of terms

Abiotic	Non-living entities within the environment
Agent	Micro-organisms or pathogens responsible for the disease and capable of infecting a host
Basic reproduction number	The average number of secondary disease cases typically caused by an infected individual
Biotic	Living organisms or entities within the environment

Cilia	Hair-like structures which protrude from a larger cell body
Compartmental classification	An approach followed by which individuals are clustered to mutually exclusive disease states in the modelling approach
Contact mixing pattern	The assumptions which characterise the manner which individuals have contact with each other
Endogenous	Internal cause or origin
Environment	Extrinsic factors which that influence the exposure and interaction between the agent and the exposure susceptible host
Fomites	Objects or materials which are likely to carry infection, such as clothes, utensils, and furniture
Force of infection	A parameter used to characterise the transmission between infected and susceptible individuals, which unifies the contact rate, transmission probability and the disease prevalence in a single expression
Herd immunity	The protective phenomenon observed when a high proportion of hosts in a population are immune against a disease, which in turn protects the few remaining susceptible individuals within the population
Host	Also susceptible host
Law of mass action	The rate at which individuals of two types contact one another in a population is proportional to the product of their densities
Morbidity	The occurrence of having a disease or a symptom of a disease
Mortality (rate)	Death of an individual, (i.e. death rate)
Prevalence	The proportion of a particular population found to be affected by a medical condition
Prophylactic (vaccination)	A vaccination strategy by which individuals are vaccinated prior to disease establishment in an attempt to prevent disease establishment and propagation

Total theoretical transmission modes	Product of the theoretical number of transmission modes for each disease and the number of literature pieces included for each disease in the dataset
Transmission mode	The manner in which a disease is transmitted between a reservoir and a susceptible host
Transmission probability parameter	A parameter used to quantify the probability that an infected host will transmit the disease to a susceptible host, given sufficient contact occurs between individuals
Reservoir	Habitat in which a disease agent lives and matures
Susceptible host	An individual which is susceptible to disease infection

Modelling approach abbreviations

ABS	Agent based simulation
ARDL	Autoregressive distributed lag model
ARIMA	Autoregressive integrated moving average
ARX	Autoregressive with exogenous variable
BRT	Boosted regression trees
CAR	Conditional autoregressive model
CASMIM	Cellular automata with social mirror identity model
DE	(Ordinary) differential equation
DLNM	Distributed lag non-linear model
FODE	Fractional ordinary differential equations
GAM	Generalised additive modelling
GEE	Generalised estimating equation
GLMM	Generalised linear mixed models
GLM	Generalised linear model
GIS	Geographic information systems

GWR	Geographically weighted regression
IBM	Individual based model
MEM	Maximum entropy method
MGWR	Mixed geographically weighted regression
MIP	Mixed integer programming
MLR	Multiple linear regression
NPBats	Non-Parametric empirical Bayesian time series analysis
PDE	Partial differential equation
PF	Particle filter
SARIMA	Seasonal autoregressive integrated moving average
STL	Seasonal trend decomposition based on losses

Compartmental classification abbreviations

Human classification

S	Susceptible
I	Infected
R	Recovered
E	Exposed
D	Death
F	Funeral / Burial
V	Vaccinate
Q	Quarantined / Hospitalised / Isolation
J	Diagnosed
C	Carrier
CT	Contact tracing
M	Maternal immunity

A	Asymptomatic
T	Treatment
Y	Sexual contact
W	Waning immunity
T	Diagnosed
SS	Super spreader

Non-human classification

B	Bacteria
W	Water
M,S	Mosquitoes, susceptible
M,I	Mosquitoes, infected
M,E	Mosquitoes, exposed

Method of model fit abbreviations

ABIC	Akaike bayesian information criterion
AIC	Akaike information criterion
AUC	Area under curve
ACF	Autocorrelation function
CI	Confidence interval
DIC	Deviance information criterion
GLS	Generalized least squares
K-S	Kolmogorov-Smirnov
LHS	Latin hypercube sampling
MCMC	Markov chain Monte Carlo
MIF	Maximizing the likelihood via iterated filtering

MAD	Mean absolute deviation
MAE	Mean absolute errors
MAPE	Mean absolute percentage errors
NMSE	Normalised mean square error
NRMSE	Normalized root mean square error
PACF	Partial Autocorrelations function
PRCC	Partial rank correlation coefficient
ROC	Receiver operating characteristic
RSS	Residual sum of squares
RMSE	Root mean square error

Mixing pattern abbreviation

WAIFW	Who acquires infection from whom matrix

Analysis terminology

S1	Observations when all theoretical transmission modes are considered for each disease.
S2	Observations which pertain only to literature pieces where a select number of transmission modes are mentioned explicitly.
S3	Observations of literature pieces categorised according to mathematical, network or simulation modelling approaches.
S4	Observations of literature pieces categorised as either a disease included in RI or not included in RI.
S5	Observations of literature pieces categorised according to the modelling rationale.
S6	Observations of literature pieces categorised according to the data source.
S7	Observations of literature pieces categorised according to the modelling scope.

S8	Observations which pertain only to literature pieces which include interventions.
S9	Observations which pertain only to literature pieces which include contextual factors.
S1N	Total number of theoretical transmission modes present in the dataset.
S2N	Total number of explicitly mentioned transmission modes present in the dataset.
S3N	Total number of instances for each of the modelling approach categories.
S4N	Total number of literature inclusions for RI and non-RI diseases.
S5N	Total number of instances for each of the modelling rationale categories.
S6N	Total number of instances for each of the data source categories.
S7N	Total number of instances for each of the modelling scope categories.
S8N	Total number of treatment and vaccination strategy inclusions.
S9N	Total number of linked to disease propagation instances and modelled contextual factor instances.

Metrics (i.e. questions) used in the validation questionnaire

Code	Questions
PU	The framework is able to assist modelling practitioners in the context of a disease outbreak.
F1	The framework is capable of informing the user of the most relevant modelling considerations.
F2	The framework is capable of guiding selection of modelling considerations.
F3	The most relevant steps in the modelling process are presented in the framework.
F4	The framework steps are clear and concise.
F5	The framework steps are easy to follow.
P1	The framework modelling steps follow each other logically.
P2	The contextualization of the outbreak characteristics are useful to guide the modelling process.
P3	The framework ensures thoroughness in the modelling process.

P4 The documentation step of the framework serves as a useful checklist for the modelling process.

P5 The documentation step of the framework is useful to assist future modelling efforts.

P6 I would recommend the framework use in a modelling context where a rapid response is required and there are no / few previous instances where the disease has been modelled in literature.

Chapter 1 Introduction

1.1 Background and origin of the problem

Throughout history, disease has been a burden which affected the health of mankind adversely to varying extents. The black death, caused by the *Y. pestis* bacteria, began to spread across Europe and Asia in 1347 and within 5 years, 25 million people had succumbed (Kelly 2005). Another example of a devastating infectious disease is measles. Caused by the measles virus, it is believed to have become established in humans 5 000 – 10 000 years ago and it is estimated that several million deaths can be attributed to it (Moss & Griffin 2012). In modern times, however, these same diseases can easily be treated by antibiotics (in the case of *Y. pestis*) or prevented by vaccination (in the case of measles), made possible following the remarkable medical breakthrough of Edward Jenner in 1796. In the context of disease management, these two interventions are classified as treatment and vaccination interventions strategies, respectively.

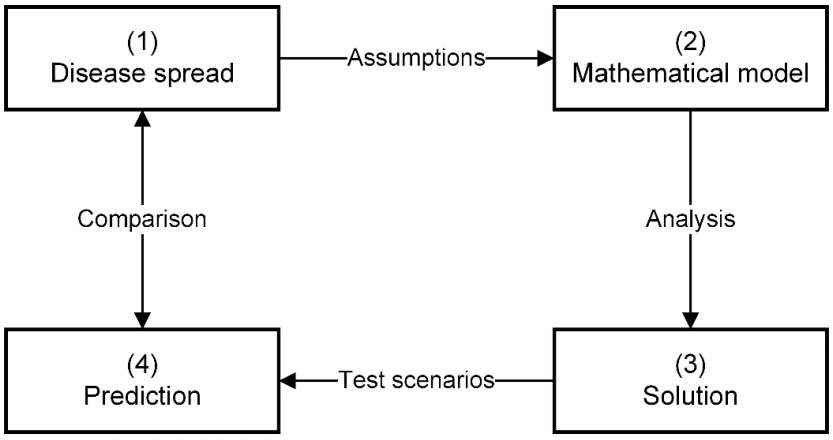

Figure 1.1: Flowchart of mathematical modelling of infectious disease, adapted from Brauer (2009).

Mathematical modelling of infectious disease is used to describe the prevalence and incidence of disease in humans. A flowchart of the relationship between infectious disease and mathematical models is illustrated in Figure 1.1. The modelling process starts with identifying a disease outbreak. Assumptions which characterise the disease outbreak are used to describe the biological problem mathematically. Analysis of the mathematical model is used to identify solutions to the disease outbreak. This subsequently allows the testing of different conditions and scenarios in the model, to estimate predicted outcomes. Comparing the outcome of the model to the real data is considered an indication of the suitability of the model in describing the biological problem mathematically.

For instance, in the context of vaccination for established childhood diseases, the WHO compiled a report to aid countries in estimating the cost of introducing new vaccines into a national immunisation

schedule (WHO 2002). In this report, some of the variables (i.e. assumptions informing model construction in Figure 1.1) used to estimate the expected vaccination rate and doses required are:

- Immunisation coverage rate (desired proportion of population to receive vaccination);
- Birth rate;
- Doses required for a fully immunised child;
- Levels of reserve stock for the following year; and
- Percentage of wasted doses.

These guidelines are used to inform the Taiwanese Centre for Disease Control in the construction of a statistical model to estimate the annual demand for vaccines that form part of the routine immunisation programme (Chiu et al. 2008). Variables pertaining to the calculation of vaccine demand (i.e. analysis of variables to construct a model solution in Figure 1.1) include the following:

- Total number of inoculations required;
- Immunisation coverage rate;
- Vaccine wastage rate;
- Number of vaccine vials in stock; and
- Price of a single or multiple dosage vaccine vial;

whereas variables pertaining to calculation of population growth included the following:

- Number of births;
- Immunisation coverage rate; and
- Vaccine wastage rate.

Different values for the variables of the model are then tested in order to obtain a vaccine demand prediction. This prediction is compared to the actual vaccine usage, indicating the ability of the model to accurately describe the problem of vaccine demand estimation.

However, in contrast to vaccines administered during national immunisation programmes, for which vaccine demand may be estimated accurately and fairly easily according to relatively stable population birth rates, vaccines required in epidemic and pandemic outbreaks of disease relate more sensitively to the underlying disease mechanics. Furthermore, as described in the above example, vaccine demand estimation may relate more sensitively to the ability of a modelling approach to capture the underlying factors which drive the dynamics of a disease outbreak, instead of solely focussing on a particular vaccination strategy.

From this isolated example, it is clear that accurately capturing the disease dynamics and contextual factors of a disease outbreak are very important goals from which secondary modelling goals typically follow (e.g. vaccine demand estimation, effect of quarantine strategies, estimation of the number of infected individuals at a specific point in time).

1.2 Problem background

As illustrated in Figure 1.2, during the past two decades the following major disease outbreaks strained the global health system:

- Severe acute respiratory syndrome (SARS), a highly contagious respiratory disease, which causes a serious form of pneumonia and could result in death (Mkhatshwa & Mummert 2011). SARS emerged in China late 2002 and rapidly spread to 32 countries, resulting in more than 700 deaths and 8000 infections worldwide. One concern of this outbreak was the occurrence of super spreading events, which relate to certain infectious individuals rapidly creating more secondary infections than the average infectious individual.
- H1N1, a new strain of influenza virus (the result of a combination of a swine, avian and human influenza virus) emerged in early 2009 (Upadhyay et al. 2014). By the end of 2009, it was reported that more than 208 countries experienced a disease outbreak (Jin et al. 2011).
- Ebola, the first documented Ebola disease outbreak appeared in Sudan and the Democratic Republic of Congo in 1976 (Al-Darabsah & Yuan 2016). In 2014, however, the largest outbreak of Ebola to date occurred in West Africa (Guinea, Liberia and Sierra Leone), with global fears of the potential of the disease outbreak to transmit beyond the borders of these three countries.
- Zika, a relatively unknown disease transmitted by mosquitoes with similar symptoms to that of dengue fever. Few human cases were reported before the first well-known outbreak in Micronesia in 2007 (Wang et al. 2017). In 2016, however, an outbreak of Zika in Brazil rapidly spread past country borders through Central and Southern America before reaching North America in the same year. Additional concerns related to this outbreak included that multiple transmission routes existed for the disease, the occurrence of birth defects following disease infection, and no availability of a prophylactic vaccine or antiviral treatments.

Disease outbreaks such as the aforementioned examples often require rapid responses and frequently result in global collaboration between various health care professionals and modellers. The literature on available disease modelling approaches is well established, but the factors which affect the selection and the application of one approach above another are not always clear. Analysts who frequently model infectious disease are likely to be very well acquainted with the process of modelling approach selection and which modelling considerations to include, but individuals who are not well acquainted with the field might not always know which considerations and incorporations are necessarily required in a particular modelling application.

Furthermore, no single response strategy is the most efficient and effective strategy for all epidemics; rather, the best strategy depends on the circumstances of the particular epidemic (Glaser 2007). This further highlights the importance of accurately describing the context in which a disease outbreak occurs in order to construct a realistic mathematical model of the disease outbreak.

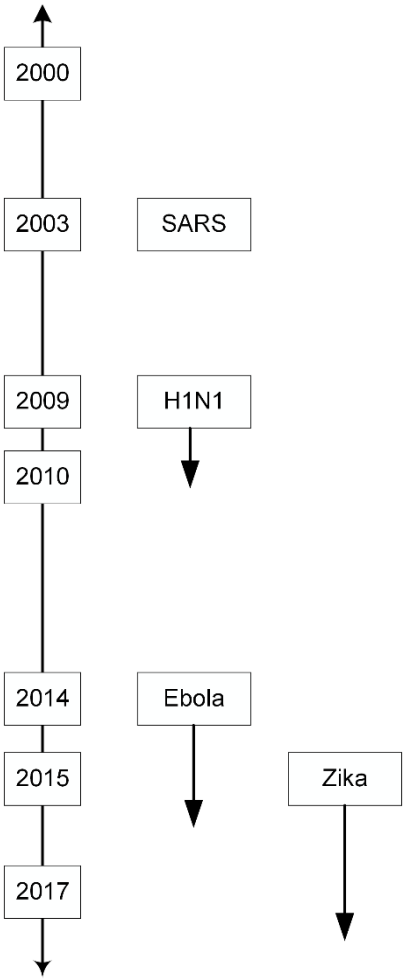

Figure 1.2: Timeline of major disease outbreaks.

1.3 Problem statement

The problem statement is visualised in Figure 1.3. Given the rapid response required for disease outbreaks, modellers and decision makers would benefit from a holistic framework capable of assisting the selection of modelling approaches and the incorporation of relevant modelling considerations. The numerous drivers of disease dynamics, such as the disease characteristics and the contextual factors of the disease outbreak, are expected to play a role in the selection of modelling approaches. Many potential approaches are available in literature, but the factors which influence the selection of a particular approach are not always evident from the literature. A structured review of the modelling literature, in the context of disease dynamics and the available modelling approaches, can be performed to construct a dataset of existing modelling approaches. This dataset is then analysed to construct the proposed modelling support framework. The framework is used to assist the modeller with developing the model, as illustrated in Figure 1.1 and considering the appropriate modelling factors in the modelling approach.

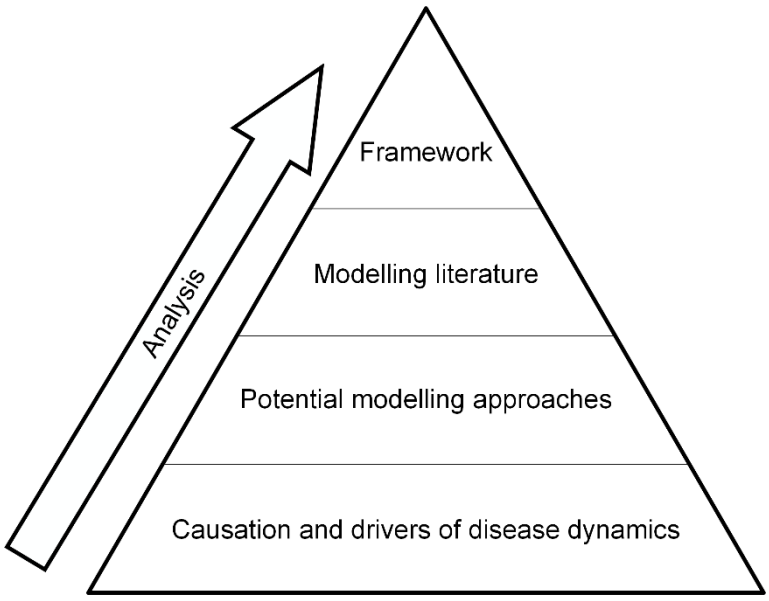

Figure 1.3: A visualisation of the problem statement.

1.4 Research aims and objectives

1.4.1 Aims

The aim of the research is to conceptualise a support tool which is used to formalise decisions and considerations which form part of modelling approach implementation. The framework consists of two modules. The first module is used to contextualise the modelling aims and considerations which relate to the context of the disease outbreak and establish relationships to the second module of the framework, which relates to modelling approach selection.

An additional aim of the framework is the inclusion of an explicit documentation step which captures the relevant decisions and the reasoning for modelling decisions according to a documentation template. This is used to guide the modeller to systematically document the modelling approach selection process, thus creating a paper trail of factors that were taken into account when selecting the model approach and developing the model. Additionally, the systematic documentation of inclusions and exclusions contributes to ensuring that the most relevant modelling considerations are incorporated in the modelling approach, with specific consideration of the contextual circumstances of the given disease outbreak.

1.4.2 Objectives

The objectives of this research project are listed as follows.

I. Contextualise the process of disease propagation and the drivers of disease dynamics, in addition to high-level modelling techniques and parameters which are typically incorporated in an infectious disease modelling context;
II. Link the drivers of disease dynamics and contextual factors affecting disease dynamics to the process of disease propagation;
III. Design and conduct a structured literature review with a view to construct a holistic disease dataset which accurately represents existing modelling applications and considerations;
IV. Analyse and interpret the dataset to assess the relationships between disease characteristics, contextual factors and modelling considerations;
V. Design, develop and describe a holistic modelling support framework in which the most salient modelling steps are formalised and modelling approach considerations are prompted, informed by die analysis completed in Objective IV; and
VI. Validate the framework with an illustrative, theoretical case study and review by appropriate subject matter experts (SMEs).

1.5 Expected contributions

In this research project an attempt to unify some of the literature pertaining to the modelling of infectious diseases (with respect to modelling approaches and considerations typically employed) is completed. As this is approached from a disease dynamics perspective instead of a purely data driven approach, additional insights are gathered into complex decisions and interactions which form part of infectious disease modelling.

An additional attempt to formalise the decisions and considerations which form part of a typical modelling implementation is completed with the construction and presentation of a holistic disease modelling support framework. In the context of a disease outbreak which requires the rapid execution of informed modelling decisions, these formalised steps may greatly assist modellers with:

- Ensuring a well-researched framework support tool is presented which formalises the most relevant decisions and considerations of the modelling process;
- Ensuring that the disease outbreak is sufficiently contextualised; and
- Linking the contextualisation to the modelling decisions and implementations.

During an outbreak limited time is available to make decisions and not all modellers are as well versed in all the intricacies of the modelling process. The framework may assist modellers to reduce decision fatigue with regards to modelling decisions and considerations and serve as a valuable tool to ensure that all relevant components are included in a modelling approach. Additionally, the documentation step of the framework may serve as a checklist and reference from which secondary applications are extended from.

1.6 Methodology

The required steps to complete the objectives for the research project as set out in §1.4 are illustrated in Figure 1.4. An inductive reasoning approach is following in this research project. As mentioned previously, modelling approach selection is a complex endeavour and decisions are not reducible to a single factor or consideration. The goal of the framework is not to establish fixed rules which are universal in all instances or to suggest every single potential theoretical modelling approach. This is infeasible due to the interaction of various factors and considerations which influence the selection of a modelling approach, in addition to the difficulty in generalising the context of a disease outbreak. Instead, the framework is used to prompt the modelling practitioner to ensure that all relevant modelling considerations are taken into account, and guides the modelling approach selection by proposing options based on analysis of observed relationships in the literature. Furthermore, relationships between disease characteristics, contextual factors and modelling approaches are only investigated if logic supports the likely existence of such a relationship. The framework research and construction thereof is based on literature analysis, gathered by means of a structured literature review and relational analysis. The validation is completed by means of an illustrative case study and semi-structured interviews with subject matter experts (SMEs) from an engineering and healthcare modelling field.

1.7 Document structure

The following document structure briefly highlights the content of each chapter within the overall document structure as illustrated in Figure 1.5.

In Chapter 2 the literature from the realm of epidemiology is reviewed in order to contextualise and characterise the field of infectious disease modelling. This includes an overview of the disease process, typical modelling approaches and a description of the chain of infection. The chain of infection is used as a reference to establish links between disease characteristics and contextual factors which potentially affect disease dynamics.

The literature presented in Chapter 2 is used in Chapter 3 to inform a structured literature review. The outcome of this review is a dataset which accurately describes the existing modelling approaches and considerations which are currently incorporated within the field of infectious disease modelling. The scope of the literature review is established, the steps of the review are formalised and the evaluation and capturing of the data from the literature to the dataset is described. A high-level overview of the dataset is also presented and referred to.

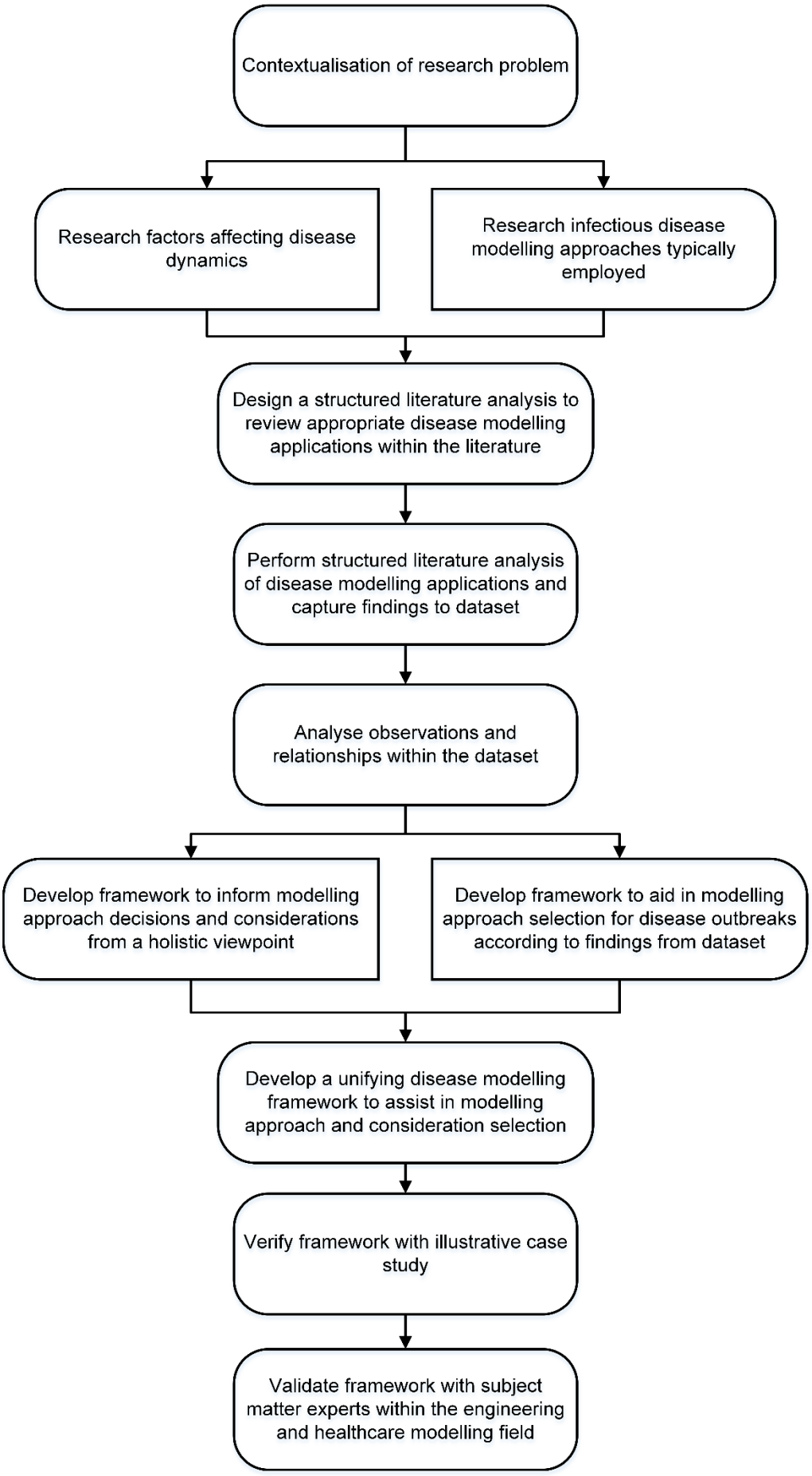

Figure 1.4: Research methodology.

The analysis of the dataset takes place within Chapter 4. The information from both Chapter 2 and Chapter 3 implicitly informs and guides the analysis process. Observations are discussed in detail with a view to analyse and determine the relevance of the observed relationships between disease characteristics, contextual factors, modelling approaches and the occurrence of various modelling considerations. Additionally, the relevance of modelling decisions and considerations which form an essential part of the modelling process are also established. One of the outcomes of the analysis is the construction of reference summary tables summarising the high-level analysis findings.

The knowledge base uncovered in the preceding chapters is used in Chapter 5 to inform the construction of an infectious disease modelling framework. The steps of the outbreak modelling contextualisation and outbreak modelling selection phase of the framework are discussed in detail, which include relevant considerations for each of the steps, links between subsequent steps and recommendations based on the analysis completed in Chapter 4.

The validation of the framework is presented in Chapter 6. A case study is used to illustrate the functioning of the framework and various SMEs within the engineering and healthcare modelling field are consulted to complete the framework validation.

The research project concludes in Chapter 7 with a brief summary and appraisal of the research project, in addition to suggested future work which originated from completion of and reflection on the research project.

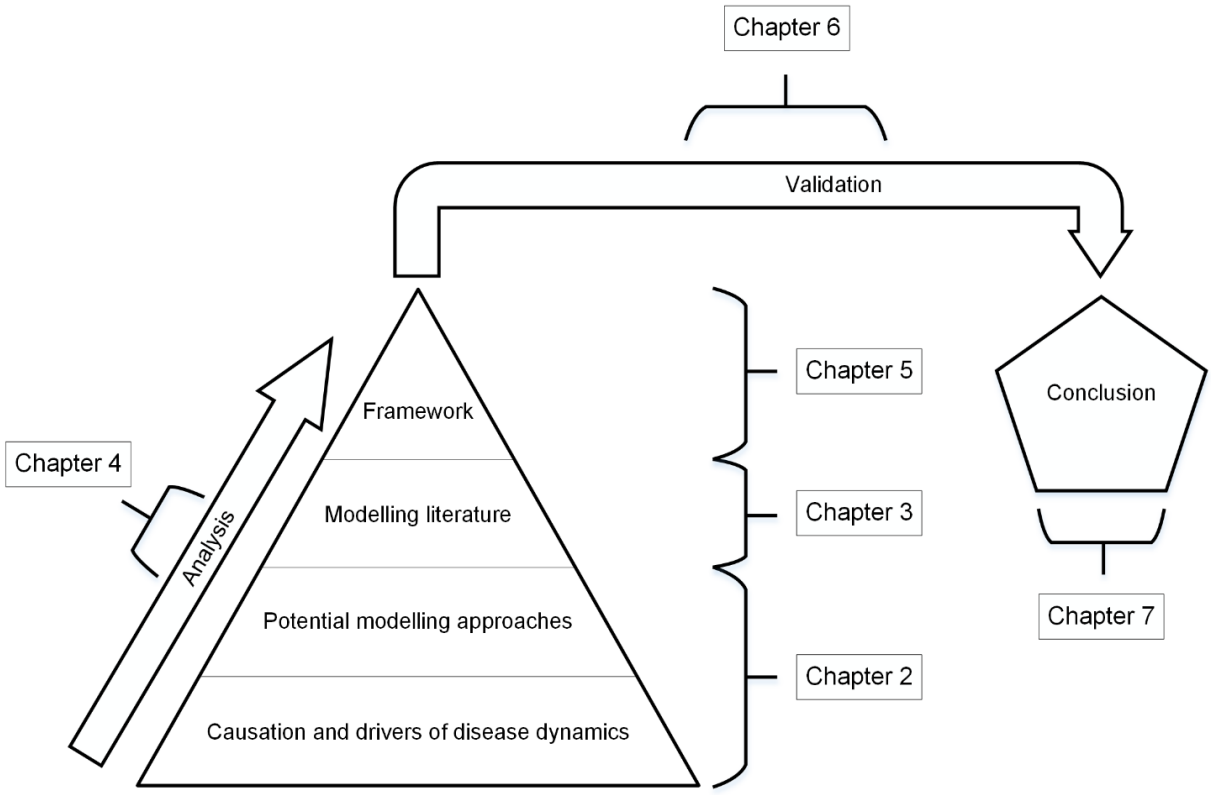

Figure 1.5: A visualisation of the document structure.

Chapter 2 Contextualisation: Disease dynamics

The modelling and control of infectious disease is a specialised modelling field within the scientific community. Modelling the spread of infectious diseases and intervention strategies used to reduce or eliminate disease spread (e.g. vaccination and quarantine) require a firm grasp of the relevant modelling methods (e.g. mathematical models and statistical analysis) and the underlying factors which affect disease dynamics. To highlight the complexity of this field not typically well known in an Engineering context, an overview is given within this chapter of the typical requirements and methods of disease modelling, in addition to factors which may affect the underlying patterns of disease propagation.

A high-level description of disease causation, in addition to an overview of the actors involved in the disease process are presented in §2.1. This is followed in §2.2 by a discussion of the chain of infection, a simple yet appropriate manner of illustrating the process of disease transmission to a susceptible individual. An overview of mathematical modelling of infectious diseases, with respect to viewpoints which may influence the modelling decisions, is presented in §2.3. The section also contains a discussion of parameters, terms and approaches that are typically used. To illustrate the complex manner in which disease dynamics are affected, a selection of contextual factors which may affect disease dynamics are reviewed in §2.4. An electronic database which serve as an excellent reference list of disease characteristics is briefly reviewed in §2.5. An initial attempt to categorise and synthesise aspects of the literature on infectious disease modelling, in order to better understand this complex modelling landscape and assist the development of a holistic disease modelling framework is discussed in the conclusion to the chapter in §2.6.

2.1 Disease causation

In order to study the field of infectious disease modelling and dynamics, a high-level overview of disease outbreak categorisation and the process which describes disease establishment in humans are required. A short overview of the disease burden with regards to chronic and infectious diseases are presented in § 2.1.1. The terms used to contextualise the nature of a disease outbreak are mentioned in §2.1.2. To understand disease causation from a systems perspective, the process of disease establishment within an individual is discussed in §2.1.3, which is followed by a discussion on types of risk factors which contribute to disease establishment in §2.1.4. A brief overview is afforded to the required actors in the process of disease establishment in §2.1.5.

2.1.1 The disease burden

The mortality and morbidity caused by disease can be ascribed to either communicable diseases (CDs) or non-communicable diseases (NCDs).

According to the Dictionary of Epidemiology (Porta 2014), NCDs (i.e. chronic or non-transmissible diseases) are diseases "for which evidence is lacking that transmission from individual to individual is possible by contagion, a vector, biological heredity or inheritance." These diseases tend to have long durations and result from an interaction of genetic, physiological, environmental and behavioural factors (WHO 2017b). According to the World Health Organisation (WHO) (WHO 2017b), NCDs kill 40 million people each year, equivalent to 70% of all deaths globally.

Although not an exhaustive enumeration, some prominent examples of NCDs include cardiovascular disease, heart-disease and stroke, obesity, cancer, and chronic respiratory disease (Iwelunmor et al. 2015; Piot et al. 2016; WHO 2017b).

According to the Dictionary of Epidemiology (Porta 2014), CDs (i.e. acute or transmissible diseases) are diseases "whose causal agent can be transmitted from successive hosts to healthy subjects, from one individual to another." Furthermore, CDs may be classified as contagious or non-contagious (e.g. relying on vector transmission). There was an expectation that as countries developed socio-economically and the occurrence of NCDs increased as a result of the adoption of a western lifestyle, that NCDs would replace CDs as the primary burden of disease. Kalyani and Shankar (2016), however, state that mortality and morbidity from CDs remain the leading cause of death in developing countries. Thus, as the incidence of NCDs increase, lower and middle income countries face a double disease burden of both CDs and NCDs (Piot et al. 2016).

Although not an exhaustive enumeration, some diseases which are classified as CDs include measles, mumps, malaria, chickenpox, hepatitis, rabies, cholera, food poisoning, tetanus, pertussis (whooping cough), influenza, yellow fever and tuberculosis. (Kalyani & Shankar 2016; WHO 2017a).

It is important to characterise the difference between CDs and NCDs, as vaccines only target CDs.

2.1.2 Differentiation between epidemic, endemic and pandemic disease outbreaks

The terms epidemic, endemic and pandemic relate to another by the element **dem** derived from the Greek word **demos**, which refers to people or a district. The prefixes of these descriptive terms may aid in deducing the meaning, as described below (Maddox 2014):

- **epi** (among) + demos = epidemic;
- **en** (in) + demos = endemic; and
- **pan** (all) + demos = pandemic.

A disease **epidemic** occurs when widespread occurrence of a disease is present in a community at a given time. More specifically, an epidemic disease outbreak is an outbreak which occurs outside

the normal expectancy within a specified community or region (Porta 2014). The re-occurrence of a disease outbreak in a region for which the disease was previously absent for a long time is also regarded as an epidemic outbreak.

A disease infection is considered **endemic** if the disease occurs habitually within a geographic region or population group (Porta 2014). In other words, a disease is regarded as endemic when it is established and expected within a particular population or geographic region.

An epidemic disease outbreak which occurs over a large geographic area, crossing country borders and infecting a large number of individuals is classified as a **pandemic** disease outbreak (Porta 2014).

From this brief discussion, it is clear that the disease classification as epidemic, endemic and pandemic depends on the history of previous outbreaks and the ability of the disease to cause widespread infection. Furthermore, a single disease may be classified as an epidemic in one country, but endemic in another, depending on the history of previous outbreaks. This highlights some the complexity and variability associated with disease classification.

2.1.3 An overview of the disease process

Three stages characterise disease establishment in individuals, namely the induction, promotion and expression stages (Jewell 2004).

The start of the etiological[1] process concerns the **induction** or start of the disease process. For NCDs, this may occur at birth or as a part of a reaction to the environment, whereas for CDs this may occur once an individual comes into contact with a disease (Jewell 2004).

The **promotion** stage is the phase associated with the multiplication of the disease pathogen within the host to the point where the clinical symptoms of the disease start to manifest. The end of the promotion stage is usually associated with a clinical diagnosis of the disease. It is quite rare to observe the exact moment that a disease starts, thus the induction and promotion phases are usually regarded as a single phase in the disease evolution (Jewell 2004).

The **latency** period exists between the start of induction and the presentation of clinical symptoms. Once clinical symptoms appear, the disease process works toward the **expression** of the disease, which relates to the outcome of the disease. Depending on the severity of the disease and the treatment strategies employed, the outcomes may range from full recovery of the disease, renewed susceptibility to infection, full immunity or death. Public health interventions typically focus on the induction and promotion stages of diseases, whereas the expression stage of a disease is usually addressed by clinical treatment interventions (Jewell 2004).

[1] The study of the causation or origin.

2.1.4 Risk factors

Epidemiology relates to the study of the determinants or links between risk factors and disease outcomes (CDC 2012). The interaction of these determinants are useful to inform health-related outcomes in the presence of various risk factors. The interaction between risk factors also affects the potential of disease establishment in an individual. The risk factors are classified according to the following three categories, with an example in the context of tuberculosis (Joubert 2014):

- **Necessary**, a risk factor that must be present in all situations in order for a disease to be present (e.g. presence of the disease pathogen);
- **Sufficient**, the minimum set of a particular combination of risk factors which together are likely to result in disease establishment in some individuals (e.g. presence of the disease pathogen and low individual immunity); and
- **Component**, the risk factors which in combination result in establishment of disease (i.e. the sufficient set of risk factors consist of a number of component risk factors).

2.1.5 Actors in the disease cycle

One of the simplest models that capture disease causation is that of the epidemiologic triangle, the traditional model used to describe infectious disease (CDC 2012). The triangle consists of the following corners:

- **Agent**, refers to the micro-organisms or pathogens responsible for the disease and capable of infecting a host (CDC 2012; Mishra et al. 2011);
- **Host**, an entity which can become infected and transmit the disease; and
- **Environment**, which refers to the extrinsic factors that influence the exposure and interaction between the agent and the susceptible host (CDC 2012). These factors may include climate, biological vectors, socio-economic factors and availability and quality of healthcare services. Some of these contextual factors are discussed in more detail within §2.4.

The interaction of these three components greatly affect the establishment and propagation of disease. In the following section (§2.2) the chain of infection is discussed in greater depth, which illustrates some of the interactions of the agent, host and environment.

2.2 Chain of infection

The chain of infection, as illustrated in Figure 2.1 is a useful analogy to study the universal characteristics of disease transmission as a series of links which must be present for disease transmission to occur. As with a chain, the links are connected successively which aptly illustrates the manner by which a disease reservoir (§2.2.1) is linked to a susceptible host (§2.2.2) by means of a transmission mode (§2.2.3).

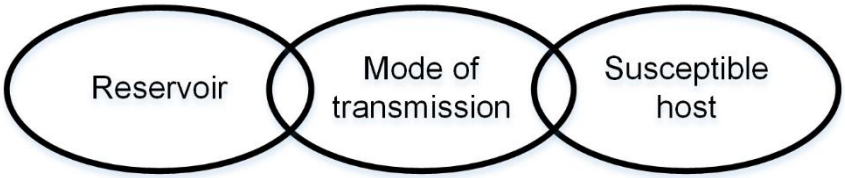

Figure 2.1: A visualisation of the chain of infection.

2.2.1 Reservoir

The first link of the chain is the **reservoir**, which is the habitat in which a disease agent lives and matures (CDC 2012). The three categories of reservoirs are human-, animal- and environmental reservoirs. It is notable that for a disease for which humans are the sole reservoir, eradication may be possible with the isolation of the last human case (CDC 2012). With regards to animal reservoirs, zoonosis refers to an infectious disease which may be transmitted from animals to humans. Alternatively, plants, soil and water serve as the environmental reservoirs of infectious diseases.

2.2.2 Susceptible host

The third link of the chain is the **susceptible host**. The susceptibility of a host relates to genetic factors, the specific immunity of the host and non-specific factors which play a role in the ability of an individual to resist infection. Specific immunity refers to protective antibodies which play a role in disease prevention. Non-specific factors which play a role in preventing disease are the skin, cilia in the respiratory tract, gastric acidity and non-specific immune response (CDC 2012). External factors (e.g. malnutrition, alcohol or drug usage) may affect either the specific or non-specific immunity adversely, or trigger a genetic weakness within the host, which could increase host susceptibility.

2.2.3 Mode of transmission

The second link of the chain is the **mode of transmission**, which serves as the connection between the first link (reservoir) and the third link (susceptible host) of the chain of infection.

Two categories are typically used to characterise the transmission mechanisms according to which diseases spread from a reservoir through the environment to a susceptible individual, namely transmission through direct contact and indirect contact. Diseases that spread either by direct contact or by droplet spread are transmitted by **direct contact**. Alternatively, diseases that spread by means of suspended air particles, vehicles (inanimate objects) or vectors (animate objects) are transmitted by **indirect contact**.

Subtle differences characterise the various direct contact transmission methods, namely (CDC 2012):

- **Direct contact**, which includes skin-to-skin contact, kissing or sexual intercourse between susceptible hosts; and

- **Droplet spread**, which includes the spray of droplets containing aerosols coming in contact with a susceptible host as a result of sneezing, coughing or talking. The transmission of droplets must occur directly from one host to another, otherwise the transmission would be regarded as indirect contact if transmission occurs as a result of environmental interaction.

Similarly, the difference between indirect contact transmission methods are as follows (CDC 2012):

- **Airborne**, which results from infectious agents that are transmitted through dust or particles suspended within the air. This may include pathogens or material that settled on surfaces which are suspended into the air or blown from soil surfaces by wind;
- **Vehicles**, which are regarded as all inanimate objects (e.g. food, water, biological material such as blood and fomites) that could possibly transmit a disease between hosts. Vehicles can either passively transport a pathogen, or provide an environment suitable for growth and multiplication; and
- **Vector-borne**, which includes animate objects (e.g. fleas, mosquitoes and ticks) and inanimate objects which either carry pathogens to the susceptible host (i.e. biological vector-borne) or provide an environment in which the pathogen may mature and grow (mechanical vector-borne).

The above mentioned transmission modes are well suited for a general consideration of disease transmission, however, a greater resolution of distinction between the different transmission modes is required to capture and characterise the variability more accurately. For instance, disease transmission through blood contact and sexual contact may both be characterised as a transmission through direct contact, however, the difference in the underlying transmission mechanisms may sensitively affect the contagiousness and dynamics of disease transmission. A more differentiated set of transmission modes were previously used to establish the initial steps required to map the global distribution of disease (Hay et al. 2013). These eleven transmission modes, reproduced below, are as follows:

- Animal contact;
- Blood / body fluid contact;
- Direct contact;
- Endogenous;
- Food / water-borne;
- Respiratory;
- Sexual contact;
- Soil contact;
- Vector-borne;
- Water contact; and
- Unknown.

These modes capture the variability in transmission modes more accurately than the broad categories defined by the CDC. For some diseases, multiple transmission modes could exist, in addition to some degree of overlap between various transmission modes. For instance, most sexually transmitted diseases are primarily transmitted by means of sexual contact, but may also spread by contact with bodily fluid containing the disease. The transmission modes as defined by Hay et al. (2013) are compared to those as defined by the CDC in Table 2.1.

Table 2.1: A comparison of mode of disease transmission categories between two sources.

<table>
<tr><th>Source</th><th colspan="6">Transmission mode</th></tr>
<tr><td rowspan="2">CDC (2012)</td><td colspan="2">Direct</td><td colspan="4">Indirect</td></tr>
<tr><td>Direct</td><td>Droplet spread</td><td>Airborne</td><td>Vehicle-borne</td><td>Vector-borne, biological</td><td>Vector-borne, mechanical</td></tr>
<tr><td>Hay et al. (2013)</td><td>Animal contact
Direct contact
Sexual contact</td><td colspan="2">Respiratory</td><td>Blood / body fluid
Food / water-borne
Soil contact
Water contact</td><td colspan="2">Vector-borne</td></tr>
</table>

One observation is that both the ‘droplet spread’ and ‘airborne’ categories of the CDC (2012) fit the ‘respiratory’ category of Hay et al. (2013). This is due to the fact that, in general, respiratory diseases are regarded as a disease which is transmissible by either direct contact (droplet spread exposure) or indirect contact (airborne exposure), depending on the specific transmission context. Additionally, Hay et al. (2013) used a more diverse set of transmission modes than the CDC (2012) in comparison to the ‘direct contact’ and ‘vehicle-borne’ categories of the CDC (2012). This provides an indication of the increased variability and dynamics of the transmission modes within these categories. As endogenous diseases are caused by internal factors within the individual and the transmission modes of the unknown category does not fit in any of the direct or indirect transmission categories, these transmission modes are not included in Table 2.1. The nine transmission categories defined by Hay et al. (2013) in Table 2.1 are well suited to capture the variability of disease transmission modes.

In conclusion, as the transmission mode may be viewed as the central link in the chain of infection, it may greatly affect the dynamics and contagiousness of a disease and should form a crucial part in the process of understanding the disease dynamics. Other contextual factors which may affect disease dynamics are discussed in greater detail in §2.4

2.3 An overview of mathematical modelling of infectious disease

As mentioned in the introduction to this chapter, the field of infectious disease modelling may appear large and densely published to the typical Engineer not well-acquainted with the medical and healthcare modelling field, however, it is a modelling field easily navigated once equipped with the necessary background information, presented within this section.

The modelling perspectives used as a departure point for modelling infectious disease dynamics are briefly highlighted in §2.3.1. In §2.3.2, important guiding principles which form part of the initial steps of mathematical modelling are discussed. Some of the most important modelling parameters, terms and assumptions pertaining to an infectious disease modelling context are discussed in §2.3.3, followed in §2.3.4 with a review of a select few modelling techniques applicable in an infectious disease modelling context. A brief discussion in §2.3.5 is afforded to some modelling mistakes which may typically occur in a disease modelling context.

2.3.1 Modelling perspectives

When modelling disease, different scientific fields, approaches and viewpoints may be adopted as a departure point for modelling or understanding disease dynamics. This influences the level of detail required for modelling purposes and model assumptions, as well as the scope of the modelling efforts. Some of these viewpoints are as follows:

- **Immunology**, where each disease is approached on the cellular level and is considered as a process of interactions between a pathogen (i.e. disease causing agent) and the defence system of an organism, which utilises immune cells and molecules to eliminate the pathogen (The American Association of Immunologists Inc. 2017);
- **Theoretical biology**, a branch of modelling which incorporates mathematics and theoretical perspectives in order to better study biological processes (Elsevier 2017), which may vary from disease modelling on the cellular level to the population level;
- **Ecological niche modelling**, concerns the study of the favourable “environmental conditions in which a species can maintain populations in the long term without need of immigration” (Escobar & Craft 2016), which focuses more on the biotic and abiotic environmental conditions required for disease establishment; and
- **Epidemiology**, which, according to a shortened definition of the Dictionary of Epidemiology (Porta 2014), is “the study of the occurrence and distribution of health-related events and the application of this knowledge to control relevant health problems,” which views disease occurrence on the population level.

The epidemiological viewpoint is considered the most suitable departure point for the modelling of infectious diseases within this research project as disease modelling on the population level is required in order to comprehend disease dynamics within a population.

2.3.2 Guiding principles for mathematical models

One of the primary guiding modelling principles is establishing a clear definition of the question which the model should answer (CSMG 2010c). This ensures that clear conclusions are drawn from clearly defined questions. An additional requirement is a high level of confidence in the ability of a model to capture and accurately represent the course of an epidemic (Daley et al. 2001). This ensures that predictions are accurate enough to make reasonable conclusions and enable improved assessment of control methods. Furthermore, three main aims typically form part of the disease modelling process. These aims are formulated as questions below and relate to the following:

- According to which methods do the diseases spread? (This is especially of importance when little information is available on a particular disease);
- What is the predicted course of an epidemic and what are the potential impacts on a population? (This aids analysis of the extent of the impact a disease outbreak might have on a population, such as medical costs associated with treatment); and
- Given an understanding of the disease dynamics, what would be the most appropriate control methods? (To ensure that the most effective and sensible intervention strategies are considered and applied).

Modelling assumptions that are typically incorporated and which are common to all modelling techniques include the following (Daley et al. 2001):

- **Population dynamics**, which may extend to the population structure (relating to susceptibility of individuals, homogeneous groups or subgroups) or whether a population is regarded as an open or closed system (depending on the influx or outflow of individuals);
- **Disease transmission mechanisms**, which is concerned with how diseases spread between individuals and the presence or absence of recovery and removal mechanisms; and
- **Mathematical modelling assumptions**, which mathematically specify the preceding assumptions.

2.3.3 Typical modelling parameters and terms in an epidemiological context

Some keywords within the definition of epidemiology are elaborated below to highlight some of the important guiding principles in epidemiology:

- **Study**, concerns surveillance, observation and research of health related events;
- **Distribution**, refers to the analysis of the frequency and patterns of health related events over space and time;
- **Determinants**, concerns the factors that bring about a change in a health condition, such as biological, geographic, social, cultural, economic or political factors;
- **Health-related states or events**, refers to activities associated with disease states, such as outbreaks, causes of death, preventative programs and health and social services; and

- **Application**, concerns the overarching goal of epidemiology, namely to promote, protect and restore public health.

When undertaking epidemiological research, two approaches are used, namely descriptive epidemiology and analytical epidemiology. Descriptive epidemiology concerns the study of the occurrence of a disease and health-related characteristics (Porta 2014). These include basic characteristics such as age, gender, occupation, social class and geographic location. People, time and place thus play an important role in descriptive epidemiology.

In contrast, analytical epidemiology concerns the testing of the validity and strength of causal links between the observed patterns and the factors which affect the risk of disease (CDC 2012). In short, whereas descriptive epidemiology is used to generate hypotheses about disease occurrence and dynamics, analytical epidemiology is used to test these hypotheses (CDC 2012).

Jewell (Jewell 2004) further states the epidemiological study of the disease process would focus on answering two questions, namely:

- Which risk factors are strongly associated with the induction, promotion and expression of a disease; and
- Which risk factors influence the length of induction, promotion and expression periods?

These research questions, in addition to risk factors relating to disease causation (previously mentioned in §2.1.4) link closely to the considerations and approaches of descriptive epidemiology.

In conclusion, the importance of viewing disease causation as a complex interaction of various risk factors may be useful when designing and adopting holistic modelling approaches. The guiding principles of epidemiology serve as a good starting point to approach disease dynamics from a high-level perspective and study of factors and interactions which potentially affect disease transmission.

This remainder of the section contains background information on a selection of modelling parameters and terms that are key to understanding the considerations which form part of the infectious disease modelling and analysis process.

Herd immunity

The protective phenomenon observed when a high proportion of hosts in a population are immune against a disease, which in turn protects the few remaining susceptible individuals within the population, is referred to as herd immunity (Altizer et al. 2006). This phenomenon is typically achieved by means of prophylactic (i.e. preventative) vaccination or as a result of immunity following previous recovery from an infection.

The law of mass action

According to Grassly and Fraser (2008), the mass action law states that "the rate at which individuals of two types contact one another in a population is proportional to the product of their densities." What this law implies is that a pattern of fast initial growth is typically associated with disease outbreaks, followed by a typical decrease in the rate of new infections once the number of infected individuals surpass the number of susceptible individuals. This phenomenon typically leads to the bell-shaped curve associated with epidemics (Grassly & Fraser 2008).

Contact mixing pattern

When modelling the spread of disease between individuals in a population, the manner in which these individuals have contact with each other is an important aspect of the modelling considerations and assumptions. The disease transmission mode may greatly influence these contact assumptions, as close proximity is required for diseases which spread by means of direct contact, whereas diseases which spread primarily by vectors such as mosquitoes might not be as dependant on contact-related assumptions.

The most common mixing pattern employed by default is homogeneous (i.e. random) mixing, which assumes that each individual has the same average rate of contact with any other individual (Mishra et al. 2011). This implies that individuals have uniform contact with each other and an equal probability of having contact with any other individual. The use of this assumption greatly simplifies mathematical modelling applications and is very commonly used.

In contrast, when adopting heterogeneous (i.e. non-random) mixing patterns in the modelling approach, the modeller allows for some individuals to have a higher average contact rate than other individuals, as a result of social, spatial or behavioural differences (Mishra et al. 2011). Some examples of heterogeneous mixing patterns include:

- Assortative mixing, when contact between individuals of similar groups (e.g. social or certain age groups) are more likely to occur; and
- Disassortative mixing, which in contrast to assortative mixing, is when contact between individuals of dissimilar groups are more likely to occur.

Transmission probability parameter

The transmission parameter β is used to quantify the probability that an infected host will transmit the disease to a susceptible host, given sufficient contact occurs between individuals (Mishra et al. 2011). This parameter forms an important part in quantifying the infectiousness of a disease, as it is one of the primary parameters which determine the probability of infection.

Basic reproduction number

The basic reproduction number Ro is the average number of secondary disease cases typically caused by an infected individual (Chowell & Nishiura 2014). One way to describe it is as

$$Ro = \beta c' D,$$

where c' is the contact rate between individuals and D is the infectiousness of the disease (i.e. the inverse of the recovery rate from the disease) (Mishra et al. 2011). This expression only holds for the case when the infected individual is located in an entirely susceptible population and when no interventions strategies are in place (Chowell & Nishiura 2014). For the disease prevalence to increase in a population, Ro must be greater than one. This parameter is therefore an indication of the ability of intervention strategies to reduce or potentially eliminate the secondary spread of disease within a population.

Force of infection

The force of infection (denoted by λ) characterises the transmission between infected and susceptible individuals. This is expressed as

$$\lambda = \beta c' p,$$

which unifies the contact rate c', transmission probability β and prevalence of the disease (refers to the proportion of individuals in a population which have a disease at a specified point in time, denoted as p) in order to quantify the transmission dynamics of a disease (Mishra et al. 2011).

Compartmental classification of models

Within epidemiology, the propagation of disease within a population is commonly modelled by means of clustering individuals according to mutually exclusive disease states, a typical approach of epidemiological modelling. Once these states are determined, various mathematical modelling approaches are available to use to describe the movement between different disease states. Four of the most commonly used categories are:

- **S**, individuals who are susceptible to disease infection, but not yet infected;
- **E**, individuals who are exposed or infected with disease pathogens, but cannot transmit the disease to other individuals yet;
- **I**, individuals who are infectious and are able to transmit the disease; and
- **R**, individuals who are not infectious anymore as a result of disease immunity following recovery or death of the individual.

Additional categories are sometimes also incorporated in modelling approaches (*e.g.* Q, when infected individuals are quarantined or V when individuals are vaccinated), depending on the nature

of the research questions. Within compartmental models, movement to other disease states are modelled according to transmission probabilities, contact rates and patterns. Mathematical modelling approaches (*e.g.* differential equations), network models and simulation approaches frequently utilise compartmental classification to characterise disease states.

2.3.4 Common modelling techniques applied in a disease modelling context

When approaching a problem with modelling techniques, there are typically more than one technique available to implement. Within this subsection, common modelling techniques which are applied in a infectious disease modelling context are briefly reviewed. These techniques include, but are not limited to, mathematical models, network models, systems thinking and system dynamics, and simulation models as discussed below.

Mathematical models

As mentioned in §2.3.3, epidemiology concerns the development of models to fit the relationship between risk factors and disease. To achieve this, data pertaining to the risk factors of the disease are collected and used to determine statistical values and associated risk factors of the disease. Mathematical models such as differential equations, regression and statistical analysis are typically utilised within epidemiological modelling (Porta 2014).

Network models

Network models consist of different nodes which are connected by lines known as graphs in order to form a network (CSMG 2010a). The use of network models in the realm of healthcare modelling is a relatively new occurrence and one of the main applications are to model the spread of disease. Other applications may include testing how alteration of the network may curb and control the spread of disease, in addition to testing vaccination strategies and identifying key immunisation targets within a community which would ensure maximum efficacy (CSMG 2010a).

Systems thinking and system dynamics

Systems thinking may be regarded as a more qualitative style of thought than a quantitative modelling technique (CSMG 2010b). This approach views a system as a whole instead of focussing primarily on the collective parts of the system, allowing for increased insight into the interactions of the parts of the system. This approach stems from the belief that the components of the system will behave differently when isolated from the rest of the system. The impact of a change in population age demography on the health care system, in addition to measuring the effect of a pandemic disease outbreak on the health care system, are some of the applications of systems thinking.

The use of system dynamics takes this approach one step further, by describing and quantifying the flows and feedback loops between the parts of the system (CSMG 2010b). One of the advantages of combining systems thinking and system dynamics are that the strengths of both quantitative and qualitative modelling techniques are incorporated. This also results in a more understandable and believable model. The drawback of this versatility is the difficulty in solving system dynamics models by analytical methods, which typically utilise numerical analysis techniques (CSMG 2010b).

Simulation

A simulation model is typically used to mimic the stochastic operation of a real-world process by means of mathematics and probability distributions (Mishra et al. 2011). As the parameters in simulation models are drawn from probability distributions, each model iteration and final solution will differ slightly from each other, which results in the mimicking of a stochastic process such as disease transmission. Monte Carlo simulation and agent based simulation (ABS) models are typically utilised to model the spread of disease between individuals. Simulation models require the most effort to successfully implement, but are more able to capture the variability and stochasticity of the disease transmission process.

2.3.5 Typical challenges experienced with the modelling of infectious diseases

Regardless of the choice of the modelling technique, some of the typical challenges when developing a model are highlighted, namely (CSMG 2010d):

- The model does not answer the stated question (i.e. the model should focus on answering the specified research questions);
- The theoretical model is incomprehensible (i.e. the model and modelling process should be transparent enough to allow experts to examine the model and validate the realism thereof);
- The model is not believable (i.e. advice from experts should guide the modelling process); and
- The model does not fit the data (i.e. the model provides an inaccurate answer to the modelled question. Even when a model fails to fit the data, however, the analysis of the reasons and model assumptions may be of use for future modelling efforts). Furthermore, to distinguish between true stochastic behaviour and model misspecification, a comparison between the simulated results and the actual data should be completed.

Knowledge of the above mentioned challenges may serve as important guiding principles during the modelling process, but additionally aid in designing a check-list or support tool in order to prevent avoidable modelling pitfalls.

2.4 Contextual factors affecting disease transmission

Hay et al. (2013) state that understanding the factors which are involved in the genesis of disease outbreaks is foundational to the development of an early warning disease system. Two sets of factors are mentioned which may attribute to the occurrence of yearly epidemic events, namely extrinsic factors (associated with climatic phenomenon) and intrinsic factors (associated with host and pathogen population dynamics) (Hay et al. 2013). Although climatic factors were specifically studied for instances of two vector-borne diseases, contextual factors play a role in disease dynamics regardless of the transmission mode, which is discussed within this section.

The first subsection (§2.4.1) relates to environmental factors which may affect disease dynamics, whereas §2.4.2 relates more to factors affecting the host population dynamics. These contextual factors are typically not incorporated explicitly in modelling approaches, possibly due to the complexity in realistically capturing these contextual characteristics within a model. The consideration of these factors are, however, useful to inform and highlight the various factors which affect disease dynamics.

It is worth noting that human activities which may play a role in disease transmission are omitted from detailed analysis, not limited to the following factors:

- Mining activities and draining of wetlands;
- Agricultural activities and deforestation;
- Resistance to control and treatment methods;
- War; and
- Urbanisation.

It is not denied that the above mentioned factors may affect disease dynamics on a high-level. For instance, the Second World War contributed to dengue fever emergence within South-East Asia through infantry movement (Ooi & Gubler 2008). Additionally, agricultural activities may alter environmental disease reservoirs and urbanisation in turn affects population density and proximity of individuals to each other (Reiter 2001). The challenge with incorporating human activities relates to the extreme difficulty in linking human factors realistically to disease dynamics and is therefore not included within the scope of this research.

2.4.1 Environmental factors

The transmission dynamics of diseases, especially that of vector-borne diseases, are greatly influenced by climatic factors (Reiter 2001). These factors include climate and seasonality, discussed in the remainder of the section.

Climate

Within the context of climate (e.g. temperature, rainfall, humidity), vector-borne diseases are the most frequently studied (Lipp et al. 2002). Furthermore, especially in tropical areas, climate may affect the transmission dynamics of vector-borne diseases. For example, Hay et al. (2013) mentions that mosquitoes responsible for transmitting malaria and dengue parasites are extremely sensitive to climate and variations thereof may affect vector populations. The effect of climatic factors may also vary according to the ecology of the vector, in addition by geographic region, which adds to the complexity of quantifying the influence of climatic conditions on disease transmission dynamics (Reiter 2001).

Theoretically, higher **temperatures** reduce the extrinsic incubation period of vectors, in addition to potentially increasing the frequency of biting and laying of eggs (Reiter 2001). This may potentially increase the transmission probability, as well as the survival rate of the vectors. Temperature may also affect human exposure to vectors, by affecting time spent in the outdoors and opening of windows in buildings to allow for ventilation (Xu et al. 2017).

Rainfall aids transmission of vector-transmitted disease by development of breeding sites and is one of the key short-term drivers affecting vector-borne disease dynamics (Reiter 2001; Xu et al. 2017). On the other hand, drought may remove sources of standing water, but may result in sources of flowing water to become stagnant and potentially result in the formation of new breeding sites (Reiter 2001).

The effect of climatic factors are not limited to vector-borne diseases. For instance, in the context of pertussis (i.e. respiratory disease), temperature is studied in relation to daily case numbers of pertussis notifications (Huang et al. 2017). Similarly, associations between climatic conditions and mumps prevalence are also studied (Li et al. 2016). In the context of rotavirus (i.e. a disease transmissible by means of body fluid and water contact), the association between climatic conditions and rotavirus prevalence is also determined (Van Gaalen et al. 2017).

Seasonality

Seasonality affects climate and in turn may drive disease dynamics. Reiter (2001) mentions that regions with a typical mild climate may experience summer temperatures which may be as high as the warm seasons of the tropics, whereas the tropical regions do not experience cold winters. This especially affects vector-borne diseases, as the vectors such as mosquitoes may be eliminated during winter, preventing vector-borne disease transmission.

Another example is that of cholera (a disease spread by means of water contact) dynamics in India, which illustrates a complex relationship between climate and seasonality. In a study performed in India, wetter regions typically experience 2 major annual peaks in cholera outbreaks, whereas drier regions typically only experience one major annual outbreak (Altizer et al. 2006). The onset of the

cholera outbreaks in the drier provinces are correlated to the onset of monsoons. However, in wetter provinces the outbreaks are more prevalent during the dry months and decline during monsoon rains (Altizer et al. 2006). This may be explained by the phenomenon that temperature affects cholera dynamics in wetter regions and rainfall affects cholera dynamics in drier regions (Altizer et al. 2006). The seasonality of monsoon rains and seasonal temperature variation on cholera dynamics illustrate the manner in which seasonality may affect disease dynamics.

Seasonal changes may also affect the behaviours of hosts, pathogens and vectors and in turn influence disease dynamics. These include changes in behaviour and contact rates of hosts and pulses of births which may be more vulnerable during winter periods and harsh weather, due to the effect on herd immunity and variations in immune defences (Altizer et al. 2006).

The effects of seasonality are not limited to vector-borne and water contact diseases. For instance, in the context of H1N1 (i.e. a respiratory disease), seasonality of disease instance are determined and analysed (Balcan et al. 2009). Similarly in the context of measles (i.e. a respiratory disease), the disease prevalence is linked to the seasonality of dust events (Ma et al. 2017).

2.4.2 Population demography and dynamics

In addition to environmental factors, the structure and composition of a population (i.e. population demography) play a role in disease dynamics. Factors which relate to demography, population density and spatial distribution, migration and socio-economic factors are discussed in the remainder of the section.

Demography

The demographics of a population play a role in the composition of a population and is typically included when conducting epidemiological research (Joubert 2014). These factors include the following, namely:

- Age;
- Sex; and
- Mortality and natality.

The selection and description of the above mentioned factors are used to model factors such as age-related disease susceptibility, contact patterns and changes in population size and distribution. For instance, in the context of pertussis, age and waning immunity are included in the modelling application to analyse the impact of an infant vaccination programme (Campbell et al. 2016). Similar studies are completed in the context of measles (i.e. respiratory disease) in relation to age-specific mixing, vaccination and outbreak risk (Bhattacharyya & Ferrari 2017). In the context of rotavirus (i.e. a disease transmissible by means of body fluid and water contact), the variability of population demographic composition, especially the variation in birth rate, is analysed and linked to the

occurrence of rotavirus epidemics (Pitzer et al. 2009). In the context of Ebola (i.e. a disease transmissible by means of direct contact, sexual contact, body fluid contact and respiratory contact), the age-related probability of contact is included in the modelling application to estimate disease transmission (Siettos et al. 2016a).

Population density and spatial distribution

Population density and spatial distribution affect the proximity of individuals to each other in a population, in turn affecting disease dynamics, regardless of the transmission mode. In the context of SARS (i.e. a respiratory disease), the connections between regions (i.e. spatial spread) and the population density are incorporated in the modelling application to model disease transmission (Yoneyama et al. 2010). In the context of smallpox, (i.e. a disease transmissible by means of direct contact, respiratory contact and body fluid contact) the population density is included in a simulation approach to test the efficacy of different vaccination strategies (Brouwers et al. 2010). In the context of Ebola (i.e. a disease transmissible by means of direct contact, sexual contact, body fluid contact and respiratory contact), the spatial spread of individuals are incorporated to analyse the dynamics of super spreading events (Lau et al. 2017).

Migration

With the increase in road building and modern transportation opportunities such as cheap air travel, remote areas that are burdened with endemic diseases may become more accessible to commuters (Reiter 2001). Commuters, now able to travel long distances by rail or by road to visit family or to seek medical attention may contribute to disease transmission from endemic rural areas to urban areas (Reiter 2001). Cheaper international air travel may also contribute to the distribution of disease. For instance, in the context of cholera (i.e. a food-borne and water contact disease) human mobility is incorporated in a modelling approach to determine the role of movement on the transmission dynamics of cholera (Njagarah & Nyabadza 2014; Perez-Saez et al. 2017). In the context of polio (i.e. a disease transmissible by means of respiratory contact, body fluid contact, food-borne and water contact), the international spread of the wild polio virus by means of travellers is believed to slow the global eradication of the disease (Wilder-Smith et al. 2015). Similarly, in the context of SARS (i.e. a respiratory disease), the effect of individual movement is modelled to determine the effect on the total number of infected individuals (Maeno 2016).

Socio-economic factors

Socio-economic factors are typically outside the control of the individual, however, it may affect access to healthcare and indirectly affect susceptibility to disease. Reiter (2001) states that the quality of the public health sector of numerous countries have degraded due to a lack of funding and

problems coupled with rapid urbanisation and development. For instance, the increased attention afforded in an attempt to manage AIDS prevalence in parts of Africa and South-East Asia reduced the ability of healthcare authorities to attend to other diseases. In the context of Ebola (i.e. a disease transmissible by means of direct contact, sexual contact, body fluid contact and respiratory contact) socio-economic factors are incorporated in a modelling approach to determine the effect thereof on the number of infected individuals (Sato et al. 2015). Similarly, in the context of rotavirus (i.e. a disease transmissible by means of body fluid and water contact) the potential effect of malnutrition is studied in relation to increased disease susceptibility in children (Paynter 2016).

2.5 Disease characteristics: Using an electronic web-based disease database

The GIDEON (Global Infectious Diseases and Epidemiology Online Network) database is a useful infectious disease knowledge management tool commonly used by health practitioners, universities and microbiologists (GIDEON 2017b; Toovey 2010). This database consist of two parts, namely a module on infectious disease characteristics and a module on microbiology. The infectious disease module of the database is used within this chapter to gather information on disease characteristics.

In order to generalise the disease characteristics as presented in the GIDEON database, some classification of the various disease characteristics is required. A brief overview of the consulted database is completed in §2.5.1. Typical vaccination and treatment strategies are briefly reviewed in §2.5.2, followed by categorisation of the transmission mode in §2.5.3. §2.5.1 and §2.5.3 relate primarily to the GIDEON database, whereas §2.5.2 does not relate solely to the GIDEON database.

2.5.1 Overview of the consulted database

Within the GIDEON database (screenshot of the GIDEON disease database interface illustrated in Figure B.1) the disease characteristics listed for each disease include the following categories, namely:

- Disease;
- Agent;
- Reservoir;
- Vector;
- Vehicle;
- Incubation period;
- Diagnostic test;
- Typical adult and paediatric therapy;
- Vaccines;
- Clinical hints; and
- Synonyms.

Within this study, the characteristics which were not studied in detail include the diagnostic test and clinical hints of disease, as this does not form part of the primary focus of the research. Additionally, the disease synonyms are not a critical requirement to categorise disease characteristics.

2.5.2 Intervention strategies

Intervention strategies are grouped between those which include vaccination, and intervention strategies which relate to treatment of individuals.

Vaccination

The first immunisation schedule published by the WHO was in 1961 as part of the 13th World Health Assembly (WHO 2008). It is notable that this initial schedule targeted communicable diseases mainly beyond the first year of life in individuals. It was only with the Expanded Programme on Immunization (EPI), an initiative founded in in 1977, that the well-known schedule for infants under one year of age was established. The first diseases targeted were tetanus, measles, tuberculosis, whooping cough, diphtheria, and poliomyelitis (WHO 2016a). Since inception of the EPI, additional vaccines such as hepatitis B and Influenza type B have been added to the routine infant immunisation schedules of various countries, including numerous low-income countries (WHO 2016a). Additionally, the pneumococcal conjugate vaccine and rotavirus vaccines are also in the process of being added to the schedules of an increasing number of countries.

Individual countries may vary national immunisation programmes, however, in South Africa the following diseases are included in routine immunisation (RI) schedules (WHO 2016a):

- Polio;
- Measles;
- Tuberculosis;
- Diphtheria;
- Pertussis;
- Tetanus;
- Influenza type B;
- Hepatitis B;
- Rotavirus;
- Pneumococcal infection; and the
- Human papilloma virus (HPV).

Vaccination strategies which are typically implemented in the literature are discussed on a high-level in Table 2.2 (p.32).

Treatment

Different treatment strategies are typically used in modelling approaches to reduce infectivity or reduce disease transmission, namely:

- Quarantine or hospitalisation (Yarmand et al. 2013);
- Drug usage (Chong & Zee 2012);
- School closure (Eames 2014); and
- Safe burial with reduced contact (Shen et al. 2015).

2.5.3 Categorising the transmission mode

It is worth noting that the GIDEON database does not contain a category for the transmission mode of a disease. Instead, vectors and vehicles responsible for disease transmission are listed for each disease. Using the nine transmission modes previously identified in Table 2.1 in §2.2.3, the vectors and vehicles responsible for disease transmission (as noted in the GIDEON database) are analysed and categorised in Table 2.3 (p.33). The selected transmission mode depends on the best fit of the vehicle or vector to one of the nine transmission categories.

To verify the accuracy of the transmission modes identified for the vectors and vehicles in Table 2.3, a comparison to an existing set of disease transmission modes used by Hay et al. (2013) is completed in Table 2.4. The vehicles and vectors for each disease are categorised according to Table 2.3 and assigned a number of transmission modes accordingly. The transmission modes highlighted in bold in Table 2.4 are additional transmission modes captured by the categories proposed in Table 2.3, but not captured by Hay et al. (2013). This highlights the increased ability of the proposed disease transmission mode categorisation of Table 2.3 in identifying multiple transmission routes for a disease, thereby capturing the variability in disease transmission more thoroughly.

Table 2.2: A high-level overview of commonly used vaccination strategies.

Name of strategy	Strategy	Advantages	Disadvantages	Source
Ring	Identify individuals with disease infection, then trace contacts for vaccination.	Minimises the required amount of vaccine doses.	Highly effective contact tracing required to limit disease transmission.	Ferguson et al. (2003)
Targeted	Vaccination of an entire population within a specific city or district.	Effective strategy if used in an eradication campaign to contain geographically localised disease transmission.	Only effective in the context of prior high levels of herd immunity.	Ferguson et al. (2003)
Mass (similar to RI)	Vaccination of an entire population in a country.	Effective at preventing and protecting against disease transmission across large areas.	Quick vaccination of large quantities of individuals are required to be effective.	Ferguson et al. (2003)
Prophylactic	Preventative vaccination before disease outbreak.	Very effective at stopping spread of disease when used for an entire population.	High long term cost when used to protect an entire population.	Ferguson et al. (2003)
Pulse	Repeated intervals of vaccination targeting a specific age range or a group of susceptible individuals.	Relative low levels of vaccination are required to ensure disease eradication.	Timing of pulses critical in the effectiveness of the strategy.	Ferguson et al. (2003)

Table 2.3: A classification of the GIDEON vehicles and vectors according to 9 disease transmission categories.

Animal contact	**Direct contact**	**Sexual contact**	**Respiratory / droplet**	**Blood / body fluid**	**Food-borne**	**Soil contact**	**Water contact**	**Vector-borne**
Amphibian	Physical contact	Sexual contact	Droplet	Breastfeeding	Dairy products	Soil contact	Water	Fly
Reptile			Dust	Fecal-oral	Eaten insect	Vegetable matter	Fecal-oral	Mosquito
Animal bite			Aerosol	Secretion	Fish			
Snail			Respiratory	Blood	Food			
Earthworm			Pharyngeal acquisition	Tissue	Meat or poultry			
Slug					Shellfish			
					Vegetable			
					Fruit			

Table 2.4: Comparison of the constructed transmission mode categorisation to a previous categorisation of disease transmission modes for different diseases.

Disease	Transmission category according to Table 2.3	Transmission category used by Hay et al. (2013)
Anthrax	Animal contact	Animal contact
Cholera	Food/water-borne, **water contact**	Food/water-borne
Dengue	Vector-borne	Vector-borne
Diphtheria	**Direct contact**, respiratory/droplet	Respiratory
Ebola	**Direct contact, sexual contact, respiratory/droplet**, blood/body fluid	Blood/body fluid
Hepatitis B	Sexual contact, **blood/body fluid**	Sexual contact
Influenza	Respiratory/droplet	Respiratory
Malaria	Vector-borne	Vector-borne
Measles	Respiratory/droplet	Respiratory
Pertussis	Respiratory/droplet, **blood/body fluid**	Respiratory
Polio	**Respiratory/droplet, blood/body fluid**, food/water-borne	Food/water-borne
Rabies	Animal contact	Animal contact
Rubella	**Direct contact**, respiratory/droplet, **blood/body fluid**	Respiratory
Rotavirus	**Blood/body fluid**, water contact	Food/water-borne
Smallpox	Direct contact, **respiratory/droplet, blood/body fluid**	Direct contact

2.6 Conclusion

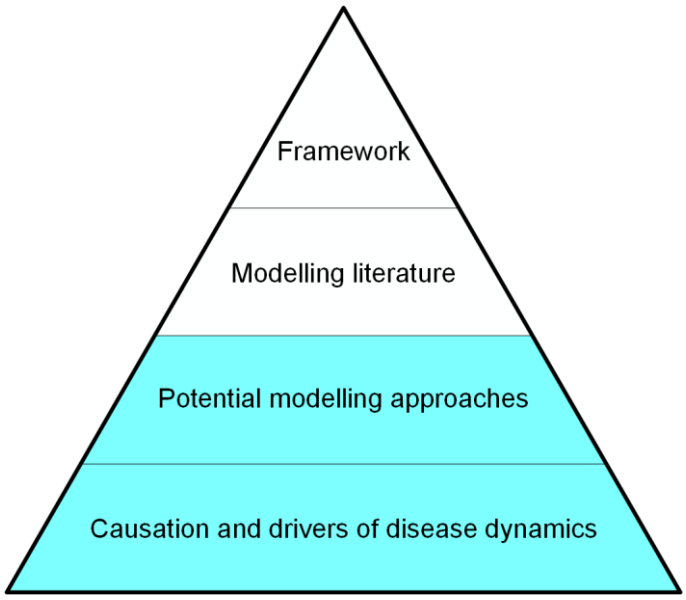

Figure 2.2: A visual summary of the content of Chapter 2.

A summary of the content of this chapter in relation to the overall document structure is illustrated in Figure 2.2. The complexity associated with infectious disease modelling is apparent from the reviews on the literature conducted in §2.1-§2.3. The information on the contextual factors in §2.4 and the disease characteristics in §2.5 are used to construct Figure 2.3, to illustrate some of the interplay between disease characteristics and the contextual factors which play a role in the dynamics of disease transmission.[2] Furthermore, an initial step towards mapping the aspects influencing disease dynamics is illustrated in Figure 2.4 (p.37).[3] This mapping forms part of the steps towards understanding the factors which play a key role in infectious disease dynamics.

[2] With respect to the linking process, it is worth noting that humans may serve as both the reservoir and the host of a disease.

[3] This mapping formed part of a poster that was presented at the 2017 inaugural London School of Economics International Health Policy Conference held in London, UK, in February 2017.

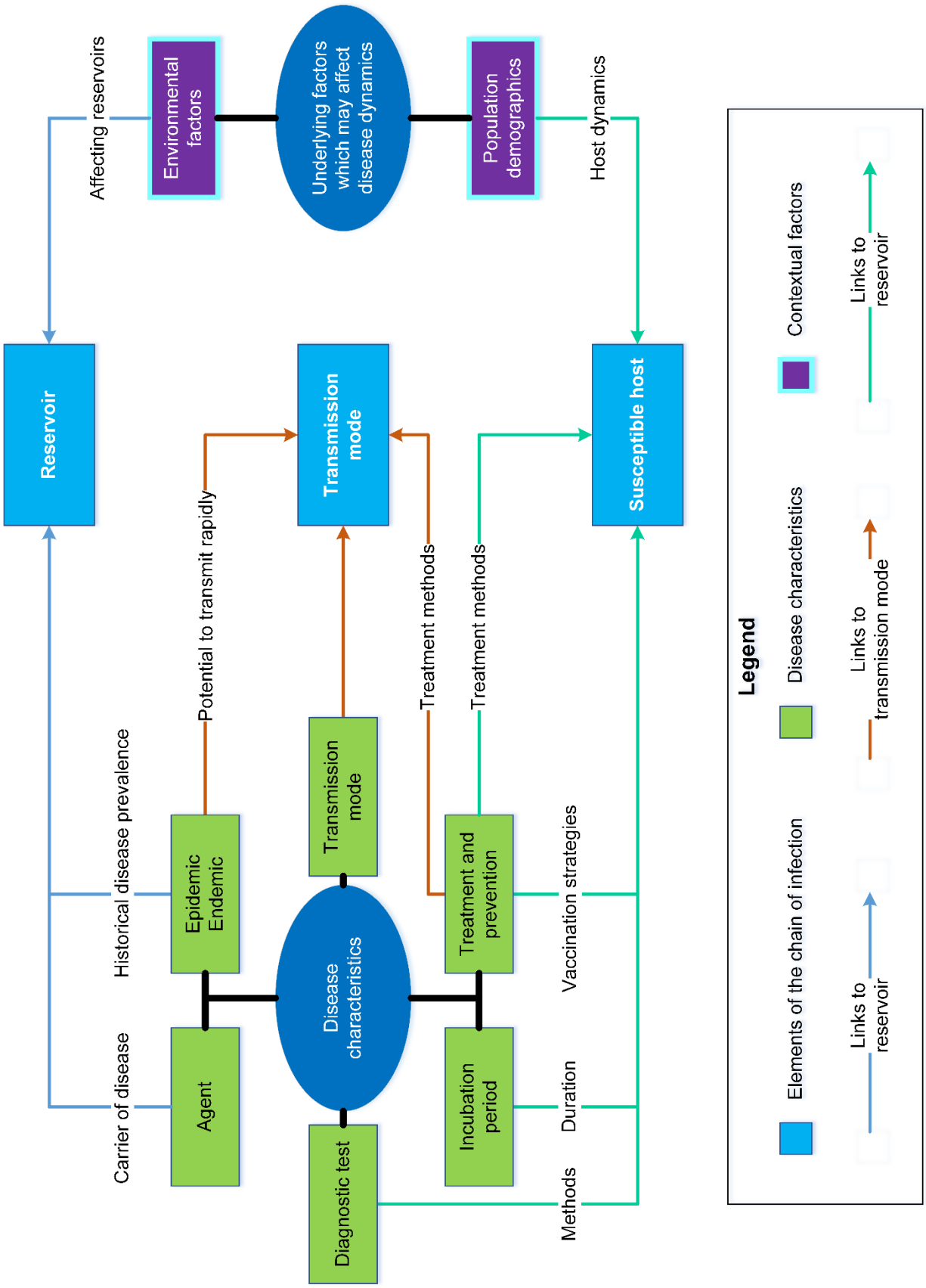

Figure 2.3: Linking disease characteristics and contextual factors to the chain of infection.

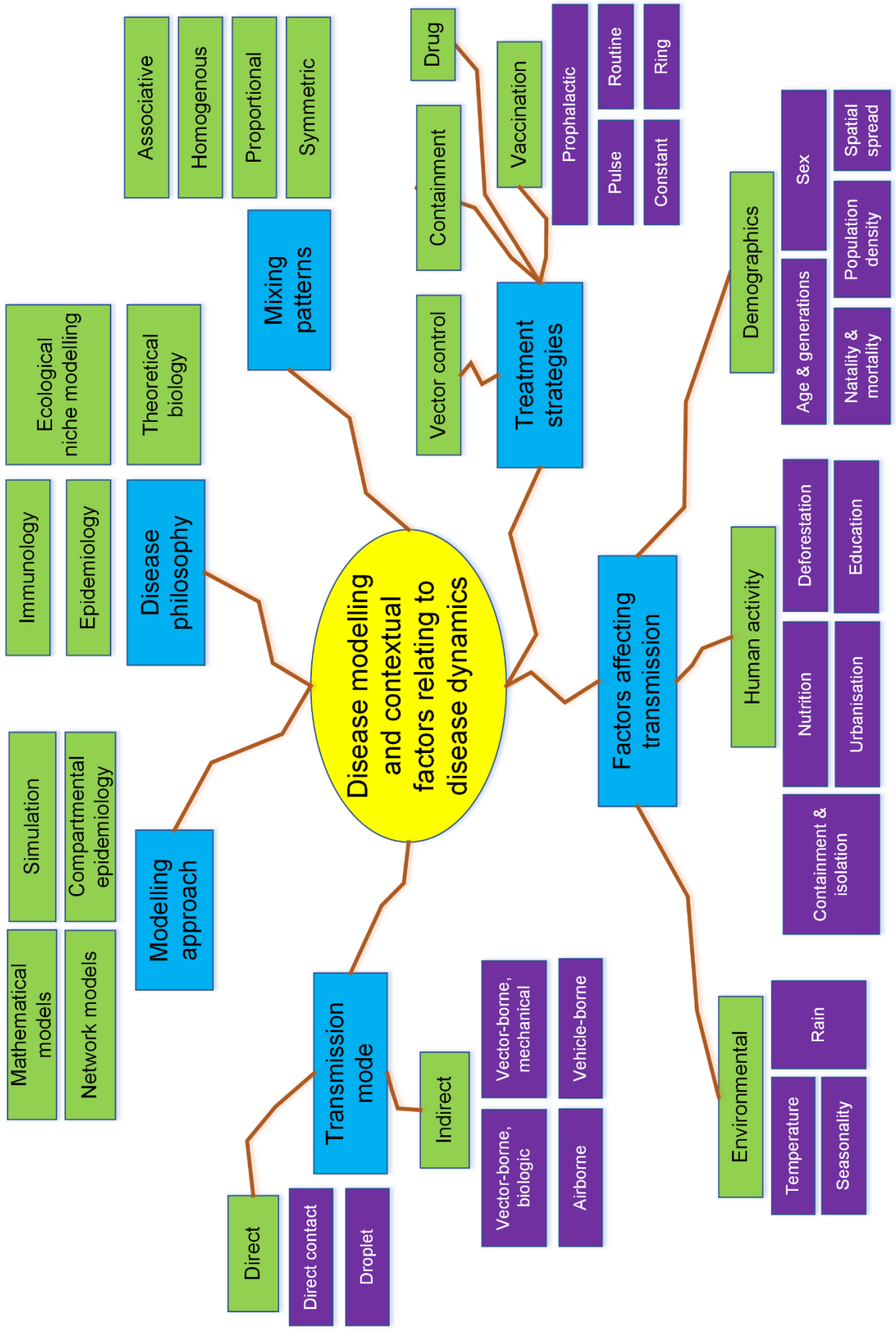

Figure 2.4: Initial mapping of factors affecting disease dynamics and the modelling choices thereof.

Chapter 3 Data gathering: Structured literature review on disease modelling

The selection of a modelling approach to utilise in a disease outbreak is characterised by numerous decisions. Some of these decisions relate to the disease characteristics and contextual factors which affect disease dynamics, in addition to selecting and incorporating a modelling approach with a view to answer context specific research questions. Fitting epidemic data to a mathematical model is probably one of the most important aspects of the process, which determines the ability of a model to capture and potentially predict the dynamics of a disease outbreak. However, modelling infectious diseases within the context of a disease outbreak require more thought than merely fitting data to a model and require a holistic modelling approach. To gather and analyse the literature on existing modelling applications typically used to model infectious diseases or test the effect of contextual factors on disease dynamics, a thorough review of the disease modelling applications and approaches that are typically employed are constructed, completed and briefly analysed within this chapter.

To guide and inform the search parameters of the structured review, a few of the factors which may affect the selection of a modelling approach, with a view to understanding the underlying disease dynamics, are highlighted within §3.1. The scope delimitation and criteria used to inform the structured literature review are discussed in §3.2, followed by a description of the steps followed in §3.3 to complete the review. Assumptions which relate to notable omissions from the review, in addition to important deviations from the steps of the review are highlighted in §3.4. A few of the high-level results are discussed in §3.5 prior to the chapter conclusion in §3.6.

3.1 Considerations affecting selection of modelling strategy

When approaching the disease modelling process from a systems thinking perspective, it becomes clear that numerous decisions, apart from fitting data to a model, play a role when selecting a modelling approach. A select few of these considerations are addressed within this section. The distinction between the pandemic, epidemic or endemic status of a disease and the potential effect on modelling choice associated with this status is discussed in §3.1.1. The transmission mode in relation to the disease dynamics is discussed in §3.1.2. A short overview of the effect of the resources that are available to modellers is presented §3.1.3. The effect of the research question on the aspired goals of a modelling applications are discussed in §3.1.4.

3.1.1 Distinction between endemic, epidemic and pandemic disease status

As mentioned in §2.1.2, diseases may be classified as either endemic, pandemic or epidemic. This distinction may affect the modelling approaches which are selected. For instance, endemic diseases might require different control methods as opposed to control methods used in epidemic or pandemic disease outbreaks. Whereas control methods for pandemic diseases may focus primarily on prevention of large-scale disease propagation, control methods for endemic diseases may afford more attention to disease eradication.

The speed of transmission to other geographic areas determine whether a disease may be classified as a localised epidemic outbreak, or have the potential of a pandemic disease outbreak. Accounting for this rate of spread may influence the choice of appropriate modelling approaches and considerations.

3.1.2 Transmission mode

One significant factor which characterises disease dynamics is the disease transmission mode. As mentioned in §2.2.3, the mode of transmission serves as the link in the chain of infection which brings the reservoir of a disease in contact with a susceptible host. The transmission mode and the number of transmission modes according to which diseases are transmitted to and between humans may greatly affect disease propagation within a region, and may potentially impact the manner in which disease dynamics and control strategies are employed.

3.1.3 Resources available to modellers

The modelling approach choice may also relate to the resources and data available to the modeller. In a comprehensive review on epidemic modelling approaches typically employed, three high-level model types are identified, namely mathematical models, complex network models, and agent based models (i.e. simulation models) (Duan et al. 2015). In Figure 3.1, a comparison between four aspects which characterise some of the differences between these models are illustrated, namely:

- Level of complexity;
- Level of detail;
- Level of mixing and
- Computing power requirements.

The availability of data may additionally influence the selection and complexity of modelling approaches, as more complex models typically require more data for parameter selection (Duan et al. 2015). In general, less complex models may be used when little is known about a disease and an initial understanding of key concepts are desired or when a novel research question is studied (Mishra et al. 2011). On the other hand, when more detailed data are available or when more accurate projections are required, more complex models are typically employed. Increased model

complexity does not, however, necessarily equate to a better model, as increased assumptions and model parameters require more validation and may be more difficult to interpret.

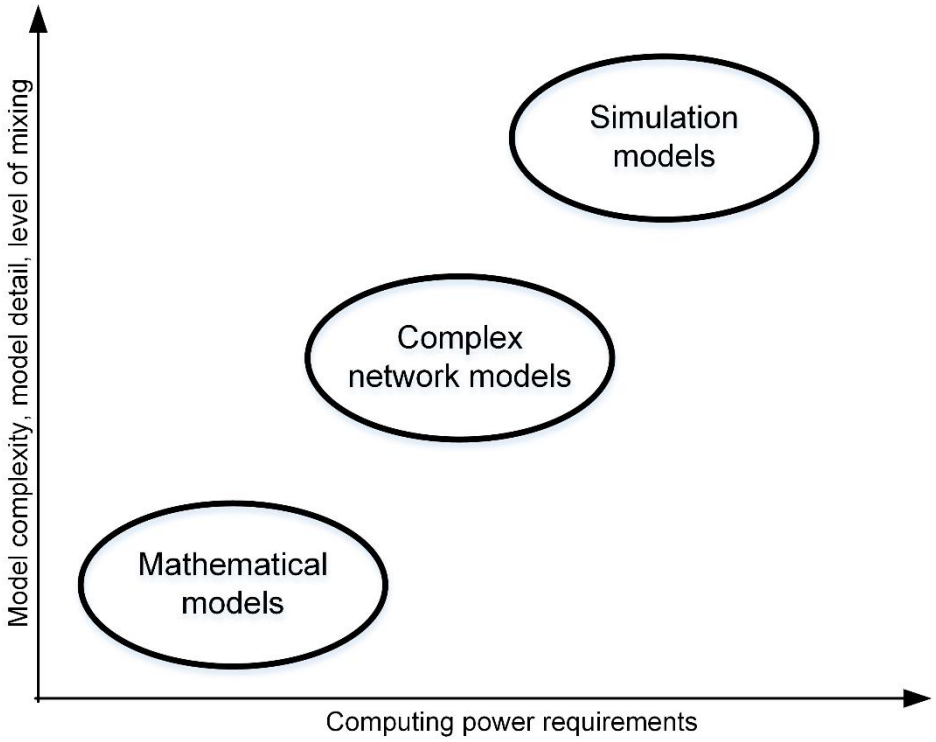

Figure 3.1: A comparison between generic model choice and complexity, adapted from Duan et al. (2015).

3.1.4 Nature of the research question

To a great extent, the nature of the research question may determine the selection of a modelling approach. If the focus of the question is primarily to understand elementary disease dynamics, a more simple modelling approach may be sufficient, however, a more complex mathematical model may be required if the detailed analysis of the effect of an intervention strategy is investigated. Intervention strategies and control methods may vary for different diseases and add additional complexity if included within the modelling process. For instance, control methods for vector-borne diseases may consider vector control as part of the strategy, whereas control strategies for diseases which spread by direct contact may focus more on reducing contact between susceptible and infected individuals.

3.2 Towards a structured literature analysis

With a view to compile a dataset of existing modelling applications within the published literature, the search protocols, scope and considerations of a structured literature review is designed and

noted. To ensure that the dataset adequately represents and includes different disease characteristics as well as modelling considerations in the context of infectious disease modelling, the scope delimitation is discussed in §3.2.1. The criteria of the disease selection are highlighted in §3.2.2, followed by timeframe selection of the review in §3.2.3.

3.2.1 Scope delimitation

As mentioned previously, the field of infectious disease modelling is a densely published field and numerous considerations form part of any modelling application, as highlighted within Chapter 2. To ensure that the necessary details pertaining to disease modelling considerations and approaches are sufficiently analysed and captured, the following categories are included in the scope of the review, namely:

- Disease modelling approaches on a population level for disease which are part of RI schedules (as discussed in §2.5.2, potentially more endemic in nature) and diseases which are not part of RI schedule (more potential to cause an epidemic or pandemic outbreak as a result of a novel outbreak);
- Intervention strategies such as vaccination and treatment methods (§2.5.2);
- Transmission mode (§2.2.3 & §2.5.3 & §3.1.2);
- Modelling applications (§2.3.1);
- Contextual factors (§2.4);
- Disease characteristics (§2.5.1);
- Data used in modelling (§3.1.3, source of data; scope of data; method of model fit); and
- The nature of the research question (§3.1.4).

These included categories are especially important to inform the steps of the structured review (as discussed further in §3.3).

3.2.2 Diseases considered

Three high-level criteria were used to select the diseases for inclusion in the dataset, namely

1. Communicable diseases with relatively short incubation times (less than 30 days), which in turn are able to spread more rapidly and are more likely to get modelled on a population level;
2. Diseases that are targeted by the WHO recommended immunisation programmes which are implemented in South Africa are selected (apart from the diseases mentioned in §3.4.1), in addition to a number of diseases which are not targeted as part of the RI schedule; and
3. Selection of the diseases must ensure that that each transmission mode category contains at least two disease instances (the information on the disease vehicles and vectors were extracted from the GIDEON database and the transmission modes were classified according to Table 2.3).

Using the above-mentioned criteria, the diseases selected for inclusion within the structured literature review are tabulated in Table 3.1, along with the total number of theoretical transmission modes of these diseases in Table 3.2. The complete set of transmission modes for each disease, as well as the associated incubation periods are tabulated in Table 3.3.

Table 3.1: Diseases included in the structured literature review.

Diseases part of RI	Diseases not part of RI
Diphtheria	Cholera
Measles	Dengue
Mumps	Ebola
Pertussis	Influenza (H1N1)
Polio	Malaria
Rotavirus	SARS
Rubella	Smallpox

Table 3.2: Total number of theoretical disease transmission modes for the studied disease set.

Direct contact	Sexual contact	Respiratory	Body fluid	Food-borne	Water contact	Vector-borne
5	1	10	8	3	3	2

Although the third selection criteria requires at least two disease instances for each transmission mode, the sexual contact category contains only one disease instance, namely Ebola. The reasons for accepting this deviation is are highlighted below, namely:

- Very few sexually transmissible disease have incubation times which satisfy the first criteria;
- Sexual contact is a very specific subset of direct contact, in addition to requiring the exchange of bodily fluids. Additionally, this type of contact between individuals does not occur as casually as other forms of contact, such as respiratory or water contact. Therefore, it is unlikely to have widespread population-level modelling of sexually transmissible diseases, adding to the difficulty in studying this transmission mode (one exception is HIV, however, HIV has extremely long incubation periods which are not associated with the potential for rapid disease propagation as with other pandemic diseases such as Ebola or H1N1); and
- Due to the scale and magnitude of the recent Ebola epidemic, it is assumed that Ebola modelling approaches will sufficiently capture the potential dynamics of this transmission category.

Table 3.3: Theoretical transmission modes and associated incubation periods of each disease included in the structured literature review.

Disease	Theoretical transmission modes (1 = present)							Incubation period range	
	Direct contact	Sexual contact	Respiratory	Body fluid	Food-borne	Water contact	Vector-borne	Lower (days)	Upper (days)
Diphtheria	1		1		1			2	5
Measles			1					8	14
Mumps			1					12	24
Pertussis			1	1				7	10
Polio			1	1	1	1		7	14
Rotavirus				1		1		0.5	2
Rubella	1		1	1				16	18
Cholera					1	1		1	5
Dengue				1			1	5	8
Ebola	1	1	1	1				5	12
Influenza			1					1	3
Malaria							1	7	30
SARS	1		1	1				3	5
Smallpox	1		1	1				7	17

3.2.3 Modelling timeframe

To ensure that a sufficiently broad timeframe is considered within the review, the starting date and estimated duration of four major epidemic disease outbreaks (namely SARS, H1N1, Ebola, and Zika) are utilised, as illustrated in Figure 1.2 (p.4). In order to capture the occurrence and modelling implementations of the outbreaks, in addition to the modelling implementations of the other diseases selected in in Table 3.1, modelling implementations published between 2000 and 2017 are considered within this review.

3.3 Steps of the structured literature review

Following identification of relevant diseases, the Scopus database is consulted for literature instances of disease modelling implementations.

The considered database and search protocols of the review are discussed in §3.3.1. The filtering criteria used to determine the relevance of the literature instances are discussed in §3.3.2, followed with a description of the iterative filtering process used to extract relevant literature instances from the database in §3.3.3. The final step of the review entails the process of capturing data from the literature instances to the dataset as described in §3.3.4.

3.3.1 Database selection and search protocols

The Scopus database is used to complete the review. The ‘name of the disease’ AND ‘model’ was used as search operators, according to matches in the titles, abstracts or keywords of the potential literature instances. As a result of using such broad search operators, a substantial portion of the potential literature might not be relevant for inclusion within this review. The main rationale for not selecting a more narrowly defined set of search protocols is to ensure that the review is not biased towards a few well-known modelling approaches. Additional filtering criteria are discussed in further detail in §3.3.2.

3.3.2 Filtering criteria for literature

The following criteria are used to determine the potential relevance of the literature instances during the review, namely:

- **Does the literature describe a modelling approach applied in the context of a specific disease outbreak or instance?** If the article only proposed a general model not applied to a specific disease instance, the literature was excluded from the dataset. Although modelling approaches for a general infectious disease may be relevant to advance the field of disease modelling, the focus in this research is specifically on disease-specific applications, in order

to gather approaches which are used in literature to model disease dynamics on a population level.

- **Does the article explicitly include the modelling or testing of the validity of a specific contextual factor?** If an article incorporates an analysis of the validity of a contextual factor for a particular disease modelling context, it was also included.

Some prominent exclusions relate to the following criteria, namely:

- Animal models were not considered for inclusion, as these do not relate explicitly to population-level modelling in humans;
- Modelling implementations which pertain to hospitalisation for a disease without extending the modelling instance to include forecasts of disease prevalence beyond hospital arrivals, as these models are assumed to neither capture nor model population-level disease dynamics;
- Modelling of immunological responses, in addition to reactions to drugs or vaccines on the cellular level of an individual; and
- Modelling instances which do not relate to disease dynamics on a population level or contextual factors affecting disease dynamics.

The scope of the filtering and exclusion criteria are purposefully not defined very narrowly, in order to reduce bias in the review process towards well-known applications and considerations (as mentioned previously regarding the broad scope of the search protocols in in §3.3.1).

3.3.3 Iterative filtering process of literature

The following steps describe the successive manner in which the literature from the Scopus database is reviewed and filtered, from the initial execution of the search protocol to the selection of literature instances for inclusion in the dataset. For each step, the number of literature results is captured according to the template in Table 3.4. The results for each of the steps are recorded to highlight the breadth of the potential literature and the labour required to successfully glean relevant literature from the Scopus database. The condensed results of the filtering process are discussed in §3.5.

Table 3.4: Template to capture the number of literature results for each of the steps of the iterative filtering process.

Search protocol	Date exclusion	Categorical exclusion	Potential titles	Potential abstracts	Available abstracts	Relevant abstracts

Search protocol

The first step entails the execution of the search protocol (as discussed in §3.3.1) in the Scopus database. This is followed by noting the total number of literature results for the search protocol execution according to the corresponding step in Table 3.4.

Date exclusion

The considered modelling timeframe of this review (as discussed in §3.2.3) informed the date exclusion of literature published before 2000 and after 2017. This is followed by noting the revised total number of literature hits according to the corresponding step in Table 3.4.

Categorical exclusion

The filtering criteria (as discussed in §3.3.2) are used to exclude literature categories (defined by the Scopus database) which are highly unlikely to include population-level modelling of diseases or investigation of contextual factors. These excluded categories include the following, namely:

- Biochemistry, Genetics and Molecular Biology, (in these categories, the disease dynamics are approached from a molecular level. This exclusion is briefly discussed in §2.3.1);
- Immunology and Microbiology, (as the immunological viewpoint of disease, briefly discussed in §2.3.1 is not considered within this study);
- Pharmacology, Toxicology and Pharmaceutics (these categories relate to safety of vaccines and drugs);
- Chemistry (this category is likely to contain literature that studies disease at a cellular level);
- Neuroscience (not relevant to the study);
- Materials Science (not relevant to the study);
- Psychology (not relevant to the study);
- Arts and Humanities (not relevant to the study);
- Dentistry (not relevant to the study); and
- Energy (not relevant to the study).

To account for the uncertainty and scope of the study, the following categories are included:

- Medicine (this category may include intervention strategies applied on the population level);
- Earth and Planetary Sciences (these categories might include investigation of contextual factors);
- Economics, Econometrics and Finance (these categories might include financial models which include population-level modelling of disease); and
- Business, Management and Accounting (similar to aforementioned reasons of Economics).

Following completion of the categorical exclusion, the revised total number of literature pieces are noted according to the corresponding step in Table 3.4. The resultant search protocol for each disease following date and categorical exclusion is included in §C.1.

Potential titles

The filtering criteria (as discussed in §3.3.2) are used to scan all titles of the potential number of literature results to determine potential relevance. All potentially relevant literature pieces are noted according to the corresponding step in Table 3.4 and used within the following steps of the filtering process.

Potential abstracts

Titles of literature pieces typically capture only a small part of the focus of the modelling application. For instance, some literature pieces may indicate that disease dynamics are modelled within the title, but from the abstract it may become clear that no specific modelling instances are presented or tested with reference to an actual disease. For this reason, reviewing both the abstracts and titles of a literature piece provides a clearer indication of the potential relevance, in contrast to solely reviewing literature titles to determine potential relevance to the study.

In this step the abstracts are evaluated for each of the literature pieces identified in the previous step. Following the determination of the potential relevance of the abstract, the revised number of potentially relevant literature pieces are noted according to the corresponding step in Table 3.4.

Available articles

Only literature with free access on the Stellenbosch University network is considered for inclusion in the dataset. The total number of potentially relevant literature pieces which are successfully downloaded from the network are noted according to the corresponding step in Table 3.4. The omission of pay-per-view literature pieces are discussed in more detail in §3.4.1.

Relevant articles

Following an in-depth analysis of all the available articles and final determination of the relevance of a literature piece, the modelling considerations of the literature pieces are captured to the dataset (according to categories which are discussed in more detail within §3.3.4). The number of relevant articles (i.e. the number of literature pieces which are included in the dataset) are noted according to the corresponding step in Table 3.4.

3.3.4 Capturing data from literature to the dataset

Following the analysis and determination of the relevance of literature pieces, the information gleaned from the review is captured to the dataset. The categories are informed by the scope delimitation previously discussed in §3.2.1 and are discussed below.

Data source

The data source used within the modelling application is noted and categorised according to the following categories and criteria, namely:

- None (e.g. no data source used);
- Case data (e.g. data on confirmed cases of disease infection);
- Travel data (e.g. data on movement of individuals);
- Parameters from literature (e.g. data on transmission parameters previously formalised in the literature);
- Population estimates (e.g. census data); and
- Assumed (e.g. data which assumes important transmission characteristics).

The data source categories noted above are not necessarily mutually exclusive, therefore a literature instance can be classified as using more than one of these data sources.

Method of model fit

Due to the vast number of model fitting methods employed, it is not practical to research each available one in order to define a set of fitting methods to use when analysing the dataset. Instead, the various methods used to fit models to the data source are noted and added to the dataset as these are serendipitously uncovered during the capturing process.

Modelling scope

The modelling scope is determined from the scope of the modelling application, which in turn is affected strongly by the scope of the data source used. The scope is noted and categorised according to the following categories and criteria, namely:

- General (i.e. a general modelling application with no indication of the scale of the application, typically a theoretical model for a specific disease instance);
- Global (i.e. disease transmission between more than two countries);
- Intercountry (i.e. disease transmission between two countries);
- Country (i.e. disease transmission within a single country);
- Provincial (i.e. disease transmission within a province); and
- Small region (i.e. disease transmission in a small region, such as a city or small village).

Rationale of article

The rationale of an article is typically not explicitly mentioned, but it is useful to note the goals of the research question (mentioned previously in §3.1.4) which are implicitly part of the modelling approaches followed in literature. The set of rationales given in the list that follows are formulated to capture the specific focus of the research questions being addressed in each article:

- Model disease transmission dynamics (develop a model to study disease transmission dynamics);
- Investigate causal relationships (develop a model to investigate the effect of factors which affect the chain of infection and correlates to changes in disease propagation or prevalence);
- Investigate super spreading events (develop a model to analyse instances of unusually high secondary infections emanating from a few individuals);
- Forecast disease instance (develop a model to not only fit data or parameters, but to explicitly forecast future disease prevalence from the model);
- Develop a model and analyse behaviour (develop a theoretical model of disease transmission and investigate behaviour of the model in the context of varying parameter values); and
- Evaluate interventions (develop a model to evaluate one or more of the treatment strategies or vaccination strategies).

The modelling rationales defined here are not necessarily mutually exclusive, therefore more than one modelling rationale may be used in a literature instance to guide the modelling process.

Compartmental classification

During the analysis of the literature, it is determined whether compartmental classification (discussed previously in §2.3.3) is incorporated within the modelling application. If it is incorporated, the compartmental classification categories that are used, as well as their descriptions, are noted and added to the dataset as these are serendipitously uncovered during the capturing process.

Modelling approaches

Similar to the reasoning provided for the methods utilised to fit models, it is not practical to research each available modelling approach in order to define a predetermined set. Such an approach could also bias the analysis by causing articles to be placed into categories that may be only a reasonably accurate classification. It is, however, practical to organise the modelling approaches into the three broad categories discussed previously in §2.3.4, namely:

- Simulation models;
- Network models; and

- Mathematical models.

Within each of these broad categories, the specific modelling approaches are noted and added serendipitously to the dataset as they are uncovered. Methods that do not fit the criteria for either the simulation or network model category, are incorporated within the mathematical category.

Mentioned transmission modes

As the transmission mode is expected to play a significant role in the disease dynamics, it is noted whether the disease transmission mode is explicitly mentioned, either within the contextualisation section or during a description of the modelling process. The reasoning is that this may indicate increased awareness of the dynamics of the specific disease transmission mode when selecting modelling approaches and incorporating contextual considerations for the particular disease outbreak.

Theoretical transmission modes

The theoretical transmission modes for each disease (as captured from the GIDEON database and mentioned in Table 3.3) are noted. In many cases, only some of the theoretical transmission modes of a disease may be explicitly mentioned in the article. Especially in cases where only some of the potential theoretical transmission modes of a disease are mentioned, it is reasonable to assume that the model was constructed to only include those transmission modes which are explicitly mentioned. When investigating the relationship between various modelling approaches and modelling considerations and the transmission mode, however, it is useful to consider both the full set of theoretical transmission modes for a disease as well as only the sub-set of transmission modes that are explicitly mentioned.

Alternative mixing patterns

The default mixing pattern in a modelling approach is the homogenous mixing of contacts, however, the incorporation of alternative (i.e. non-standard) mixing patterns are captured to the dataset as these are serendipitously uncovered during the capturing process.

Intervention strategies

The set of intervention strategies discussed in §2.5.2 are used as an initial template to categorise the incorporation of intervention strategies in the dataset. As additional intervention strategies are uncovered serendipitously during the capturing process, these are added to the dataset.

Contextual factors

During the analysis of the literature piece, it is determined whether contextual factors are incorporated in the modelling application. The two categories of contextual factors considered within the analysis are highlighted in Table 3.5 and the nature of the incorporation is noted according to the following criteria, namely:

- **Mentioned** (a counter to keep track of contextual factors present in modelling applications);
- **Linked to disease transmission** (when the link between a contextual factor and the effect on disease propagation is investigated); and
- **Modelled** (when a contextual factor is explicitly modelled or included in a modelling application).

Table 3.5: Predetermined categories used to capture the contextual factors.

Environmental (criteria discussed in more detail in §2.4.1)	**Demographics (criteria discussed in more detail in §2.4.2)**
Climate Seasonality	Demography Population density Migration Socio-economic factors

Table 3.6: Summary of the omissions and deviations to the steps of the 'iterative filtering' process and 'capturing data from the literature to the dataset' process.

Omission and related section		**Deviation and related section**	
Transmission modes omitted from the review.	§3.2.2	Additional keyword exclusion as part of the iterative filtering process.	§3.3.3
RI diseases and non-RI diseases not included in the review.	§3.3.2	Additional timeframe exclusion as part of the iterative filtering process.	§3.3.3
Pay-per-view articles not included in the dataset.	§3.3.3	Mathematical vs simulation classification assumption.	§3.3.4
Referencing literature instances of the dataset in the bibliography.	§3.3.3	Assumption relating to capturing mixing patterns to the dataset.	§3.3.4

3.4 Notable omissions and deviations

The detailed steps in §3.3 describe the process followed from execution of the literature search protocol to capturing the information in the literature instances to the dataset. There are, however, some notable omissions to and deviations from these steps. The omissions are described in §3.4.1 followed by a description of the deviations in §3.4.2. The sections which the omissions and deviations are relevant to are tabulated in Table 3.6.

3.4.1 Omissions

An explanation of the notable omissions tabulated in Table 3.6, as well as a rationale for the omissions, is provided below.

Transmission modes omitted from structured literature review

Diseases which are transmissible by means of animal and soil contact are not included within the review.[4] It is very unlikely that these transmission modes would lead to an epidemic outbreak, as sustained contact with animals and soil are required to ensure continuous propagation of the disease. However, one potential exception is that of anthrax. Two reasons for the exclusion of this disease are the following:

- Most examples of anthrax modelling efforts focus on transmission between animals; and
- The few examples of anthrax transmission modelling between humans relate to very specific examples of bioterror attacks and are not considered for generalised population-level disease modelling (one example is (Wanying et al. 2016)).

RI diseases and non-RI diseases not included

A complete list of the diseases which are not included in the structured review, as well as a reason for each omission, is provided in Table 3.7.

Pay-per-view articles

On average, the proportion of the pay-per-view articles amounted to 11.9% of the 'potential abstracts' literature instances. The maximum percentage of articles not available for a given disease are 20% of the total potential literature instances. The typical price for a pay-per-view article amounts to 30 US$. In order to obtain access to these additional articles, an estimated 1 950 USD$ would be required, which equals to R23 400 at a conservative exchange rate of 12 ZAR / 1 USD$. The number of literature pieces that are available free of charge through the Stellenbosch University license are

[4] The complete set of transmission modes are discussed in Table 2.1.

deemed sufficient to eliminate the need to acquire funding to access the pay-per-view articles. The number of pay-per-view articles for each disease is produced in §C.2.

Referencing literature uncovered during the iterative filtering process in the bibliography

As part of the iterative filtering process, the number of potential literature instances are noted for each of the steps. Only the final number of 'relevant articles' for each disease are referenced in Appendix H. Thus, none of the potential literature instances which are eliminated in the iterative filtering process are included in this reference list.

Table 3.7: Rationale for omission of particular diseases from the structured review.

Disease	Reason for omission
Hepatitis B (RI)	Hepatitis is a disease which causes inflammation of the liver (WHO 2016b). Even though Hepatitis B is included within the vaccine schedule, the incubation period which ranges between 60 and 90 days (GIDEON 2017a) is considerably longer than the incubation cut-off time of 30 days specified in §3.2.2.
HIV (non-RI)	Although HIV is one of the more frequently modelled sexual and body fluid transmissible diseases, the unusually long incubation period which varies between 60 days and 10 years (GIDEON 2017a) falls outside the scope as specified in §3.2.2.
HPV (RI)	The various strains of HPV are known to cause diseases which range in severity from warts (short incubation period between 2 weeks and 8 months) to various cancers in both males and females (GIDEON 2017a). As the focus of this study is on specific communicable diseases, HPV related modelling and diseases are considered to fall outside the scope of the review.
Influenza type B (RI)	As the H1N1 strain of influenza is already included within the study, the inclusion of an additional influenza strain is deemed superfluous.
Pneumococcal (RI)	The pneumococcal vaccine targets general respiratory bacteria, therefore there isn't a specific disease that is associated with the vaccine and for which the spread through a population can be modelled (GIDEON 2017a).
Tuberculosis (RI)	Even though the study of the modelling of TB is an important research field, especially due to the presence of multiple drug resistant strains, the long incubation period which varies between 28 and 84 days (GIDEON 2017a) falls outside the scope of this study as specified in §3.2.2.
Tetanus (RI)	Tetanus is a disease transmitted by means of contact with contaminated objects such as rusty metallic objects. As this disease is transmitted in extremely rare cases (only transmissible by a vehicle described as trauma (GIDEON 2017a)) it is not considered within the review.

3.4.2 Deviations

An explanation of the notable deviations tabulated in Table 3.6, as well as the rationales for the deviations, are provided below.

Additional keyword exclusion

As tabulated in Table C.4, the number of potential articles for three of the diseases following categorical exclusion are:

- H1N1 (1489);
- Malaria (3131); and
- Dengue (1399).

The total number of potential literature titles requiring review for these three diseases add up to 6019 instances, which amounts to 46% of the potential literature instances for this step of the iterative filtering process. It is deemed unnecessary to devote nearly 50% of the literature title review workload to three disease instances. To reduce the number of potential titles, an additional keyword exclusion was performed on the three aforementioned diseases. The complete list of keywords included in the deviant Scopus search protocol is reproduced in §C.1.9 (dengue), §C.1.11 (H1N1) and §C.1.12 (malaria).

Additional timeframe exclusion

As tabulated in Table C.4, following the additional keyword exclusion, the revised number of potential literature titles for two of the diseases following the additional keyword exclusion are:

- Malaria (1581); and
- Dengue (818).

The total number of potential titles for these three diseases add up to 2399 instances, which amounts to 22% of the literature title review step. It is deemed unnecessary to devote nearly 25% of the literature title review workload to two disease instances. To further reduce the number of potential literature instances included in the review process, an additional timeframe exclusion is performed on these two diseases. This timeframe is selected to only consider literature instances published between 2015 and 2017. The reason for not including H1N1 in the additional timeframe exclusion is that a major outbreak of H1N1 occurred between 2009 and 2010, as illustrated in Figure 1.2. The deviant Scopus search protocol for dengue and malaria following the timeframe exclusion is reproduced in §C.1.9 and §C.1.12, respectively.

Mathematical vs simulation approach classification

Some mathematical modelling approaches (e.g. linear programming approaches) stated that results are 'simulated' with different parameters. This is not regarded as true stochastic simulation (as discussed previously in §2.3.4) and is still regarded as a mathematical modelling approach.

Mixing pattern capturing logic

In some literature pieces, the assumption of homogeneous mixing is mentioned. As homogeneous is regarded as the default mixing pattern, an article was only marked as incorporating alternative mixing patterns if non-standard mixing patterns were mentioned and incorporated in the modelling approach.

3.5 Descriptive analysis of dataset (REF A)

A summary of the results for each of the steps of the iterative filtering process (with the additional steps as described in the section on deviations in §3.4.2) is produced in Table 3.8. This highlights the magnitude of the iterative filtering process used to gather the most relevant literature pieces to include in the dataset. After the execution of various exclusion steps based on article attributes (including the publication date, keywords, etc.), 9051 article titles were screened and 980 abstracts were reviewed, 522 literature pieces were reviewed in depth before 283 articles were selected for inclusion in the dataset. The complete overview of the number of literature instances considered for each disease as part of the iterative filtering process is produced in Table C.4.

Table 3.8: High level results of the structured literature review.

Search protocol	Date exclusion	Categorical exclusion	Keyword exclusion	Year exclusion	Potential titles	Potential abstracts	Available abstracts	Relevant abstracts
47666	**38438**	**12986**	**10697**	**9051**	**980**	**611**	**522**	**283**

In order to become more familiar with the dataset at a high-level before embarking upon the detailed analysis that relates specifically to modelling considerations described in the next chapter, the dataset was probed through a number of high-level descriptive analyses. These analyses included questions such as whether any trends in the use of specific modelling approaches at different publication dates is evident. The complete set of descriptive analyses that were performed are summarised in Table 3.9. Though the findings are likely to be interesting to an individual working in the field of epidemiological modelling, the descriptive analyses did not uncover any findings that influence the detailed analysis on modelling considerations described in the following chapter, or that are relevant to the development of the framework that is the subject of this research. For this

reason, the discussion of the descriptive analyses is included in various sections of §C.3 of this document, as indicated in Table 3.9, rather than in the main thesis document. As indicated in Table 3.9, all analysis steps are assigned a reference (REF) code to keep track of the findings and reporting of results. The use of REF codes, as well as normalisation of the data and the use of data subsets are described in more detail in §4.1.2 and §4.1.3.

Table 3.9: REF A analysis steps.

Categories compared		**REF**	**Section**	**Normalisation**	**Subset**
Year published	Modelling approaches	A1	§C.3.2	×	
Year published	Modelling scope	A2	§C.3.3	×	
Year published	Interventions	A3	§C.3.5	×	
Year published	Data source	A4	§C.3.3	×	
Number of diseases	RI and non RI	A5	§C.3.1	×	
Mathematical modelling	Breakdown of all approaches	A6	§C.3.2	×	
Network modelling	Breakdown of all approaches	A6	§C.3.2	×	
Simulation modelling	Breakdown of all approaches	A6	§C.3.2	×	
Contextual factors		A7	§C.3.4	×	
General observations		A7	§C.3.6	×	

3.6 Conclusion

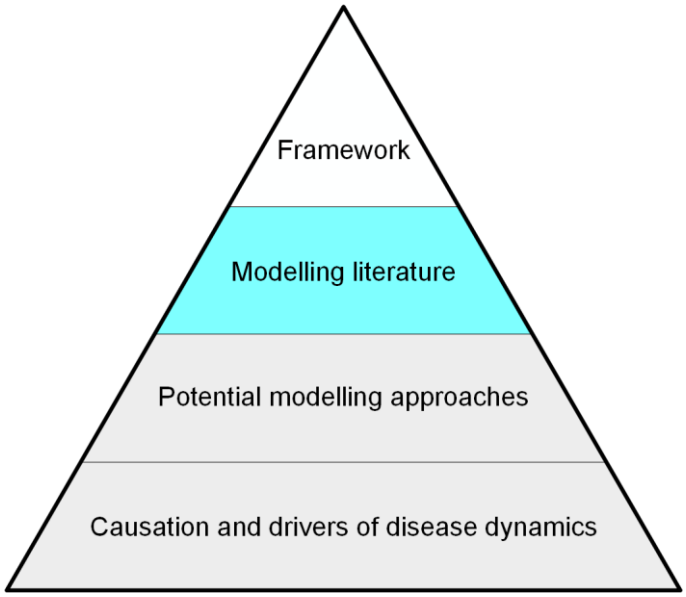

Figure 3.2: A visual summary of the content of Chapter 3.

A summary of the content of this chapter in relation to the overall document structure is illustrated in Figure 3.2. The contextualisation of the causation and drivers of disease dynamics and the potential modelling approaches is presented in Chapter 2. Further investigation of the considerations which affect modelling decisions (which are discussed in §3.1), however, highlight the need to make modelling decisions in an informed manner. In order to construct a framework to suggest modelling approach and consideration incorporation, a thorough review on existing modelling literature is completed in this chapter (described in detail in §3.2 - §3.4). This is undertaken in order to create a dataset that is thoroughly representative of the existing modelling literature pertaining to infectious disease modelling, in addition to considerations and contextual factors which are typically incorporated within modelling approaches. The magnitude of the iterative filtering process used to filter and select literature for inclusion is briefly highlighted below:

- 9051 → Number of titles of literature pieces scanned;
- 980 → Number of abstracts reviewed;
- 522 → Number of literature pieces reviewed in depth; and
- 283 → Final number of literature pieces included within the dataset.

This overview highlights the depth of analysis completed in order to select literature for inclusion in the dataset. The description of the logic of the literature review and filtering protocol as well as the rationale provided for each omission and deviation, motivates that the dataset can be viewed as a valid basis for the construction of a framework to guide decision-making related to the modelling of infectious diseases.

Chapter 4 Analysis of dataset

The analysis of the disease dataset is performed within this chapter, with a view to determine relationships between the disease characteristics, modelling approaches and considerations as these are typically employed within the modelling literature. It would not be practical to study the relationship between every single disease characteristic, modelling approach and modelling consideration, therefore a relationship is only investigated if logic supports the likely existence of such a relationship.

The structure of the analysis is described briefly in §4.1. This section also contains a brief discussion on the normalisation of the data used within the analysis. The part of the analysis which pertains to the transmission mode (i.e. the disease characteristics) in the context of modelling considerations is completed in §4.2, whereas an analysis of the relationships between various modelling considerations in the dataset is completed in §4.3. A summary of the most salient findings of the dataset analysis is presented in §4.4 prior to the chapter conclusion in §4.5.

The observations and findings from the analysis are captured to Table 4.6 – Table 4.10, which is presented at the end of the chapter. These observations are used to inform the framework development (constructed and described in detail in Chapter 5).

4.1 Preamble to analysis

In this section, background information that motivates the manner in which the analysis presented in this chapter is structured and executed, is provided. The rationale for differentiating between theoretical and explicitly contextualised transmission modes is discussed in §4.1.1, followed by the rationale for normalising the data in §4.1.2. The terms as well as the subsets of data used within the analysis are defined and explained in §4.1.3. The datasets and respective tables used in the analysis are also defined and referred to in this section.

4.1.1 Rationale for analysing theoretical and contextualised transmission modes

Throughout the analysis of the dataset, the transmission mode is viewed as one of the central drivers of disease dynamics. The total instance of transmission modes within the dataset is calculated as the product of the theoretical number of transmission modes for each disease (Table 3.3) and the number of literature pieces included for each disease in the dataset (Table C.2 and Table C.3).

Of the 283 literature inclusions in the dataset, however, only 190 (67%) explicitly mention at least one potential transmission mode of the disease within the modelling approach. As the transmission mode is viewed as one of the central drivers of disease dynamics in this research, the literature

pieces which include an explicit statement of a disease transmission mode are captured to a distinct subset of data as it is assumed that, when a potential transmission mode is explicitly mentioned, it is more likely that this transmission mode has been taken into consideration when formulating a modelling approach. This subset of data (i.e. explicitly mentioned transmission modes) is used in conjunction with the complete dataset within the analysis. For the complete dataset, all of the potential theoretical transmission modes for a disease have been taken into consideration during the analysis, though it is not clear whether all of these potential transmission modes have in fact been taken into consideration when formulating the modelling approaches.

4.1.2 Rationale for normalisation of data

Different transmission modes are not equally represented within the dataset (for example, ten of the diseases in the dataset can be transmitted via respiratory contact, while only three of the diseases can be transmitted via food-borne vectors). In order to overcome biased conclusions due to the disproportional representation of certain categories of data (e.g. of specific transmission modes), the dataset is normalised in appropriate ways to facilitate the interpretation of the observations. This normalisation is performed not only in the context of transmission mode occurrences, but also for other subsets of the dataset as described in §4.1.3.

4.1.3 Terms and subsets used within the analysis

As briefly mentioned in §3.5, all analysis steps are assigned a REF code to keep track of the findings and reporting of results. The REF codes are assigned according to three categories, namely:

- REF A contains observations and analysis of general high-level descriptive findings based on the dataset, described in §3.5 (and in more detail in §C.3);
- REF B contains comparisons between disease transmission modes and various modelling considerations and implementations within the dataset, based on normalised data and described in §4.2 (and in more detail in Appendix D); and
- REF C contains comparisons between modelling considerations and implementations within the dataset, based on normalised data and described in §4.3 (and in more detail in Appendix D).

Different subsets are constructed from the dataset, to focus on particular comparisons and relationships of modelling considerations. The various subsets extracted from the main dataset are described in Table 4.1. The subsets formed to normalise the data are also described in Table 4.1. The tables which contain the subset data and normalisation data are summarised in Table 4.2.

Table 4.1: Description of subsets and normalisation subsets extracted from the dataset and used in the analysis.

Data subset	Number of instances	Description of subset	Normalisation subset	Description of subset
S1	283	Observations when all theoretical transmission modes are considered for each disease.	S1N	Total number of theoretical transmission modes present in the dataset.[5]
S2	190	Observations which pertain only to literature pieces where a select number of transmission modes are mentioned explicitly.	S2N	Total number of explicitly mentioned transmission modes present in the dataset.
S3	283	Observations of literature pieces categorised according to mathematical, network or simulation modelling approaches.	S3N	Total number of instances for each of the modelling approach categories.
S4	283	Observations of literature pieces categorised as either a disease included in RI or not included in RI.	S4N	Total number of literature inclusions for RI and non-RI diseases.
S5	283	Observations of literature pieces categorised according to the modelling rationale.	S5N	Total number of instances for each of the modelling rationale categories.
S6	283	Observations of literature pieces categorised according to the data source.	S6N	Total number of instances for each of the data source categories.
S7	283	Observations of literature pieces categorised according to the modelling scope.	S7N	Total number of instances for each of the modelling scope categories.
S8	120	Observations which pertain only to literature pieces which include interventions.	S8N	Total number of treatment and vaccination strategy inclusions.
S9	169	Observations which pertain only to literature pieces which include contextual factors.	S9N	Total number of linked to disease propagation instances and modelled contextual factor instances.

[5] The calculation of the theoretical transmission modes are described in §4.1.1.

Table 4.2: Reference to data tables and normalisation tables used in the analysis.

Data prior to normalisation			Normalisation data		
Subset	**Data table**	**Section**	**Subset**	**Data table**	**Section**
S1	Table D.9	§D.2	S1N	Table D.1	§D.1
S2	Table D.10	§D.3	S2N	Table D.1	
S3	Table D.11	§D.4	S3N	Table D.2	
S4	Table D.12	§D.5	S4N	Table D.3	
S5	Table D.13	§D.6	S5N	Table D.4	
S6	Table D.14	§D.7	S6N	Table D.5	
S7	Table D.15	§D.8	S7N	Table D.6	
S8	Table D.16	§D.9	S8N	Table D.7	
S9	Table D.17	§D.10	S9N	Table D.8	

4.2 Analysis on the disease transmission mode (REF B)

With reference to the transmission mode as the central link between the disease reservoir and the susceptible host (as illustrated in Figure 2.3), it is expected that the transmission mode would play an important role in the disease dynamics and consequently in the incorporation of modelling considerations. Various modelling considerations that are analysed in relation to the transmission mode are summarised in Table 4.3. These analyses are coded as the REF B analyses.

For the sake of brevity, the entire set of analysis summarised in Table 4.3 is presented in Appendix D (as noted in Table 4.3), rather than in the main thesis document. However, a description of two of the analyses is duplicated in the remainder of this section to illustrate how the analyses are typically conducted.[6] The analysis of the intervention strategy use in relation to the transmission mode is produced in §4.2.1, including a discussion of treatment strategies (as an example of a specific type of intervention strategy) in relation to the transmission mode. The analysis of the population demographic factors in relation to the transmission modes is produced in §4.2.2.

[6] The two analyses that are presented here in the main thesis document are repeated in the appendix so that Appendix D, from §D.11 to §D.22, can be read as a coherent narrative describing all of the analyses that were performed (with the exclusion of the descriptive analysis of the dataset discussed in §3.5.

Table 4.3: REF B analysis steps.

Categories compared		REF	Section	Normalisation	Subset
Theoretical transmission modes	Mentioned transmission mode	B1	§D.12.1	✓	S1N
Transmission mode	Modelling scopes	B2.1	§D.13	✓	S1N + S2N
Transmission mode	Alternative mixing patterns	B2.2 and B2.3	§D.14 and §D.17.1	✓	S1N + S2N
Transmission mode	Overall modelling categories	B3.1	§D.12.2	✓	S1N + S2N
Transmission mode	Mathematical modelling approaches	B3.2	§D.12.3	✓	S1N + S2N
Transmission mode	Network modelling approaches	B3.3	§D.12.4	✓	S1N + S2N
Transmission mode	Simulation modelling approaches	B3.4	§D.12.5	✓	S1N + S2N
Transmission mode	Intervention strategies	B4	§4.2.1 and §D.15	✓	S1N + S2N
Transmission mode	Interventions, treatment strategies	B4.1	§4.2.1 and §D.15.1	✓	S1N + S2N
Transmission mode	Interventions, vaccination strategies	B4.2	§D.15.2	✓	S1N + S2N
Transmission mode	Contextual factors linked to propagation	B5.1	§D.16	✓	S1N + S2N
Transmission mode	Contextual factors modelled	B5.1	§D.16	✓	S1N + S2N
Transmission mode	Environmental factors	B5.2	§D.16.1	✓	S1N + S2N
Transmission mode	Population demographics	B5.2	§4.2.2 and §D.16.2	✓	S1N + S2N
Transmission mode	Compartmental classification	B6	§D.20.2	✓	S1**N + S**2N

4.2.1 First transmission-mode related analysis example (REF B4)

The proportion of literature pieces in the dataset which include the modelling of intervention strategies for each of the transmission modes are illustrated in Figure 4.1 (S1) and Figure 4.2 (S2), (this analysis is coded REF B4 in Table 4.3).

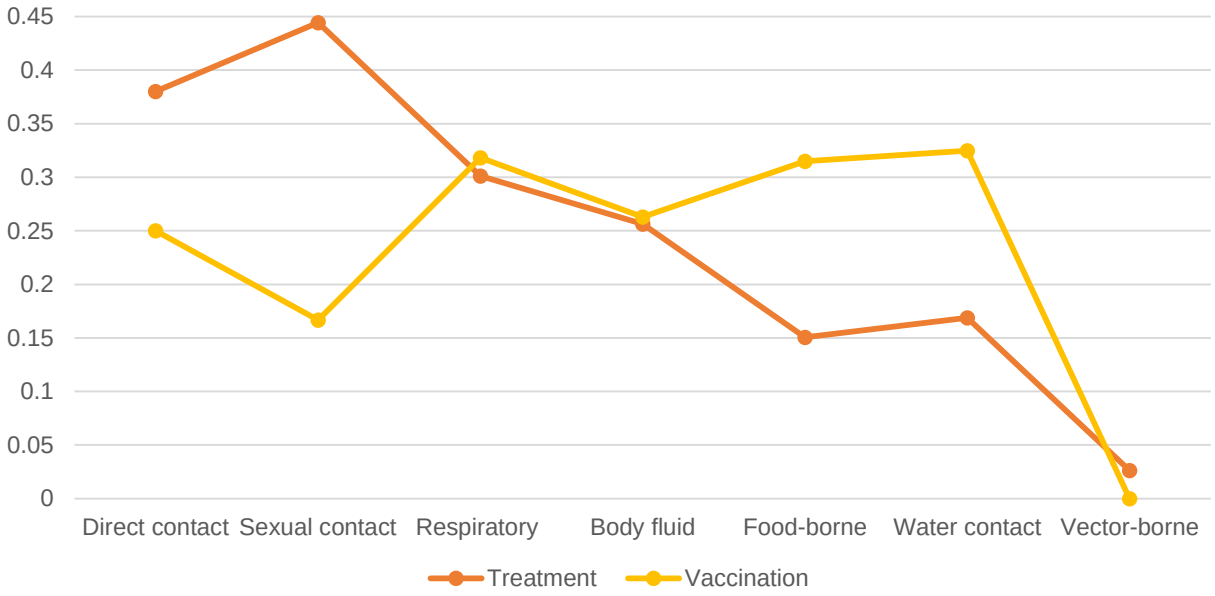

Figure 4.1: Proportion of all theoretical transmission modes in the dataset which include two intervention strategies, normalised according to S1N.

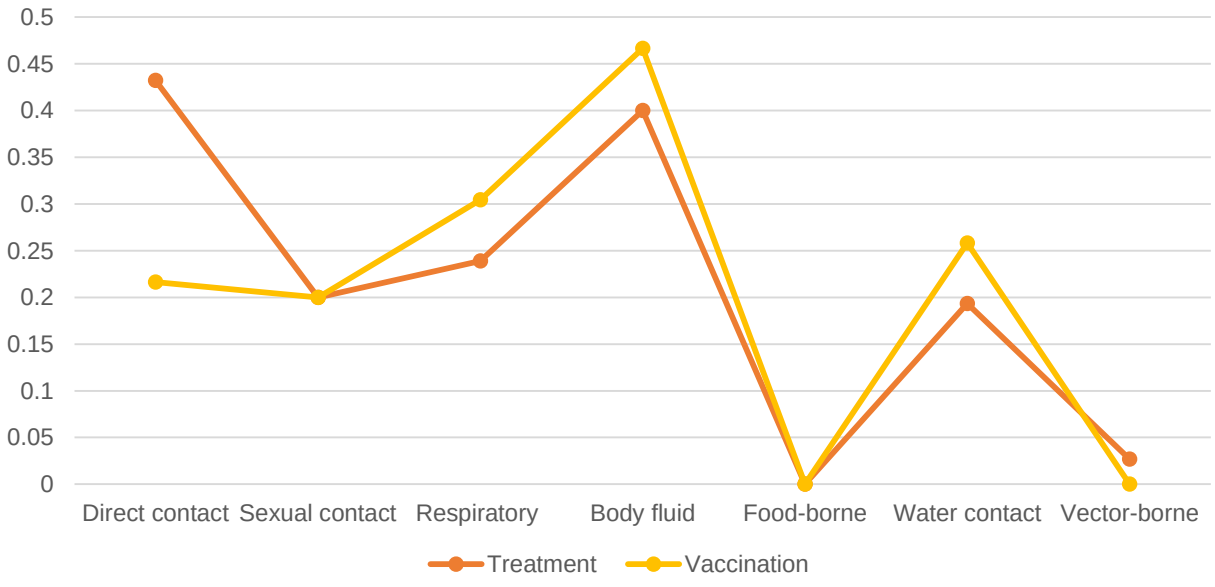

Figure 4.2: Proportion of all mentioned transmission modes in the dataset which include two intervention strategies, normalised according to S2N.

As a general observation, it is clear that treatment strategies are most frequently applied in the context of the first four transmission modes, in addition to the water contact transmission mode. This

is particularly interesting, as these transmission modes are dependent on direct contact between humans, apart from body fluid and water contact which requires indirect contact.

In S2, vaccination strategies are the most frequently observed relative to body fluid and respiratory transmission modes, in addition to direct, sexual and water contact transmission modes. Additionally in S2, no vaccination strategies are observed for food-borne and vector-borne transmission modes. The existence of vaccination strategies for the food-borne category in S1 is an unexpected finding, as there are currently no vaccines for food-borne diseases. This can, however, be explained when one considers that food-borne is one of the theoretical transmission modes of cholera. In line with expectations, there are no mentioned food-borne literature occurrences which incorporate vaccination strategies in S2. This is a more realistic representation of vaccination strategy usage in the context of food-borne diseases. Furthermore, no vaccination strategies are observed for vector-borne disease, as vaccines are not currently available for vector-borne disease in general.

Apart from these high-level observations, it is not possible to directly quantify the intervention strategy selection solely from the transmission mode, but it is still useful to note some of the relationships to the transmission modes. A selection of these observations are captured to Table 4.6 in REF B4. The treatment strategies and vaccination strategies are analysed in more detail in §D.15.1 and §D.15.2, respectively.

Treatment strategies

The proportion of literature pieces in the dataset which include treatment strategies relative to the transmission modes are illustrated in Figure 4.3 (S1) and Figure 4.4 (S2).

In both S2 and S1, quarantine is observed only for the transmission modes which rely on contact between humans. Furthermore, in S2 it is observed that very similar treatment strategies are applied in relation to the direct contact and body fluid transmission modes. With reference to S2, reduced contact is observed especially in relation to the direct contact, body fluid and water contact transmission mode. Furthermore, with reference to S1 it is observed that reduced contact is also a strategy that is applied for all transmission modes, except for a vector-borne transmission mode.

The least amount of treatment strategies are applied in relation to the vector-borne transmission mode, with drug usage as the only observed treatment strategy. In S1 disinfection is observed only for the food-borne and water contact transmission modes.

In S2 it is observed that the most diverse amount of treatment strategies are applied in relation to the body fluid transmission mode. Additionally, no treatment strategies were observed for the food-borne transmission mode.

Apart from these high-level observations, it is not possible to directly quantify the treatment strategy selection solely from the transmission mode, but it is still useful to note some of the relationships to the transmission modes. A selection of these observations are captured to Table 4.6 in REF B4.1.

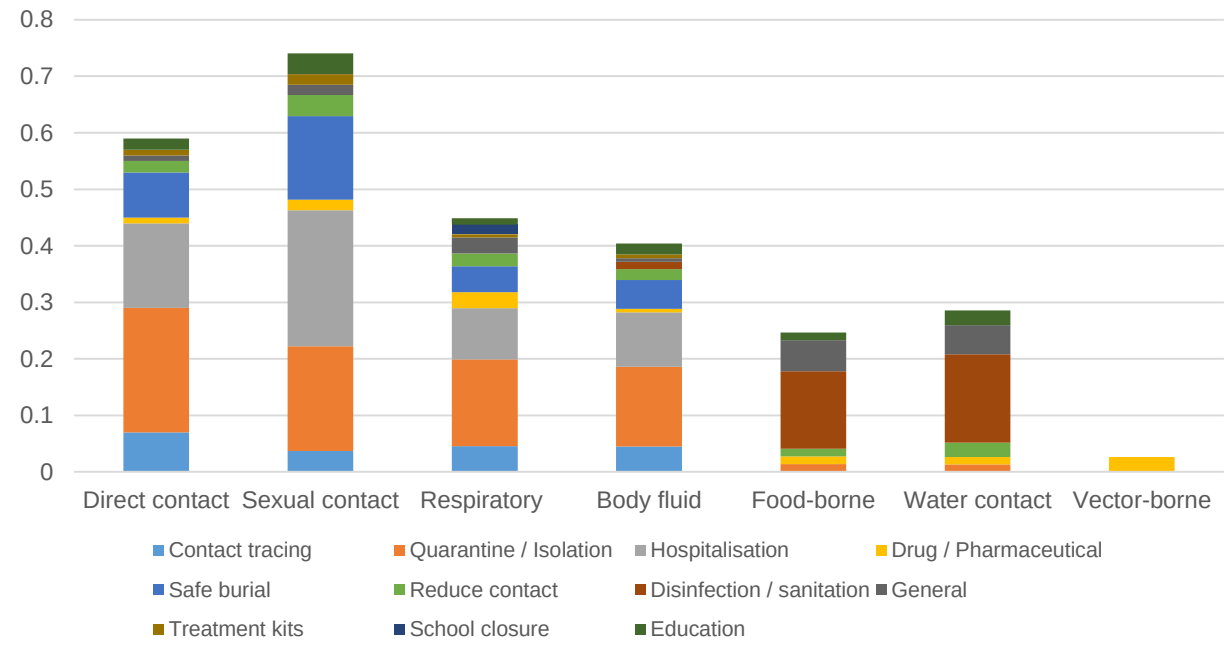

Figure 4.3: Proportion of all theoretical transmission modes in the dataset which include different treatment strategies, normalised according to S1N.

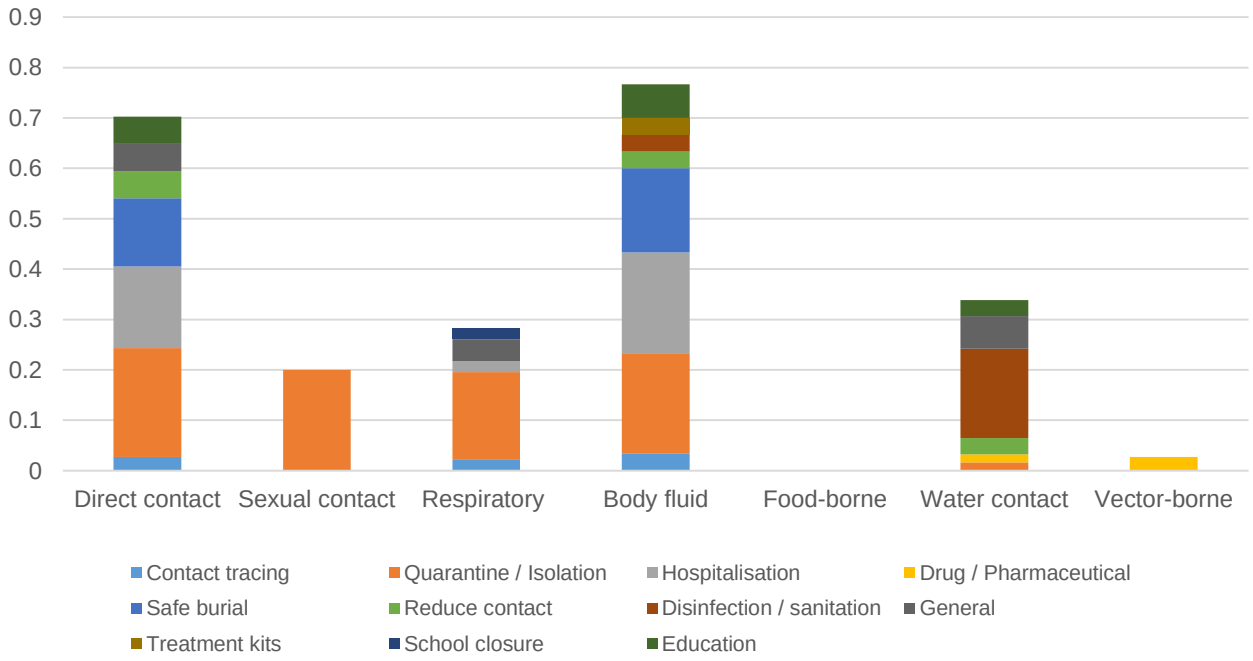

Figure 4.4: Proportion of all mentioned transmission modes in the dataset which include different treatment strategies, normalised according to S2N.

4.2.2 Second transmission-mode related analysis example (REF B5.2)

The population demographic contextual factors linked to disease propagation and the modelled population demographic contextual factors are analysed in relation to the transmission modes below (this analysis is coded REF B5.2 in Table 4.3).

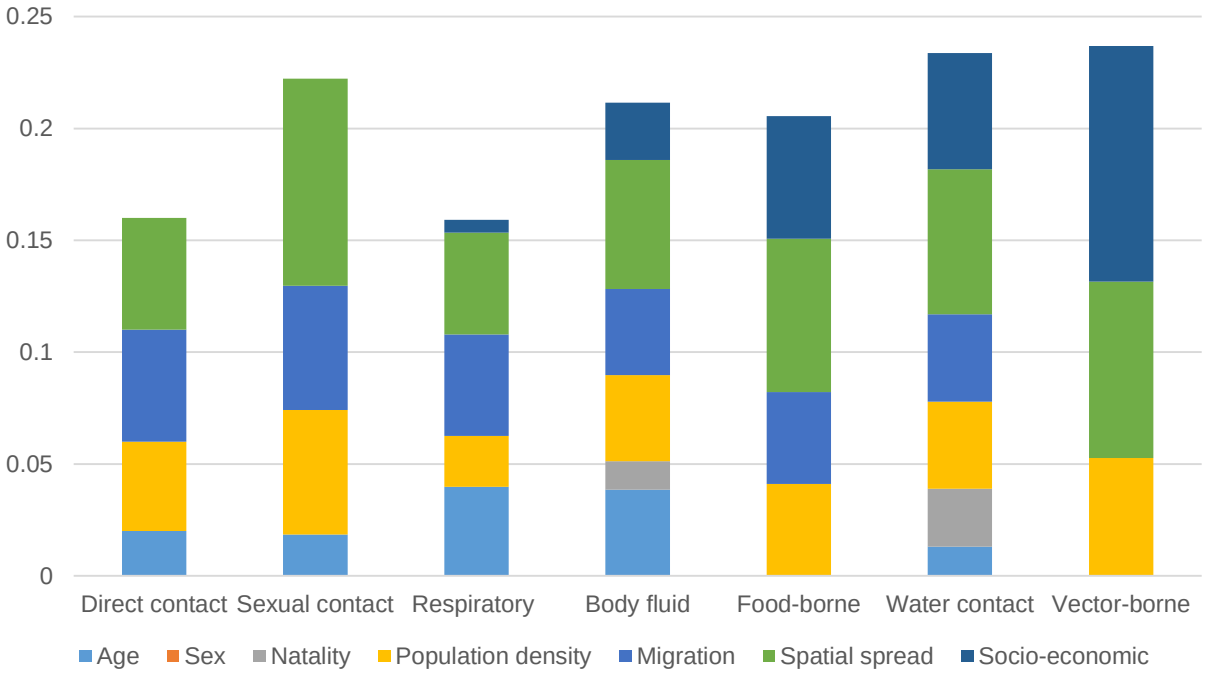

Figure 4.5: Proportion of all theoretical transmission modes in the dataset which include population demographic contextual factors linked to disease propagation, normalised according to S1N.

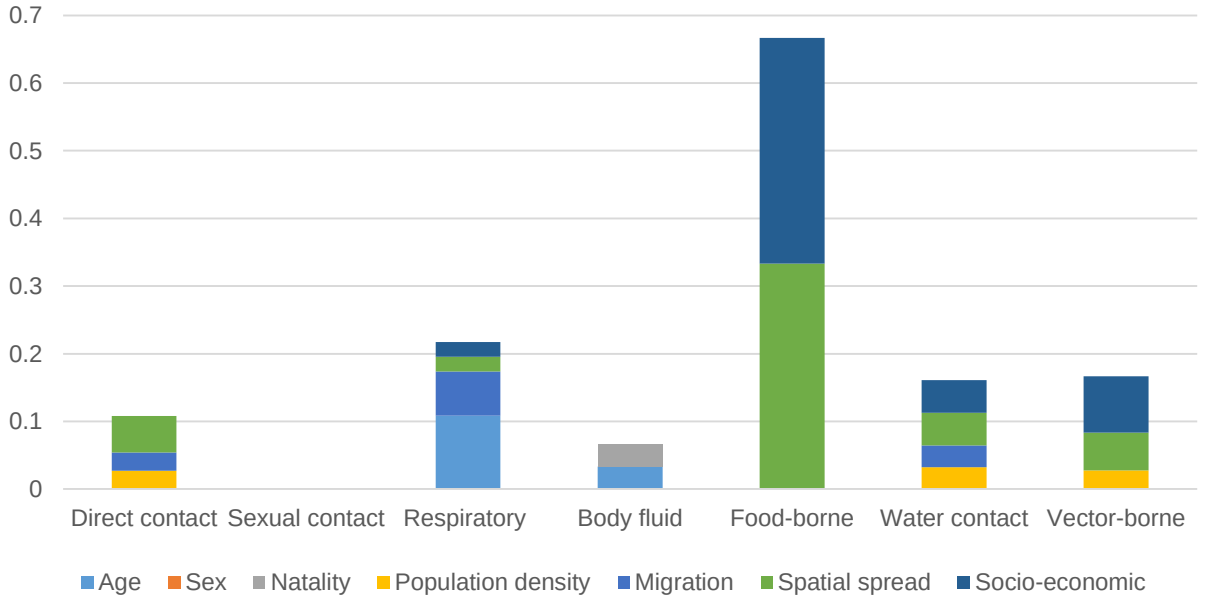

Figure 4.6: Proportion of all mentioned transmission modes in the dataset which include population demographic contextual factors linked to disease propagation, normalised according to S2N.

Linked to disease propagation factors

The proportion of literature pieces in the dataset which include population demographic factors linked to disease transmission in relation to the transmission modes are illustrated in Figure 4.5 (S1) and Figure 4.6 (S2).

In both S2 and S1 it is observed that spatial spread is a frequently included contextual factor within the modelling approaches of all transmission modes (apart from sexual contact and body fluid), in addition to population density, migration and age of the population. It is interesting to note the inclusion of socio-economic factors in many of the transmission modes of S2, in relation to vector-borne, water contact and especially food-borne (e.g. cholera) transmission modes.

Apart from these high-level observations, it is not possible to directly quantify the population demographic contextual factor inclusions solely from the transmission mode, but it is still useful to note some of the relations to the transmission modes. A selection of the observations are captured to Table 4.6 in REF B5.2.

Modelled factors

The proportion of literature pieces in the dataset which include modelled population demographic factors in relation to the transmission modes are illustrated in Figure 4.7 (S1) and Figure 4.8 (S2).

In both S2 and S1 it is observed that spatial spread is a frequently modelled contextual factor within the modelling approaches of all transmission modes (apart from sexual contact), in addition to population density, migration and age of the population. It is interesting to note the modelling of socio-economic factors in all transmission modes (apart from sexual contact and vector-borne), but a higher inclusion in relation to vector-borne, water contact and especially food-borne (e.g. cholera) transmission modes. Furthermore, when comparing S2 to S1, it is notable that direct contact, respiratory, body fluid and water contact have similarities in the diversity and proportion of modelled population demographic factors.

When comparing the proportions of contextual factors that are linked to disease propagation (illustrated in Figure 4.5 and Figure 4.6) to the contextual factors that are modelled, but not necessarily linked to the propagation of the disease (illustrated in Figure 4.7 and Figure 4.8), it is interesting to observe a higher occurrence of modelled population demographic factors than population demographic factors linked to disease propagation. This suggests the importance of modelling population demographic contextual factors in relation to the transmission mode.

Apart from these high-level observations, it is not possible to directly quantify the population demographic contextual factor inclusions solely from the transmission mode, but it is still useful to note some of the relations to the transmission modes. A selection of these observations are captured to Table 4.6 in REF B5.2.

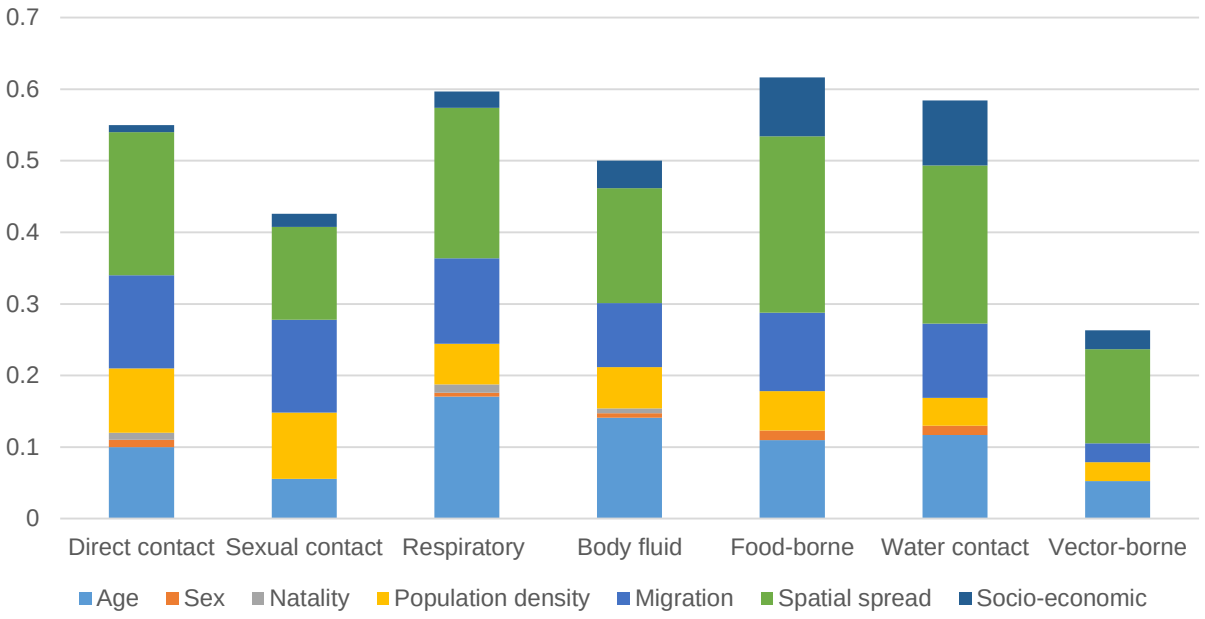

Figure 4.7: Proportion of all theoretical transmission modes in the dataset which include modelled population demographic contextual factors, normalised according to S1N.

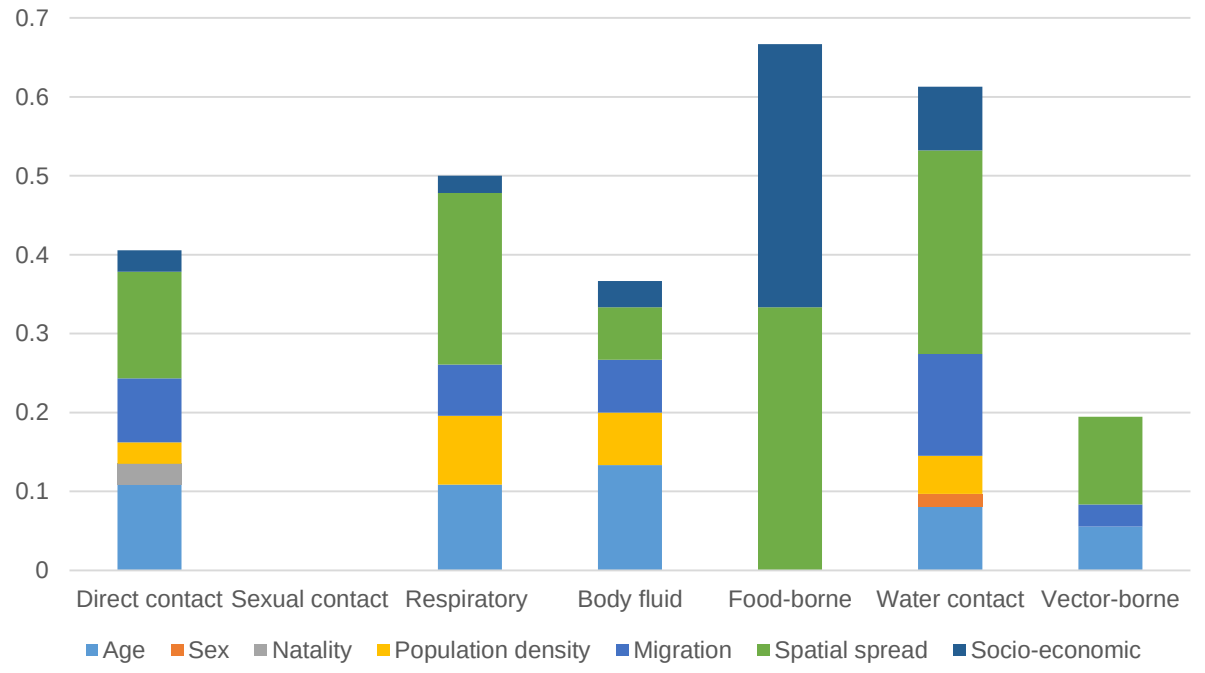

Figure 4.8: Proportion of all mentioned transmission modes in the dataset which include modelled population demographic contextual factors, normalised according to S2N.

Table 4.4: REF C analysis steps.

Categories compared		REF	Section	Normalisation	Subset
How does the presence of alternative mixing patterns relate to:	Contextual factors	§4.3.1 and C1.1	§D.17.2	✗	
	Modelling approaches	C1.2	§D.17.3	✗	
	Modelling rationales	C1.3	§D.17.4	✓	S5N
How does data source affect:	Method of model fit	C2.1	§D.18.4	✗	
	Intervention strategies	C2.2	§D.18.2	✓	S8N
	Modelling approaches	C2.3	§D.18.1	✓	S3N
	Contextual factors	C2.4	§D.18.3	✓	S9N
How is compartmental classification affected by the presence of:	Treatment strategies	C3.1.1	§D.20.3	✗	
	Vaccination strategies	C3.1.2	§D.20.3	✗	
How does modelling approaches with RI and non RI diseases compare with respect to:	Modelling approaches	C4.1	§D.22.1 – §D.22.4	✓	S4N
	Modelling scopes	C4.2	§D.22.6	✓	S4N
	Contextual factors	C4.3	§D.22.7	✓	S4N
	Transmission mode mentioned	C4.4	§D.22.8	✓	S4N
	Modelling rationales	C4.5	§D.22.9	✓	S4N
	Data sources	C4.6	§D.22.5	✓	S4N

Categories compared		REF	Section	Normalisation	Subset
Is compartmental classification influenced by:	Modelling approaches	C5	§D.20.1	✓	S3N
Is there a relationship between the modelling approach and the:	Modelling rationales	C6.1	§D.21.1	✓	S3N
	Modelling scopes	C6.2	§D.21.2	✓	S3N
	Intervention strategies	C6.3	§D.21.3	✓	S3N
Is there a relationship between the modelling scope and the:	Data sources	§4.3.2 and C7.1	§D.19.1	✓	S6N
	Modelling rationales	§4.3.3 and C7.2	§D.19.2	✓	S5N
	Alternative mixing patterns	C7.3	§D.19.3	✓	S7N

4.3 Analysis on modelling considerations (REF C)

In addition to analysis of the transmission mode (i.e. disease characteristics) in relation to various modelling considerations detailed in §4.2, various modelling considerations are also analysed in relation to one another as set out in Table 4.4. These analyses are coded as the REF C analyses.

For the sake of brevity, the entire set of analyses summarised in Table 4.4 is presented in Appendix D (as noted in Table 4.4). However, three of these analyses are duplicated in the remainder of this section as examples of how the analyses are typically conducted.[7] The analysis of the use of data sources in the context of different modelling scopes is presented in §4.3.1. The analysis on population demographic inclusions in relation to alternative mixing patterns is produced in §4.3.2. Finally, the analysis on modelling scope use in the context of the modelling rationale is presented in §4.3.3.

[7] The two analyses that are presented here in the main thesis document are repeated in the appendix so that Appendix D, from §D.11 to §D.22, can be read as a coherent narrative describing all of the analyses that were performed (with the exclusion of the descriptive analysis of the dataset discussed in §3.5.

4.3.1 First modelling consideration-related analysis example (REFC1.1)

Although the transmission mode plays an important role in the dynamics of a disease, other factors most likely also play a role in the incorporation and selection of alternative mixing patterns. As the population demographics describe the stratification and structure of a population, it would make sense to investigate a possible relationship between the incorporation of alternative mixing patterns and the incorporation of population demographics in a modelling application, as illustrated in Figure 4.9.

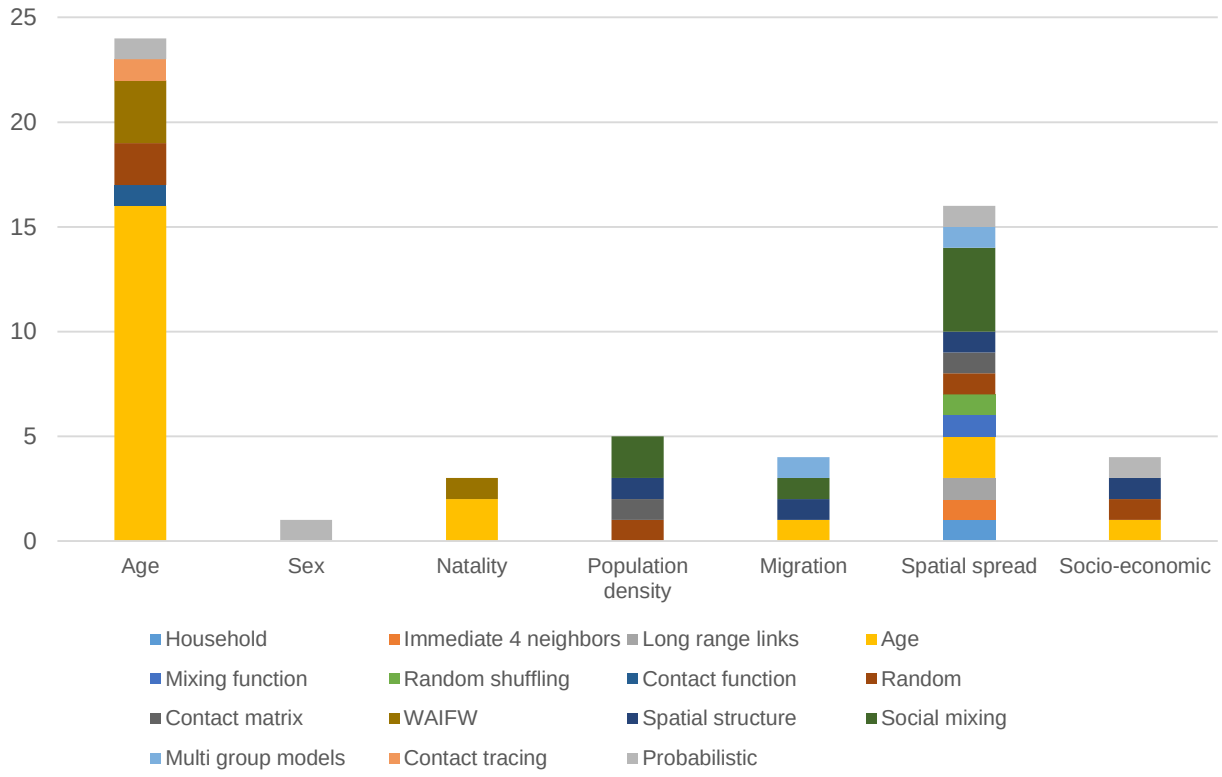

Figure 4.9: Number of alternative mixing patterns included in modelling instances when different population demographic contextual factors are also included.

It is observed that the highest occurrence of alternative mixing patterns is present when the age and spatial spread population demographic factors are taken into account during modelling. This observation is as expected. Furthermore, the most diverse number of alternative mixing patterns are applied to instances which included the spatial spread demographic factor in the modelling approach. This is an important observation, as it implies that incorporation of spatial spread in a modelling study requires consideration of non-standard mixing patterns. There is also indication in the diversity of the alternative mixing patterns in the context of population density and migration factors that, even though few of these instances are observed, these contextual factors may play a role in the selection of alternative mixing patterns. This is included in the observations as it is logical to assume that population density and migration sensitively affect the distribution of people within a population and in turn affect the manner in which individuals in the population interact with one another.

The potential relationship between environmental contextual factors and mixing patterns are not analysed in the same rigorous manner as the population demographic contextual factors, as there is no logical argument to support a relationship between mixing patterns and factors such as climate or seasonality (i.e. environmental contextual factors). A selection of these observations are captured to Table 4.9 in REF C1.1.

4.3.2 Second modelling consideration-related analysis example (REF C7.1)

The proportion of modelling scopes applied in the context of different data sources are illustrated in Figure 4.10. The normalisation of the subset (S6) is completed according to the total number of instances of each data source category (S6N) to highlight the proportions of the data sources included in the context of different modelling scopes.

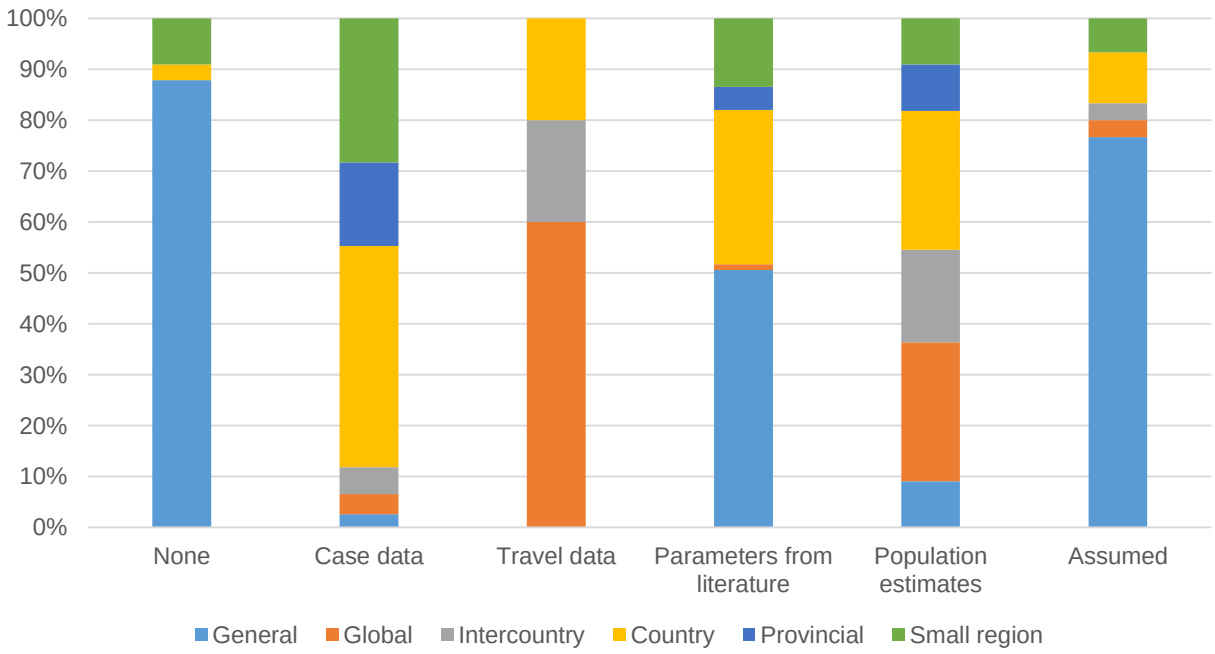

Figure 4.10: Proportion of models to which various modelling scopes have been applied, for each data source, normalised according to S6N.

It is observed that when no data source or an assumed data source was used in the modelling application (e.g. for theoretical models without a real-life application) that a general modelling scope was adopted the most frequently (88% and 77%, respectively). Travel data is applied exclusively within the global, intercountry and country modelling scope. Case data (the most frequently occurring data source in the dataset) is used the most frequently in a country, small region and provincial modelling scope. Parameters from literature are used the most frequently in a general modelling scope, but also in a country and a small region modelling scope. Population estimates are used the most often in a global and country modelling scope, in addition to an intercountry modelling scope.

With respect to the modelling scope, it is observed that the country modelling scope is the only modelling scope applied in the context of all types of data sources. Furthermore, it is observed that case data and population estimates are used in the context of all modelling scopes.

Although it is not possible to directly quantify modelling scope based solely on the data source selection, the observations on some of the observed relationships are captured to Table 4.7 in REF C7.1.

4.3.3 Third modelling consideration-related analysis example (REF C7.2)

The proportion of modelling scopes applied in the context of different modelling rationales are illustrated in Figure 4.11. The normalisation of the subset (S5) is completed according to the total number of instances for each modelling rationale category (S5N) to highlight the proportions of the modelling rationales incorporated in the context of different modelling scopes.

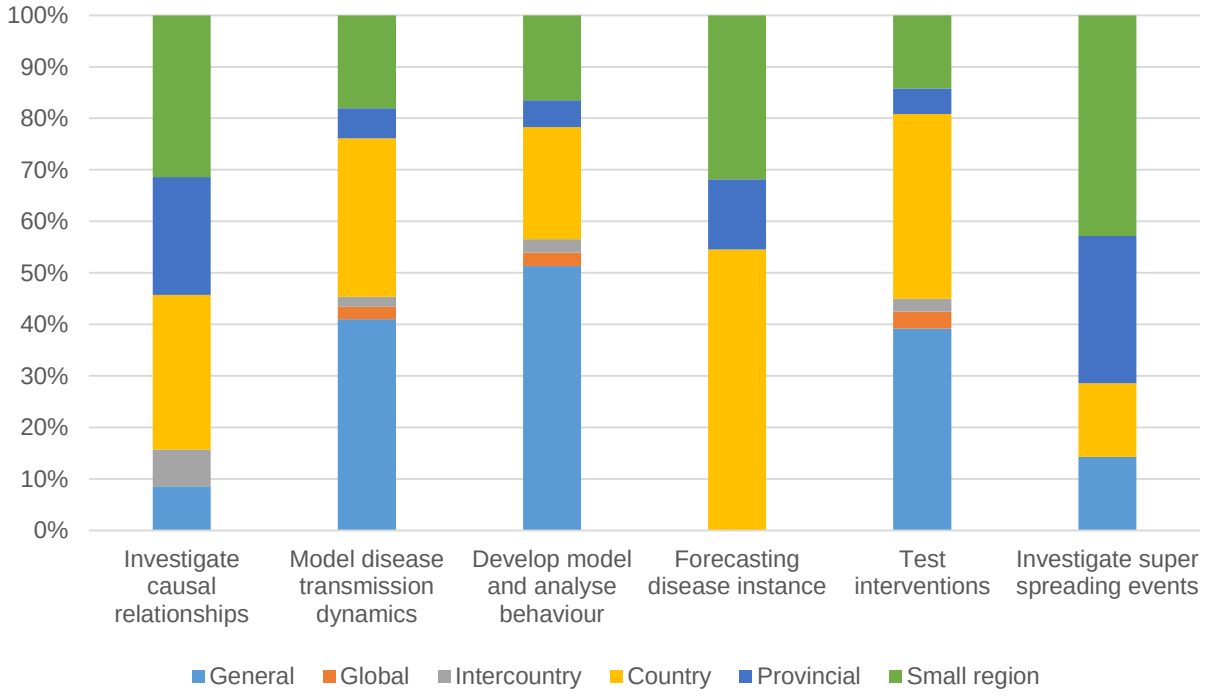

Figure 4.11: Proportion of models to which various modelling scopes have been applied, for each modelling rational, normalised according to S5N.

The two most frequently applied scopes used when investigating causal relationships are the small region and country modelling scope. The ‘model disease transmission dynamics’, ‘develop a model and analyse behaviour’ and ‘test interventions’ modelling rationales all had a general modelling scope as the most frequently applied modelling scope, followed by a country scope and a small region modelling scope. The ‘forecast disease instance’ rationale is only used in a country scope, followed by a small region scope. It is interesting to see that the ‘test interventions’ rationale is applied the most frequently in a general scope, followed by a country and a small region scope. The

'investigation of super spreading events' rationale is applied the most often in a small region modelling context, followed by a provincial scope modelling context. A selection of these observations are captured to Table 4.10 in REF C7.2.

4.4 Summary of analysis

The conclusions of the complete set of analyses summarised in Table 4.3 (REF B) and Table 4.4 (REF C), are presented in this section.[8] The conclusions are also summarised in various tables that are produced at the end of the chapter, as noted in Table 4.5.

Table 4.5: Reference to sections of §4.4 and associated summary tables.

Observations in the context of / in relation to:	Section	Summary table
Disease transmission mode	§4.4.1	Table 4.6 (p.83)
Modelling scope	§4.4.2	Table 4.7 (p.84)
Modelling approach	§4.4.3	Table 4.8 (p.85)
Contextual factors	§4.4.4	Table 4.9 (p.85)
Modelling rationale	§4.4.5	Table 4.10 (p.85)

4.4.1 Observations and relationships in relation to the disease transmission mode

B1: Potential relevance of transmission mode

The diseases with the highest instance of explicitly mentioned transmission modes were vector-borne (95%) and water contact diseases (80%), followed by direct contact (37%), respiratory (27%) and body fluid (19%). The transmission modes described the least frequently were sexual contact (9%) and food-borne (4%). From this observation it appears that the vector-borne and water contact transmission modes are considered to be particularly salient in modelling disease dynamics, while direct contact, respiratory and body fluid transmission modes appear to be moderately relevant.

[8] To ease the readability of the appendix, the conclusions are duplicated in the appendix.

B2.1: Modelling scopes most often observed

Apart from high-level observations, it is not possible to directly quantify the modelling scope selection solely from the transmission mode, but it is still useful to note some of the relationships to the transmission modes.

B2.2: Relevance of alternative mixing patterns

Alternative mixing patterns are applied most often for diseases which are transmissible by respiratory contact, direct contact and body fluid.

B2.3: Mixing patterns most often observed

Age stratification of humans was the most prevalent manner in defining alternative mixing patterns in the dataset, followed by social mixing, especially for the direct contact, respiratory and body fluid transmission modes.

B3.1: Modelling approaches most often observed

Mathematical modelling is the most frequently used approach across all transmission modes. Mathematical approaches are less prominently used for modelling respiratory transmission where network and simulation approaches represent 18% and 12% of the dataset instances respectively. Mathematical approaches are used in more than 90% of modelling instances for the body fluid, water contact, and vector-borne transmission modes.

B3.2: Mathematical approaches most often observed

Differential equations (DEs) are the most frequently used mathematical modelling approach. Additionally, the transmission modes with the most diverse range of mathematical modelling approaches used are respiratory, water contact and vector-borne.

B3.3: Network approaches most often observed

Metapopulation network models are used for all transmission modes and small world network models are used mainly for direct and sexual contact, respiratory and body fluid transmission modes. Similar to the observation for mathematical approaches, the transmission modes with the most diverse categories of network approaches were respiratory, followed by body fluid.

B3.4: Simulation approaches most often observed

ABS is the most frequently applied simulation technique. Similar to the observations for network approaches, three of the four transmission modes which are dependent on human host interactions are modelled with a similar proportion of diverse simulation modelling techniques. The human host transmission mode to which these observations don't apply is sexual transmission.

B4: Relevance of treatment

As a general observation, it is clear that treatment strategies are most frequently applied in the context of the direct contact, body fluid, respiratory, and sexual transmission modes, in addition to the water contact transmission mode. These transmission modes are dependent on direct contact between humans, apart from body fluid and water contact which requires indirect contact.

B4.1: Treatment strategies observed

Quarantine is a treatment strategy that is observed only for the transmission modes which rely on contact between humans. Furthermore, very similar treatment strategies are applied in relation to the direct contact and body fluid transmission modes. Reduced contact is a treatment strategy that is observed particularly frequently especially in relation to the direct contact, body fluid and water contact transmission mode.

B4: Relevance of vaccination

Vaccination strategies are the most frequently observed in relation to body fluid and respiratory transmission modes, in addition to direct, sexual and water contact transmission modes. Additionally, no vaccination strategies are observed for food-borne and vector-borne transmission modes.

B4.2: Vaccination strategies observed

The vaccination strategy that is applied the most frequently is the vaccination of a proportion of the susceptible population. Additionally, the most diverse number of vaccination strategies are applied in relation to the respiratory transmission mode. Of the commonly applied vaccination strategies mentioned in Table 2.2, it is interesting to note that the more reactive strategies, such as ring and targeted vaccination do not occur as frequently as the proactive vaccination strategies, such as vaccination of a proportion of the susceptible population, general vaccination rate and prophylactic vaccination strategies.

B5.1: Linking contextual factors to disease propagation

The transmission modes for which disease propagation are most frequently linked to contextual factors are respiratory, water contact and especially vector-borne.

B5.1: Modelling contextual factors

With reference to contextual factors included in modelling approaches, it is observed that similar proportions of all the theoretical transmission modes included contextual factors in the modelling approach, with the lowest proportion of inclusions for the sexual contact and vector-borne transmission modes.

B5.2: Relevance of environmental contextual factors

It is interesting to note a higher occurrence of environmental contextual factors linked to disease propagation than modelled environmental contextual factors. This suggests the importance of linking disease propagation to environmental contextual factors in relation to the transmission mode.

B5.2: Environmental contextual factors linked to disease propagation

The respiratory, body fluid, food-borne, water contact and vector-borne transmission modes are the only transmission modes which have inclusions of all four environmental contextual factors within the modelling approach linked to disease propagation.

B5.2: Environmental contextual factors modelled

The food-borne, water contact and vector-borne transmission modes have the highest proportion of inclusion of all four environmental contextual factors within the modelling approach.

B5.2: Relevance of population demographics contextual factors

It is interesting to observe a higher occurrence of modelled population demographic factors than population demographic factors linked to disease propagation. This suggests the importance of modelling population demographic contextual factors in relation to the transmission mode.

B5.2: Population demographics contextual factors linked to disease propagation

Spatial spread is a frequently included contextual factor within the modelling approaches of all transmission modes apart from sexual contact and body fluid. Other contextual factors that are observed include population density, migration and age of the population.

B5.2: Population demographics contextual factors modelled

Spatial spread is a frequently modelled contextual factor within the modelling approaches of all transmission modes (apart from sexual contact), in addition to population density, migration and age of the population. It is interesting to note the modelling of socio-economic factors in all transmission modes (apart from sexual contact and vector-borne), but a higher inclusion in relation to vector-borne, water contact and especially food-borne (e.g. cholera) transmission modes.

B6: Compartmental classification categories observed

It is not possible to generalise the compartmental classification solely from the transmission mode.

4.4.2 Observations and relationships in the context of the modelling scope

C6.2: Modelling approach

All three modelling categories are suitable for application in the context of all the modelling scopes, however, as noted in Table 4.7, a higher occurrence of some applications are observed for a selection of the rationales.

C7.1: Data source most commonly associated with scope

Although it is not possible to directly quantify modelling scope based solely on the data source selection, some general observations are summarised in Table 4.7.

C7.3: Inclusion of alternative mixing patterns

From the limited number of observations, it is not possible to directly relate the inclusion of alternative mixing patterns based solely on the modelling scope, however it is noted that alternative mixing patterns are most frequently included in models with a small scope, in addition to being fairly frequently included in models with a general scope and a country scope.

4.4.3 Observations and relationships in the context of the modelling approach

C1.2: Inclusion of alternative mixing patterns

It is observed that the highest occurrence of alternative mixing patterns is present when the age and spatial spread population demographic factors are taken into account during modelling.

C2.3: Data source

From this analysis it is deduced that all three modelling approach categories are suitable for application in the context of all types of data sources, even though a marginally higher occurrence of some modelling approach categories are observed for certain data sources.

C6.3: Intervention strategies

Very similar proportions of mathematical and network modelling approaches incorporate treatment and vaccination strategies, however, it is observed that, relative to mathematical and network modelling approaches, a larger proportion of the studies that utilised simulation modelling approaches incorporated treatment and vaccination strategies.

4.4.4 Observations and relationships in relation to contextual factors

C1.1: Inclusion of alternative mixing patterns

It is observed that the highest occurrence of alternative mixing patterns is present when the age and spatial spread population demographic factors are taken into account during modelling. Furthermore, the most diverse number of alternative mixing patterns are applied to instances which included the spatial spread demographic factor in the modelling approach.

C2.4: Data source

Case data is utilised the most frequently to model contextual factors and investigate the effect on disease propagation. Parameters from literature are also used frequently to model population demographics and environmental contextual factors.

4.4.5 Observations and relationships in the context of the modelling rationale

C1.3: Inclusion of alternative mixing patterns

It is clear that there are no modelling rationales which clearly incorporate alternative mixing patterns more than any other modelling rationales.

C6.1: Modelling approach

From this analysis it is deduced that all three modelling categories are suitable for application in the context of all the modelling rationales, however, a higher occurrence of some applications are observed for a selection of the rationales, as summarised in Table 4.10.

C7.2: Modelling scope

From this analysis it is observed that some modelling scopes are used more frequently in the context of some modelling rationales. A selection of these observations are captured to Table 4.10.

4.5 Conclusion

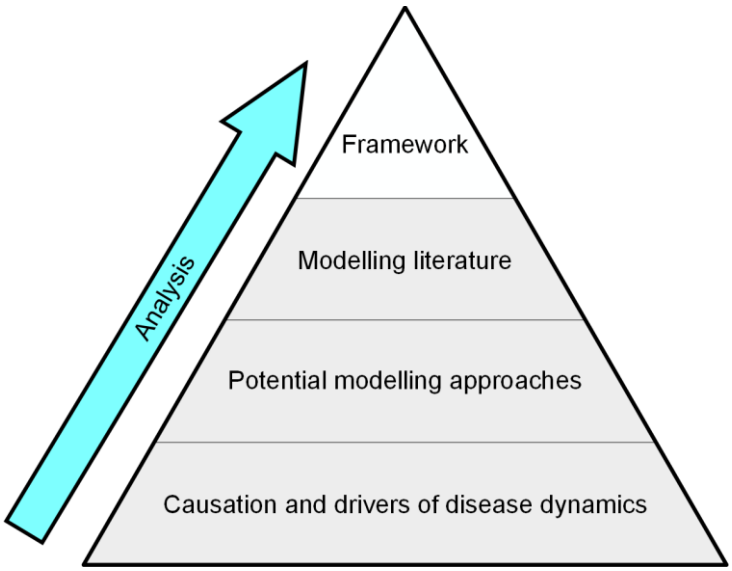

Figure 4.12: A visual summary of the content of Chapter 4.

A summary of the content of this chapter in relation to the overall document structure is illustrated in Figure 4.12. The analysis of the dataset was conducted according to three broad categories, namely:

- REF A in §3.5, which pertains to a high-level overview of the dataset (noted in Table 3.9);
- REF B in §4.2, which pertains to the analysis of the relationships between the transmission mode of a disease and the modelling approach and other modelling considerations (noted in Table 4.3); and
- REF C in §4.3, which pertains to the analysis of the relationships between different modelling considerations (noted in Table 4.4).

The summarised findings of the analysis are presented in §4.4. Within the analysis, clearly and moderately evident relationships are observed. These observation are captured to Table 4.6 – Table 4.10, serving as a reference set to quantitatively inform modelling approach and consideration selection.

During the analysis of the REF B set in particular, a selection of the relationships differed from the expected observations in some of the S1 analysis (e.g. as highlighted in the analysis example in §4.2.1). However, when the results were viewed in conjunction with the results from S2, in which the disease transmission mode is explicitly mentioned, these discrepancies were resolved. This

highlights the importance of not only considering the theoretical transmission modes, but also considering the context-specific transmission modes which play a role in the selection of a modelling approach and other modelling considerations.

In some instances, no clearly evident relationships were observed between various modelling decisions and considerations (e.g. as highlighted in the analysis examples in §4.3.1 and §4.3.3). It is, however, still of interest to note and discuss these findings. For such instances, the findings are interpreted by considering what the selection of a particular modelling consideration would imply in a typical modelling selection context. This supports the proposition that the selection of a particular modelling approach or consideration does not relate to a single factor, but rather relates to the simultaneous consideration of numerous factors. One conclusion of this observation is that the context of a particular disease outbreak plays an important role in the selection of modelling approaches and considerations.

Additionally, very few conclusive relationships are observed between the modelling approach and consideration selection and the diseases that are part of RI and are not part of RI (as mentioned in §D.22). As previously discussed in §3.1.1, the nature of the disease outbreak could influence the selection of a modelling approach and other modelling considerations. However, to assume that diseases that are part of RI can always be considered endemic diseases and that outbreaks of diseases which are not part of RI are always epidemic or pandemic is not accurate, as such an assumption does not consider the particular context of the disease outbreak.

The observations which relate to the importance of the context of a disease outbreak, in addition to the observed relationships, are used as an important departure point to inform the construction of the disease modelling framework in the following chapter.

Table 4.6: Observations and relationships of modelling approaches and considerations in relation to the disease transmission mode.

CAT	REF	Direct contact	Sexual contact	Respiratory	Body fluid	Food-borne	Water contact	Vector-borne
Potential relevance of transmission mode	B1	Moderate relevance	Low relevance	Moderate relevance	Moderate relevance	Low relevance	High relevance	High relevance
Modelling scopes most often observed	B2.1	Country Global	Country General	Country Global Provincial	Country	General Small region	General Provincial	Small region Provincial
		Country and general used the most frequently in all examples, respiratory and direct contact most diverse scope applications						
Relevance of alternative mixing patterns	B2.2	High relevance	Less relevance	High relevance	High relevance	Less relevance	Moderate relevance	Moderate relevance
Mixing patterns most often observed	B2.3	Age & social	N/A	Age & social	Age & social	N/A	N/A	N/A
Proportion of modelling approaches often observed	B3.1	Simulation and network	Simulation and network	Simulation and network	Simulation and network	Mathematical	Mathematical	Mathematical
Mathematical approaches most often observed	B3.2	DE FODE	DE	DE Regression	DE	DE, PDE and Regression	DE Regression	DE Regression
Network approaches most often observed	B3.3	Small world Metapopulation	Small world Metapopulation	Small world Metapopulation	Small world Metapopulation	Metapopulation	Metapopulation	Metapopulation
Simulation approaches most often observed	B3.4	ABS	ABS	ABS	ABS	ABS	ABS	ABS
Relevance of treatment	B4	High relevance	High relevance	High relevance	High relevance	Less relevance	Less relevance	Low relevance
Treatment strategies observed	B4.1	Quarantine Hospitalisation	Quarantine	Quarantine Hospitalisation	Quarantine Hospitalisation	Disinfection	Disinfection Drug usage	Drug usage
		In general, similar methods observed				In general, similar methods		N/A
		Diverse strategies observed				N/A	Diverse strategies	N/A
Relevance of vaccination	B4	High relevance	High relevance	High relevance	High relevance	Low relevance	High relevance	Low relevance
Vaccination strategies observed	B4.2	A proportion of susceptible Ring	A proportion of susceptible	A proportion of susceptible Ring	A proportion of susceptible Ring	N/A	A proportion of susceptible	N/A
Linking contextual factors to disease propagation	B5.1	Less relevance	Less relevance	High relevance	High relevance	High relevance	High relevance	Very high relevance

CAT	REF	Direct contact	Sexual contact	Respiratory	Body fluid	Food-borne	Water contact	Vector-borne
Modelling contextual factors	B5.1	High relevance	Low relevance	High relevance	High relevance	High relevance	High relevance	Less relevance
Relevance of environmental contextual factors	B5.2	Low	Low	Moderate	High	High	High	Very high
Environmental contextual factors linked to disease propagation		N/A	N/A	Climate & seasonality & rainfall	N/A	Climate & rainfall	Climate & temperature & rainfall	Climate & temperature & rainfall
Environmental contextual factors modelled		Seasonality	N/A	Seasonality	Seasonality			
Relevance of population demographics contextual factors	B5.2	Very high	Low	Very high	High	Moderate	Very high	Moderate
Population demographics contextual factors linked to disease propagation		Age & population density & migration & spatial spread	N/A	Age & population density & migration & spatial spread	Age & population density & migration & spatial spread	Spatial spread & socio economic	Spatial spread & socio economic	Spatial spread & socio economic
Population demographics contextual factors modelled								Age & spatial spread
Compartmental classification categories observed	B6	E / F / V / Q	V	E / V / Q	E / F / V / Q	N/A	B / W	M

Table 4.7: Observations and relationships of modelling approaches and considerations in the context of the modelling scope.

CAT	REF	General	Global	Intercountry	Country	Provincial	Small scope
Modelling approach	C6.2	All three high-level modelling approaches are suitable in the context of each modelling scope					
Modelling approach most commonly associated with scope		Mathematical	Network		N/A	N/A	Simulation
Data source most commonly associated with scope	C7.1	None & assumed & parameters from literature	Travel & case data & population estimates	Travel & population estimates	Travel & population estimates & parameters from literature	Case data & parameters from literature	Case data & parameters from literature
Inclusion of alternative mixing patterns	C7.3	High	Moderate	Moderate	High	Moderate	Highest

Table 4.8: Observations and relationships of modelling considerations in the context of the modelling approach.

CAT	REF	*Most common inclusion*	Mathematical	Network	Simulation
Inclusion of alternative mixing patterns	C1.2	*Age and social mixing* *Potentially WAIFW matrix*	Largest number of inclusions	Few inclusions	Second largest number of inclusions
Data source	C2.3	*Case data and parameters from literature*	All modelling approaches are suitable for all mentioned data sources		
Data source with highest utilisation of a modelling approach			Parameters from literature	Travel data and assumed	Case data & population estimates
Intervention strategies	C6.3	*N/A*	Both treatment and vaccination strategies are observed in the context of each modelling approach, no preferred modelling approach for these high-level strategies		

Table 4.9: Observations and relationships of modelling considerations in relation to contextual factors.

CAT	REF	Environmental		Demographics	
		Linked to disease propagation	**Modelled**	**Linked to disease propagation**	**Modelled**
Inclusion of alternative mixing patterns	C1.1	N/A		High inclusion of alternative mixing: Age and spatial spread High diversity in alternative mixing: Population density & migration	
Data source	C2.4	Case data	Case data	Case data	Case data & parameters from literature

Table 4.10: Observations and relationships of modelling approaches and considerations in the context of the modelling rationale.

CAT	REF	Model disease dynamics	Investigate causal relationships	Investigate super spreading events	Forecast disease instance	Develop a model and analyse behaviour	Test interventions
Inclusion of alternative mixing patterns	C1.3	Frequently observed	Less observed	Frequently observed	Frequently observed	Less observed	Frequently observed
Modelling approach	C6.1	All approaches are observed in the context of each modelling rationale					
Modelling approach with highest utilisation (ranked)		Mathematical Simulation Network	Simulation Network Mathematical	Network Mathematical Simulation	Mathematical Simulation Network	Simulation Mathematical Network	Simulation Network Mathematical
Modelling scope	C7.2	All scopes are observed in the context of each modelling rationale					
Scope modelled exclusively in a particular rationale		N/A	N/A	N/A	Country provincial small region	N/A	N/A

Chapter 5 Framework design

This chapter comprises a brief overview of the construction of the framework, followed by the presentation of the framework itself. The developed modelling framework has two goals, namely:

1. Inform modelling approach decisions and considerations from a holistic viewpoint; and
2. Aid in modelling consideration selection according to findings of the analysed dataset.

The comprehensive steps of the framework are illustrated in Figure 5.1. A preamble to the framework is discussed in §5.1. The documentation step of the framework that runs concurrently through each of the framework steps is discussed in §5.2. The framework consists of two main phases, namely the modelling contextualisation phase (mapping disease characteristics and informing modelling approach decisions) presented in §5.3 and the outbreak modelling selection phase (modelling approach and consideration selection), presented in §5.4. Some notable omissions to the framework are highlighted in §5.5 prior to the chapter conclusion in §5.6.

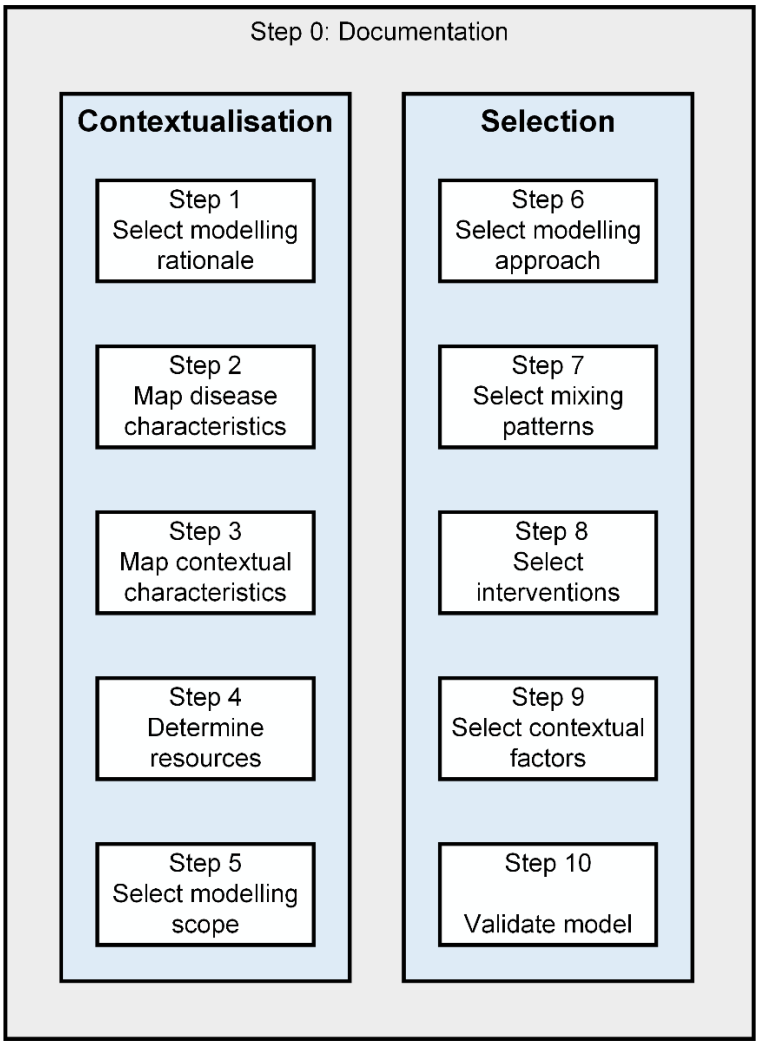

Figure 5.1: High-level overview of framework.

5.1 Preamble to framework

A brief overview of the construction of the framework is completed in §5.1.1, followed in §5.1.2 with a reference to the sections of Appendix E containing additional figures and tables used in support of the framework construction.

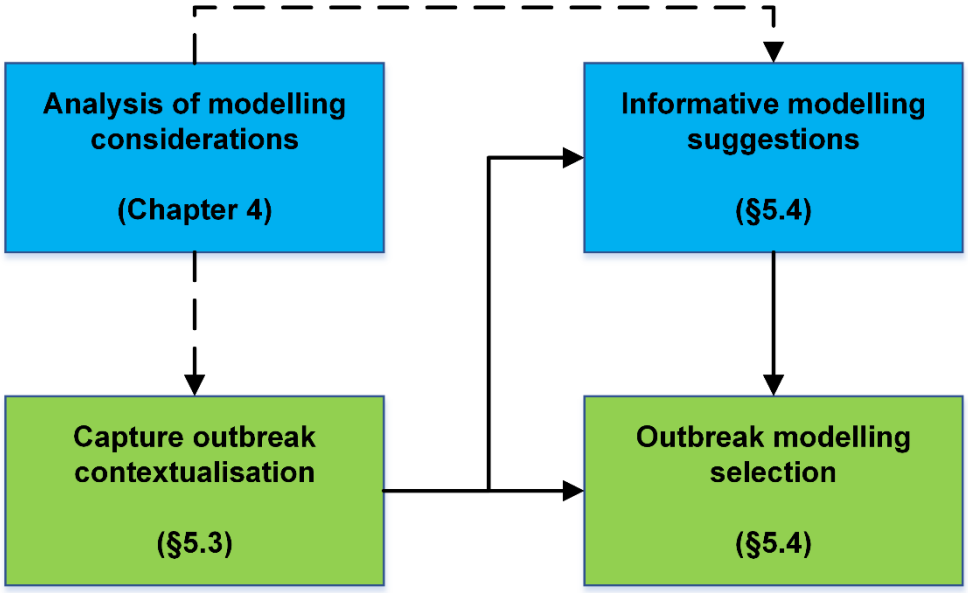

Figure 5.2: High-level overview of the framework construction.

5.1.1 Overview of construction and operation of the framework

The framework construction as illustrated in Figure 5.2 relies on three steps, namely:

- **Analysis of modelling considerations**, though it is not possible to generalise all modelling decisions from the analysis performed in Chapter 4, the observations from this analysis are used to inform the preparation (i.e. contextualisation) considerations;
- **Capturing the outbreak modelling contextualisation**, the first phase of the framework consists of various tables to capture the context and relevant characteristics of the disease outbreak; and
- **Outbreak modelling selection**, the second phase of the framework pertains to the selection of outbreak modelling decisions and considerations, based on the captured characteristics and the informative modelling suggestions.

In addition to the analysis performed in Chapter 4, elements from Chapter 2 and occasionally Chapter 3 are included as part of the construction of the framework.

In §5.3, the modelling application is contextualised and the outbreak characteristics are captured to various tables. In §5.4, recommendations pertaining to the incorporation and selection of the modelling approach and modelling considerations are completed according to various informative

tables. The informative tables are constructed according to the analysis performed in Chapter 4 and some of the suggestions are retrieved according to the disease and contextual characteristics in captured §5.3.

5.1.2 Appendix reference

For the sake of brevity additional tables and figures are presented in the sections of Appendix E, namely:

- §E.1 contains tables that serve as a reference guide to tables and sections of Chapter 4 and Appendix D which are used to construct the recommendation tables of the outbreak modelling selection phase of the framework; and
- §E.2 contains figures which highlight the analysis steps performed to establish the relationships between the steps of the outbreak modelling contextualisation and outbreak modelling selection.

5.2 Step 0: Documentation

The documentation of the modelling approach is a step that runs concurrently through each of the steps of the framework. This step serves the purpose of documenting both the aspects of the outbreak modelling contextualisation (i.e. modelling preparation) and the outbreak modelling selection phase, analogous to creating a roadmap of the modelling process. The main reasons for incorporating this step in the framework are as follows:

- Modelling assumptions and selections are captured clearly and concisely.
- Assurance is provided to the modeller that all relevant factors were considered in the modelling process, in addition to describing why some considerations were omitted and how the outbreak context relates to the selection of the modelling application.
- The ability to extend or clarify aspects of the modelling application in future work is assisted, in the sense of indicating which modelling considerations are incorporated or explicitly omitted from the modelling application.

The steps of the outbreak modelling contextualisation are documented according to the steps in Table 5.1, whereas the decisions pertaining to the outbreak modelling selection are documented according to the steps in Table 5.2. Table 5.3 serves as a checklist in the outbreak modelling contextualisation phase of the framework and is used to capture the high-level modelling considerations which are considered for inclusion within the modelling application. Table 5.4 is used as the main documentation table of the framework, which is used to capture the selection of modelling decisions during the modelling selection process. The modelling assumptions and any

additional details (i.e. additional comments) which are considered part of the modelling selection process are also captured to Table 5.4.

Table 5.1: Outbreak modelling contextualisation documentation steps.

Step(s)	Framework step	Section	Documentation table
1	Select modelling rationale	§5.3.1	Table 5.3
2	Describe disease characteristics	§5.3.2	Table 5.6
2	Describe disease interventions	§5.3.2	Table 5.7
3	Describe environmental contextual factors	§5.3.3	Table 5.8
3	Describe population demographic contextual factors	§5.3.3	Table 5.9
3	Describe mixing pattern consideration	§5.3.3	Table 5.9
4	Determine resources	§5.3.4	Table 5.10
1 – 4	Document high-level outbreak modelling consideration	§5.3.1 – §5.3.4	Table 5.3 (p.91)

Table 5.2: Outbreak modelling selection documentation steps.

Step(s)	Framework step	Section	Documentation table
5	Select modelling scope	§5.3.4	Table 5.4 (p.92)
6	Select modelling approach	§5.4.1	
6	Select compartmental classification	§5.4.1	
7	Select mixing pattern(s)	§5.4.2	
8	Select intervention strategies	§5.4.3	
9	Select contextual factors	§5.4.4	
10	Validate model	§5.4.5	
1-10	Future work considerations	§5.2 – §5.4	

Table 5.3: Reference table to capture decisions of the outbreak modelling contextualisation phase.

Modelling rationale	**Selected (✓ / ✗)**	**Treatment included (✓ / ✗)**	**Vaccination included (✓ / ✗)**	**Environmental factors included (✓ / ✗)**	**Demographics included (✓ / ✗)**	**Alternative mixing patterns included (✓ / ✗)**
Model disease dynamics						
Investigate causal relationships						
Investigate super spreading events						
Forecast disease instance						
Develop a model and analyse behaviour						
Evaluate interventions						

Table 5.4: Reference table to capture decisions of the outbreak modelling selection phase.

CAT		Selection (✓)	Methods and/or categories selected	Modelling assumptions	Additional comments
Modelling scope	General		N/A		
	Global				
	Intercountry				
	Country				
	Provincial				
	Small region				
Modelling application	Mathematical				
	Network				
	Simulation				
	Compartmental classification				
Mixing patterns	Homogeneous		Homogeneous		
	Alternative				
Intervention and control	None		N/A		
	Treatment				
	Vaccination				
Contextual factors	None		N/A		
	Environmental				
	Demographics				
Validate model	Does the model answer research question?		N/A		
	Is the model comprehensible?				
	Is the model believable?				
	Does the model fit the data?				
	Fitting methods used:				
Future work					
Documentation completed	Outbreak modelling contextualisation	Table 5.3	Table 5.6 – Table 5.10		
	Outbreak modelling selection	Table 5.4	Table 5.11 – Table 5.15		

5.3 Outbreak modelling contextualisation

In order to holistically approach the disease modelling process, the context-specific characteristics of the disease are characterised prior to any modelling approach selection and implementation. The steps which form part of the outbreak contextualisation are illustrated in Figure 5.1, namely:

- Select the modelling rationale in §5.3.1;
- Capture and describe disease characteristics and interventions in §5.3.2;
- Capture and describe (contextual) environmental factors in §5.3.3;
- Capture and describe (contextual) population demographics in §5.3.3;
- Capture and describe available resources (i.e. data sources) in §5.3.4; and
- Consideration and selection of the modelling scope in §5.3.5.

The steps of the outbreak modelling selection are documented according to the steps in Table 5.1.

5.3.1 Step 1: Select modelling rationale

The relationships analysed in Chapter 4 between the modelling rationale and the overall modelling framework steps are illustrated in Figure E.1.The first and most important step of the modelling contextualisation is the selection of the rationale of the modelling approach. Setting the rationale (i.e. modelling goal) of the modelling application as part of the modelling contextualisation will guide the modelling process and aid in identifying and incorporating relevant outbreak modelling considerations. The set of potential modelling rationales that can be selected (previously formalised in §3.3.4) are reproduced below, namely:

- Model disease transmission dynamics;
- Investigate causal relationships;
- Investigate super spreading events;
- Forecast disease instance;
- Develop a model and analyse behaviour; and
- Evaluate interventions.

These rationales aim to capture the guiding principles discussed in §2.3.2 and §3.1.4. Following the modelling rationale selection (which is noted in Table 5.3), the strength of the relationships to a select number of outbreak modelling considerations are produced in Table 5.5. The strength of the relationships are characterised according to the following guidelines, namely:

- **Strong**, the modelling consideration has a significant relevance in the context of the selected modelling rationale;
- **Potentially**, the modelling consideration is typically included in the context of the selected modelling rationale, however, the inclusion thereof is not a set requirement; and

- **Context**, the context of the modelling application will determine the potential inclusion of the modelling consideration (i.e. the modelling consideration is not explicitly related to the modelling rationale).

As mentioned previously, more than one modelling rationale may be selected for a modelling approach. The above mentioned guidelines serve as prompts to inform the potential relevance of modelling considerations of Step 2 and Step 3 in the context of the selected modelling rationale. For each rationale, the modeller may choose to incorporate or leave out modelling considerations depending on the context-specific requirements of the modelling application.

Table 5.5: Relevance of the selection of the modelling rationale on the outbreak modelling contextualisation steps.

Selected modelling rationale	**Interventions (i.e. Step 2)**	**Contextual factors (i.e. Step 3)**	**Mixing patterns (i.e. Step 3)**
Model disease dynamics	Potentially	Potentially	Potentially
Investigate causal relationships	Context	Strong	Context
Investigate super spreading events	Potentially	Strong	Strong
Forecast disease instance	Context	Potentially	Potentially
Develop a model and analyse behaviour	Potentially	Context	Context
Evaluate interventions	Strong	Potentially	Potentially

5.3.2 Step 2: Contextualisation, describe disease characteristics

The relationships analysed in Chapter 4 between the disease characteristics and the overall modelling framework steps are illustrated in Figure E.2. The chain of infection (as illustrated in Figure 2.1) is used as the reference to describe the disease characteristics as illustrated in the conceptual diagram in Figure 5.3 (adapted from Figure 2.3 to only illustrate the considerations which are included in the framework construction). The disease characteristics which relate to the transmission mode, incubation period and intervention strategies are captured within this section. The captured disease transmission modes are used in the steps that follow to inform the selection of the modelling considerations.

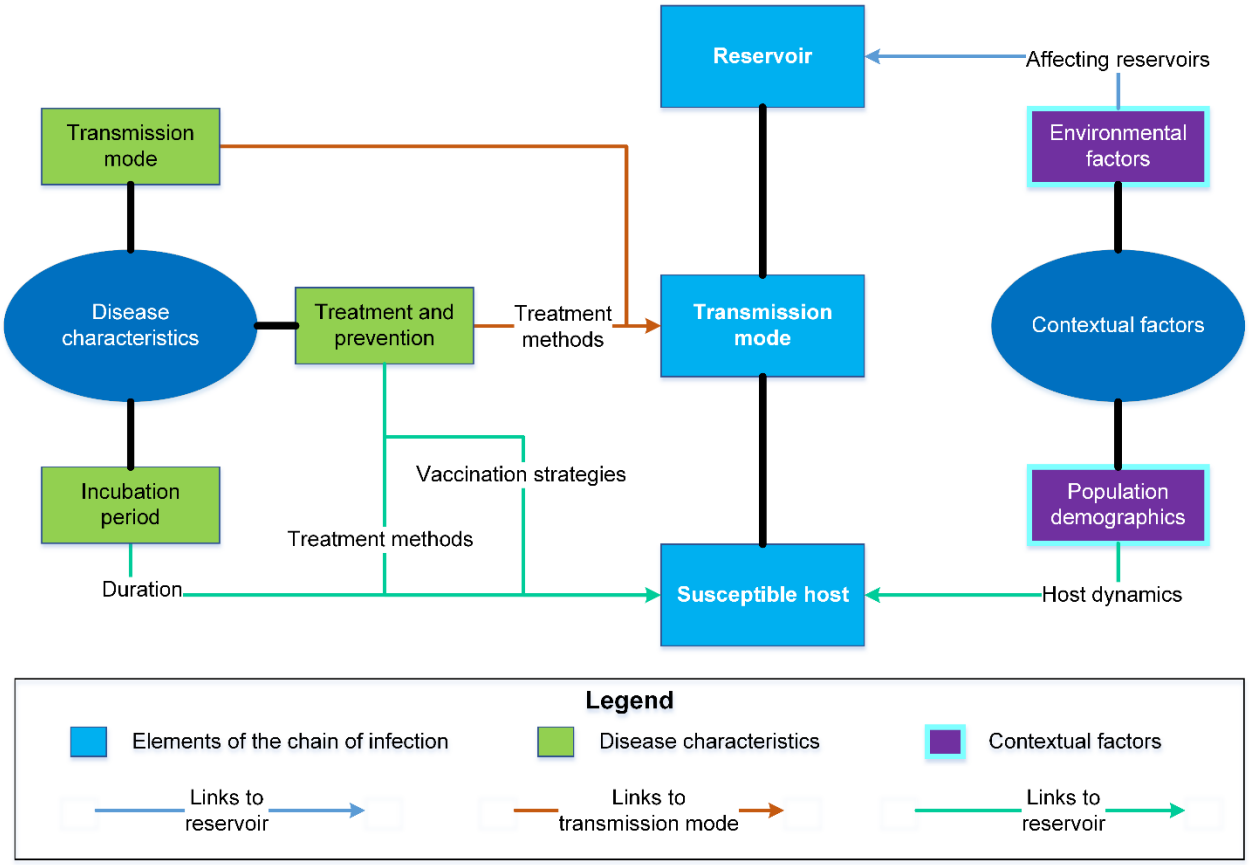

Figure 5.3: The chain of infection as linked to the disease characteristics and contextual factors.

Table 5.6: Mapping disease characteristics.

CAT		Transmission modes present (✓ / ✗)	Modelling assumptions	Additional information
Incubation period	Lower	N/A		
	Upper			
Disease transmission mode	Direct contact			
	Sexual contact			
	Respiratory			
	Body fluid			
	Food-borne			
	Water contact			
	Vector-borne			

Transmission mode

The disease characteristics which relate to the incubation period and the transmission mode are captured and described according to Table 5.6. The upper and lower duration of the incubation period is noted, which may indicate how fast a disease leads to expression of symptoms and is able to transmit between individuals. Additionally, the information on the vehicles and vectors which are responsible for disease transmission are noted according to available clinical knowledge of the disease, or retrieved from the GIDEON database (mentioned previously in §2.5). The transmission mode is then determined using Table 2.3 (described previously in §2.5.3). This is performed to ensure a consistent approach to determining the transmission mode categories. All potential disease transmission modes are then captured to Table 5.6. With the goal to capture additional information or modelling assumptions of these categories (such as the most prominent transmission mode or additional details pertaining to the transmission vehicles), columns for modelling assumptions and additional information are available.

Table 5.7: Mapping disease intervention strategies and modelling assumptions.

CAT	Accounted for (✓ / ✗)	Modelling assumptions	Additional information
Availability of vaccine			
Treatment options			

Intervention strategies

In addition to the transmission mode, the consideration of intervention strategies also forms part of the disease characteristics. This describes aspects of both the transmission mode and the susceptible host of the chain of infection as illustrated in Figure 5.3. The following data is captured and described in Table 5.7 according to available clinical knowledge of the disease, or retrieved from the GIDEON database, namely:

- **Vaccines** which are available; and
- **Treatments** which can be used.

This will give background on interventions which are typically incorporated in the context of the disease management and which may be considered for incorporation within the modelling approach.

To inform the potential relevance of the inclusion of intervention strategies when modelling a given disease, the following guidelines are used, namely:

- Potential relevance of intervention strategies in relation to the transmission mode in Table 5.15; and
- Relevance of intervention strategies in the context of the selected modelling rationale as described in Table 5.5.

Additional columns for modelling assumptions and additional information are available to capture any additional information relevant to the consideration and selection of intervention strategies in Table 5.7.

Following the considerations of this step of the framework, the inclusion or exclusion of

- treatment; and
- vaccination;

in the proposed modelling approach are noted in Table 5.3.

5.3.3 Step 3: Contextualisation, describe contextual characteristics

The relationships analysed in Chapter 4 between the contextual factors and the overall modelling framework steps are illustrated in Figure E.3. The chain of infection (as illustrated in Figure 2.1) is used as the reference to describe the contextual characteristics which relate to the disease outbreak as illustrated in Figure 5.3. The contextual factors which relate to the reservoir (i.e. typically environmental contextual factors) and the susceptible host (i.e. typically population demographic contextual factors and mixing pattern selection) are captured within this section. Following the considerations of this step of the framework, the inclusion or exclusion of:

- environmental factors;
- population demographics; and
- alternative mixing patterns;

in the proposed modelling approach are noted in Table 5.3.

Environmental factors

The environmental factors which are considered within the disease modelling approach are described and captured in Table 5.8. The suggested factors to consider include the following:

- **Seasonality** of disease dynamics;
- **Climate**, which may include rainfall and temperature; and
- **Additional factors**, which are determined at the discretion of the modeller.

To inform the potential relevance of the inclusion of environmental contextual factors when modelling a given disease, the following guidelines are used, namely:

- Potential relevance of environmental factors in relation to the transmission mode in Table 5.16; and
- Relevance of contextual factors in the context of the modelling rationale as described in Table 5.5.

During the process of describing the environmental factors in increased detail, additional columns for modelling assumptions and additional information are available to capture any additional information relevant to the considered factors in Table 5.8.

Population demographics

The population demographic factors which are considered within the disease modelling approach are described and captured in Table 5.9. The suggested factors to consider include the following:

- **Population structure**, which relates to the age structure of the population;
- **Spatial spread**, how the population is dispersed geographically;
- **Mixing and migration** of the population, directly affecting the manner in which individuals move, interact and create potential contacts which may facilitate disease transmission;
- **Socio-economic** profile, which may indirectly affect the susceptibility of individuals; and
- **Additional factors**, which are determined at the discretion of the modeller.

To inform the potential relevance of the inclusion of population demographic contextual factors when modelling a given disease, the following guidelines are used, namely:

- Potential relevance of population demographic factors in relation to the transmission mode in Table 5.16; and
- Relevance of contextual factors in the context of the modelling rationale as described in Table 5.5.

During the process of describing the population demographics factors in increased detail, additional columns for modelling assumptions and additional information are available to capture any additional information relevant to the considered factors in Table 5.9.

Mixing pattern selection

In addition to the population demographics, the mixing pattern consideration is also part of the ‘mixing and migration’ population demographic factor. The default mixing pattern in modelling approaches is homogenous mixing of contacts.

To inform the potential relevance of the inclusion of alternative mixing patterns when modelling a given disease, the following guidelines are used, namely:

- Transmission mode in Table 5.14; and

- Relevance of alternative mixing patterns in the context of the modelling rationale as described in Table 5.5.

Any additional detail regarding the mixing assumptions or considerations of the population are subsequently captured to the 'mixing and migration' row of Table 5.9.

Table 5.8: Mapping environmental contextual factors.

CAT	Accounted for (✓ / ✗)	Modelling assumptions	Additional information
Seasonality			
Climatic factors			
Additional factors			

Table 5.9: Mapping population demographic contextual factors.

CAT	Accounted for (✓ / ✗)	Modelling assumptions	Additional information
Age structure			
Spatial spread			
Mixing			
Migration			
Socio-economic			
Additional factors			

5.3.4 Step 4: Requirements, determine available resources

The relationships analysed in Chapter 4 between the data source and the overall modelling framework steps are illustrated in Figure E.4. Following the contextualisation of the chain of infection of the outbreak, the next contextualisation step is describing the available data sources in Table 5.10. The data source categories typically employed in modelling approaches (previously formalised in §3.3.4) are reproduced below:

- Case data;
- Parameters from literature;
- Population estimates;

- Travel data;
- Assumed; and
- None.

The data source does not necessarily imply or limit modelling considerations such as the modelling scope, modelling approach or incorporation of mixing patterns, but merely the resolution at which the disease outbreak may be described within the population. For instance, some data source categories may describe contextual factors such as population age structure or climate data on a country level, whereas other data sources relate to clinical instances of the disease on a provincial level. In order to better describe and capture the use of the data source, additional columns for modelling assumptions and additional information are available to capture any additional information relevant to the data source in Table 5.10.

Table 5.10: Mapping quality and source of data.

CAT	Data source used (✓ / ✗)	Modelling assumptions	Additional information
Case data			
Parameters from literature			
Population estimates			
Travel data			
Assumed			
None			

Previous modelling applications

Another resource apart from data which may prove useful is the availability of previous modelling applications. This may serve as a starting point for the current modelling application or enable the use of a previous modelling application following small extensions and alterations of the model. This would be context-specific for each modelling application and require sufficient research of the modelling literature. This would ideally be used to guide the selection and mapping of disease characteristics within the following phase. It is not possible to generalise this aspect of the resources available to the modeller, nonetheless, it is useful to take note of the option of considering previous modelling applications with a view to inform the current modelling application.

5.3.5 Step 5: Select modelling scope

The relationships analysed in Chapter 4 between the modelling scope and the overall modelling framework steps are illustrated in Figure E.5. Although the modelling scope selection is presented as part of the outbreak contextualisation phase, the selection of the modelling scope is also viewed as a one of the outbreak modelling selection steps. The options for selecting the scope of the modelling application (previously formalised in § 3.3.4) are the following:

- General;
- Global;
- Intercountry;
- Country;
- Provincial; and
- Small region.

The modelling scope selection relates to the resolution of the area which the modelling application should model. To aid the modeller in the selection of the modelling scope, the selections of the following modelling considerations are used in Table 5.11:

- Modelling rationale (captured in Table 5.3);
- Transmission mode (captured in Table 5.6) ; and
- Data source (captured in Table 5.10).

The aforementioned three categories (completed as part of the outbreak contextualisation) guide and recommend the selection of the modelling scope in Table 5.11. The selection of the modelling scope does not, however, relate solely to these three modelling considerations and the modeller has the freedom to select a different modelling scope regardless of the recommendations, should this be a modelling application requirement. In short, any modelling scope requirement is selectable, as long as the modelling approach and the data source are implemented so as to realistically and verifiably model the selected modelling scope. Following the considerations and recommendations, the modelling scope selection is noted in Table 5.4.

Table 5.11: Scope consideration and selection guidance within the framework.

CAT	Effect on incorporation		Modelling scope					
			General	Global	Intercountry	Country	Provincial	Small region
General observation	Scope most frequently observed:		✓			✓		
Modelling rationale	Most modelling scopes are used and suitable in the context of all modelling rationales, however, the three modelling scopes which are most frequently employed for each modelling rationale are:	Investigate causal relationships			✓		✓	✓
		Model disease transmission dynamics	✓			✓		✓
		Develop a model and analyse behaviour	✓	✓				✓
		Forecast disease instance				✓	✓	✓
		Evaluate interventions	✓	✓		✓		
		Investigate super spreading events				✓	✓	✓
Transmission mode	The most diverse modelling scope is applied to respiratory transmission modes, followed by direct contact and water contact transmission modes. Frequently observed modelling scopes in relation to the transmission mode are:	Direct contact	✓	✓	✓	✓		
		Sexual contact	✓			✓		
		Respiratory	✓	✓	✓		✓	✓
		Body fluid	✓		✓	✓		
		Food-borne	✓					✓
		Water contact	✓			✓	✓	
		Vector-borne	✓				✓	✓
Data source	Not all data sources are observed in the context of the modelling scope. The recommended scope for each data source category is:	Case data		✓	✓	✓	✓	✓
		Parameters from literature	✓			✓	✓	✓
		Population estimates		✓	✓	✓		
		Travel data		✓	✓	✓		
		Assumed	✓			✓		
		None	✓					

5.4 Outbreak modelling selection

Following the description of the background information (i.e. outbreak contextualisation) of the disease outbreak, the next phase of the framework entails the steps in the outbreak modelling selection phase. The steps which form part of the outbreak modelling contextualisation are as follows:

- Modelling approach selection in §5.4.1;
- Mixing pattern selection in §5.4.2;
- Selection of interventions strategies in §5.4.3;
- Selection of contextual factors in §5.4.4; and
- Model validation in §5.4.5.

The steps of the outbreak modelling selection are documented according to the steps in Table 5.2. Not all steps of the outbreak modelling selection phase are necessarily required within all modelling applications. It is worth noting that the steps of the outbreak modelling selection phase that should always be included are the selection of a modelling approach (i.e. Step 6), model validation (i.e. Step 10) and documentation of the modelling process (i.e. Step 0). The inclusion of the remaining steps described in §5.4.2, §5.4.3, and §5.4.4 relate to the context-specific modelling goals, in addition to the following:

- Resources (§5.3.4); and
- Context-specific choices of the modeller.

In conclusion, the selections within the outbreak modelling selection phase of the framework depend on the interaction of numerous factors that are not necessarily generalisable to a single factor. Based on the suggestions of this section, however, the modeller may select the steps for inclusion based on the context and the modelling requirements.

5.4.1 Step 6: Select modelling approach

The modelling approach selection is the first step of the outbreak modelling phase. In the framework, three broad modelling approach categories are available for selection, namely:

- Mathematical;
- Network; and
- Simulation.

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Table 5.12: Modelling approach consideration and selection guidance within the framework.

CAT	Effect on decision		Modelling approach categories		
			Mathematical	**Network**	**Simulation**
Methods observed most frequently	Numerous modelling approaches exist for the three categories, however, the following approaches are observed the most frequently:		DE Regression	Small world Metapopulation	ABS
Modelling rationale	All three modelling approaches are used and suitable in the context of all modelling rationales, however, the modelling approach which is used the most frequently per modelling approach category is:	Investigate causal relationships	✓		
		Model disease transmission dynamics			✓
		Develop a model and analyse behaviour		✓	
		Forecast disease instance	✓		
		Evaluate interventions			✓
		Investigate super spreading events			✓
Transmission mode	All three modelling approaches are used and suitable in the context of all transmission modes, however, the modelling approach(es) which are used the most frequently per transmission mode category are:	Direct contact		✓	✓
		Sexual contact	✓		
		Respiratory		✓	✓
		Body fluid		✓	✓
		Food-borne	✓		
		Water contact	✓		
		Vector-borne	✓		
Data source	All three modelling approaches are used and suitable in the context of all types of data sources, however, the modelling approaches which are used the most frequently per data source category are:	Case data			✓
		Parameters from literature	✓		
		Population estimates			✓
		Travel data		✓	
		Assumed		✓	
		None			✓
Modelling scope	All three modelling approaches are used and suitable in the context of all modelling scopes, however, when selecting a modelling approach, the modelling approach which is most frequently used for a given scope is:	General	✓		
		Global		✓	
		Intercountry		✓	
		Country	✓	✓	✓
		Provincial		✓	✓
		Small region			✓

Table 5.13: Compartmental classification consideration and selection guidance within the framework.

CAT	Effect on decision		Transmission mode						
			Direct contact	**Sexual contact**	**Respiratory**	**Body fluid**	**Food-borne**	**Water contact**	**Vector-borne**
Compartmental categories in relation to the transmission mode	Modelling delay or exposure to disease	E	✓		✓	✓			✓
	Isolation from population	Q	✓		✓	✓			
	Prevent transmission with safe burial	F	✓			✓			
	Dependant on availability of (theoretical) vaccine	V	✓	✓	✓	✓		✓	
	Water-bodies are studied in relation to human populations	B W						✓	
	Mosquito populations are studied in relation to human populations	M							✓
General observation	It is not possible to recommend incorporation of compartmental classification based solely on the disease characteristics or contextual factors. Furthermore, all three broad modelling approaches are suitable to incorporate compartmental classification.								

To aid in the modeller in the selection of a modelling approach category, the previous selections of the following modelling considerations are used in Table 5.12 to gather modelling suggestions, namely:

- Modelling rationale (captured in Table 5.3);
- Transmission mode (captured in Table 5.6);
- Data source (captured in Table 5.10); and
- Modelling scope (selected in Step 5).

Similar to the section in which the modelling scope selection is described, the modeller has the freedom to select any modelling approach regardless of the recommendations, especially if a particular modelling approach is a requirement.

Following the considerations and recommendations of this modelling step, the modelling approach selection is noted in Table 5.4.

Select compartmental classification

The choice of incorporating compartmental classification of individuals is an additional step of the modelling approach selection. It is not possible to generalise the inclusion of compartmental classification, however, recommendations on the selection of disease states are produced in Table 5.13 in the context of the transmission mode of the disease. It is worth noting that some intervention strategies such as vaccination, quarantine and hospitalisation (discussed in more detail in §5.4.3) are occasionally incorporated as part of the compartmental classification.

Following the considerations and recommendations, if compartmental classification is incorporated, the selected compartmental categories are noted in Table 5.4.

5.4.2 Step 7: Select mixing pattern(s)

Depending on the mapping completed relating to the contextualisation steps, the inclusion of alternative mixing patterns may form part of the outbreak modelling phase. The default mixing pattern in modelling approaches is homogenous mixing of contacts. Although alternative mixing patterns reflect the interactions between contacts more realistically, it is more difficult to incorporate these mixing patterns in modelling applications.

The selection in Table 5.3 which relates to the incorporation of alternative mixing patterns is used to guide the mixing pattern selection. If alternative mixing patterns are not deemed necessary at this stage of the modelling application, the default mixing pattern of homogeneous mixing is selected. If alternative mixing patterns are required, the previous selections of the following modelling considerations are used in Table 5.14 to gather modelling suggestions, namely:

- Transmission mode (captured in Table 5.6);

- Modelling scope (selected in Step 5);
- Population demographics (captured in Table 5.9); and
- Modelling approach (selected in Step 6).

It is worth noting that the following population demographic factors play an important role in mixing patterns:

- Age distribution and age related susceptibility;
- Population density; and
- Spatial spread of contacts.

If additional detail is required at this stage of the modelling process, the modeller may amend the details of the population demographics (Table 5.9) or the data source (Table 5.10) in order to realistically incorporate the alternative mixing patterns.

Following the considerations and recommendations, the mixing pattern selection is noted in Table 5.4.

5.4.3 Step 8: Select intervention strategies

Depending on the mapping completed relating to the contextualisation steps, intervention strategies may form part of the outbreak modelling phase. These intervention strategies relate to treatment or vaccination of individuals. The selection in Table 5.3 which relates to the inclusion of treatment and vaccination are used to guide the inclusion of treatment and vaccination strategies, respectively. If intervention strategies are required, the previous selections of the following modelling considerations are used in in Table 5.15 to gather modelling suggestions, namely:

- Recommended strategies in relation to the transmission mode (captured in Table 5.6);
- Data source (captured in Table 5.10); and
- Modelling approach (selected in Step 6).

Treatment strategies

The transmission modes captured in Table 5.6 are used to find potentially appropriate treatment methods in Table 5.15. It is useful to note that the most frequently modelled treatment strategies relate to the reduction of contact between individuals (i.e. quarantine and hospitalisation). Similarly to previous modelling considerations, the modeller has the freedom to select different or additional treatment strategies regardless of the recommendations if these are a modelling requirement and the strategies are modelled realistically.

Following the considerations and recommendations, the treatment strategy inclusion and selection is noted in Table 5.4.

Table 5.14: Alternative mixing pattern consideration and selection guidance within the framework.

CAT	Effect on decision		Mixing incorporated	Occurrence of inclusion
Mixing methods observed most frequently	Of alternative mixing patterns included in modelling approaches, age and social mixing are the most frequently modelled. WAIFW matrices to model probability of disease transmission between different age groups or compartmental groups are also utilised to model alternative mixing patterns		N/A	
Transmission mode	When considering the inclusion of alternative mixing patterns in relation to the transmission mode, the following recommendations are made:	Direct contact	✓	High
		Sexual contact		N/A
		Respiratory	✓	High
		Body fluid	✓	High
		Food-borne		N/A
		Water contact	✓	Moderate
		Vector-borne	✓	Moderate
Modelling scope	Alternative mixing patterns are applied in the context of all modelling scopes, however, not all modelling scopes have equal proportions of inclusion of alternative mixing patterns. The occurrence of alternative mixing patterns in the context of the modelling scope guide the following recommendations:	General	✓	High
		Global	✓	Moderate
		Intercountry	✓	Moderate
		Country	✓	High
		Provincial	✓	Moderate
		Small region	✓	Very high
Population demographics	The following population demographic contextual factors are typically present in modelling approaches when alternative mixing patterns are included in the modelling approach:	Age and spatial spread Potentially population density	N/A	N/A
Modelling approach	Alternative mixing patterns are included in all three modelling approaches, however, based on the most frequent inclusion of age and social mixing in the context of the modelling approach, the following modelling approaches are recommended for usage of alternative mixing patterns:	Mathematical	✓	N/A
		Network		
		Simulation	✓	

Table 5.15: Intervention strategy consideration and selection guidance within the framework.

CAT	Effect on decision		Treatment	Vaccination
Potential relevance of intervention strategies in relation to the transmission mode	When considering the inclusion of intervention strategies, the relevance of the treatment and intervention strategies in relation to the transmission mode are:	Direct contact	High	High
		Sexual contact	High	High
		Respiratory	High	High
		Body fluid	High	High
		Food-borne	Moderate	Low
		Water contact	Moderate	High
		Vector-borne	Low	Low
Intervention strategies in relation to the transmission mode: Recommended strategies	The intervention strategies which are observed the most frequently in relation to the transmission mode are:	Direct contact	Quarantine Hospitalisation	A proportion of susceptible Ring
		Sexual contact	Quarantine	A proportion of susceptible
		Respiratory	Quarantine Hospitalisation	A proportion of susceptible Ring
		Body fluid	Quarantine Hospitalisation	A proportion of susceptible Ring
		Food-borne	Disinfection	N/A
		Water contact	Disinfection Drug usage	A proportion of susceptible
		Vector-borne	Drug usage	N/A
Data source	All six data sources are suitable in the context of intervention strategies, and the data source is not expected to play a role in the inclusion of intervention strategies. However, the ‘case data’ and ‘parameters from the literature’ data sources are observed in the highest proportion of modelling approaches which include treatment and vaccination strategies.			
Modelling approach	All three modelling approaches are suitable in the context of intervention strategy inclusion and the selection of a modelling approach is not expected to play a role in the inclusion of intervention strategies.			

Vaccination strategies

The transmission modes captured in Table 5.6 are used to find vaccination strategies relevant to the transmission modes in Table 5.15. It is useful to note that the most frequently incorporated vaccination strategies are ring vaccination and a general vaccination of a portion of the susceptible population. Additional vaccination strategies which are also available for incorporation are summarised in Table 2.2. Similarly to previous modelling considerations, the modeller has the freedom to select different or additional vaccination strategies regardless of the recommendations if this is a modelling requirement and the strategies are modelled realistically.

Following the considerations and recommendations, the vaccination strategy inclusion and selection is noted in Table 5.4.

5.4.4 Step 9: Select contextual factors

Depending on the decisions captured as part of the modelling contextualisation phase, contextual factors may form part of the outbreak modelling selection phase. These contextual factors relate to environmental or population demographic factors. The selection in Table 5.3 which relates to the inclusion of environmental contextual factors and demographics is used to guide the inclusion of environmental and population demographic factors, respectively. If contextual factors are required, the previous selections of the following modelling considerations are used in Table 5.16 to gather modelling suggestions, namely:

- Recommended environmental factors in relation to the transmission mode (captured in Table 5.6);
- Recommended population demographic factors in relation to the transmission mode (captured in Table 5.6); and
- Data source (captured in Table 5.10).

Environmental factors

The transmission modes captured in Table 5.6 are used to find potentially relevant environmental contextual factors in relation to the transmission modes in Table 5.16. Similarly to previous modelling considerations, the modeller has the freedom to include or model different or additional environmental factors regardless of the recommendations if this is a modelling application requirement and it is modelled realistically.

Following the considerations and recommendations, the environmental factor inclusion and selection is noted in Table 5.4.

Table 5.16: Contextual factor consideration and selection guidance within the framework.

CAT	Effect on decision		Contextual factors	
			Linked to disease propagation	**Modelled**
Potential relevance of environmental factors in relation to the transmission mode	When considering the inclusion of environmental contextual factors, the relevance to the transmission mode are:	Direct contact	Low	
		Sexual contact	Low	
		Respiratory	Moderate	
		Body fluid	High	
		Food-borne	High	
		Water contact	High	
		Vector-borne	Very high	
Environmental factors in relation to the transmission mode: Recommended factors to consider	The environmental contextual factors which are observed the most frequently in relation to the transmission mode are:	Direct contact	N/A	Seasonality
		Sexual contact	N/A	
		Respiratory	Climate & seasonality & rainfall	Seasonality
		Body fluid	N/A	Seasonality
		Food-borne	Climate & rainfall	
		Water contact	Climate & temperature & rainfall	
		Vector-borne	Climate & temperature & rainfall	
Potential relevance of demographic factors in relation to the transmission mode	When considering the inclusion of population demographic contextual factors, the relevance of the to the transmission mode are:	Direct contact	Very high	
		Sexual contact	Low	
		Respiratory	Very high	
		Body fluid	High	
		Food-borne	Moderate	
		Water contact	Very high	
		Vector-borne	Moderate	
Population demographic factors in relation to the transmission mode: Recommended factors to consider	The population demographic contextual factors which are observed the most frequently in relation to the transmission mode are:	Direct contact	Age & population density & migration & spatial spread	
		Sexual contact	N/A	
		Respiratory	Age & population density & migration & spatial spread	
		Body fluid	Age & population density & migration & spatial spread	
		Food-borne	Spatial spread & socio economic	
		Water contact	Spatial spread & socio economic	
		Vector-borne	Spatial spread & socio economic	Age & spatial spread
Data source	The only two data sources which were used in the context of all contextual factors were case data and parameters from the literature. Population estimates and travel data are only used in the context of population demographic factors.			

Population demographic factors

The transmission modes captured in Table 5.6 are used to find potentially relevant population demographic contextual factors in relation to the transmission modes in Table 5.16. Similarly to previous modelling considerations, the modeller has the freedom to include or model different or additional population demographic factors regardless of the recommendations if it is a modelling application requirement and is modelled realistically. It is useful to note that the most frequently included demographic factors are the spatial spread of individuals, population density, migration and age stratification of individuals within the population.

Following the considerations, the population demographic factor inclusion and selection is noted in Table 5.4.

5.4.5 Step 10: Validate model

Following the modelling application selection and implementation, the model is validated to ensure that the modelling application and modelling results accurately reflect the disease outbreak. The challenges when developing models previously mentioned in (§2.3.5) are formulated as questions to guide the validation process:

- Does the model answer the research question (i.e. modelling rationale and modelling goals)?
- Is the model comprehensible (i.e. ability to analyse and examine the model)?
- Is the model believable (i.e. an accurate reflection of reality)?
- Does the model fit the data (i.e. verify the model operation)?

As mentioned previously in §D.18.4, it is not possible to generalise the methods used to fit the modelling data to a modelling application. This does not reduce the importance of fitting the data to a model or the validation thereof, but the selection of a fitting method is left to the discretion of the modeller. A checklist is available for use in Table 5.4 to ensure the validation questions are considered as part of the validation, in addition to noting the selection of a fitting method.

5.5 Omissions from the framework

A selection of notable omissions from the framework, in addition to a brief reason for each of the omissions are presented in Table 5.17.

Table 5.17: Summary of major omissions to the framework.

Omitted factor	Section omitted from	Section first mentioned	Reason for omission
Risk factors	§5.3.2	§2.1.4	This omission does not reduce the importance of determining the risk factors in the context of disease propagation, however, it is not possible to generalise the quantification of disease risk factors in relation to the disease characteristics and contextual factors and the potential effect on disease propagation.
Disease agent	§5.3.2	§2.1.5	A characterisation of the disease agent is not a key requirement of the disease characteristics which affect modelling considerations, as the immunological modelling perspective (§2.3.1) is not adopted in the research.
Distinction of disease status	§5.3.2	§3.1.1	Although this is an important consideration of a disease outbreak, it is not possible to generalise suggestions based on the disease status (i.e. endemic or epidemic) classification.
Human factors	§5.3.3	§2.4	As mentioned in §2.4, it is not possible to generalise human activities such as deforestation or mining activities on a macro scale and realistically link the effect thereof to population-level disease dynamics.
Modelling parameters	§5.4.1	§2.3.3	This omission does not reduce the importance of the calculation of these parameters. As the literature on the incorporation and calculation of these parameters is already well established, it is deemed superfluous to analyse and determine the relationships of these modelling parameters to the modelling considerations and contextual factors.

5.6 Conclusion

A summary of the content of this chapter in relation to the overall document structure is illustrated in Figure 5.4. A preamble to the framework construction and design is presented in §5.1, followed by a description of the documentation steps of the framework in §5.2 which runs concurrently through each of the steps of the framework. The framework consists of two main phases, the first phase relates to the contextualisation of the disease characteristics, outbreak context and modelling goals in §5.3, whereas the second phase relates to the selection of various modelling considerations in §5.4. The steps of the modelling contextualisation and selection are captured according to various summary tables, with additional tables which suggest modelling approach selection and modelling

consideration incorporation based on the disease characteristics and the context of the disease outbreak. The main omissions from the framework are highlighted briefly in §5.5.

Modelling a disease outbreak is a challenging endeavour with numerous factors that need to be considered. The described modelling framework in this chapter formalises the most important modelling considerations and decisions logically, as an integrated process between the contextualisation of the disease outbreak and the modelling application selection.

The utilisation of disease characteristics to guide the modelling process, in addition to a selection of contextual factors which may potentially affect disease transmission is a novel approach to solve the problem of suggesting modelling approaches and considerations in the context of a disease outbreak.

It is not always possible to generalise modelling considerations and suggestions. Additionally, it seems that some considerations may be selected regardless of the context and characteristics of the disease outbreak. This is still a relevant answer and advances the literature, as the steps of the modelling process are formalised and the relevant relationships between the modelling considerations are analysed and used to construct the framework. Additionally, a novel support system is proposed to capture the relevant considerations required to contextualise a disease outbreak, in addition to suggesting the most relevant modelling considerations in the context of a disease outbreak.

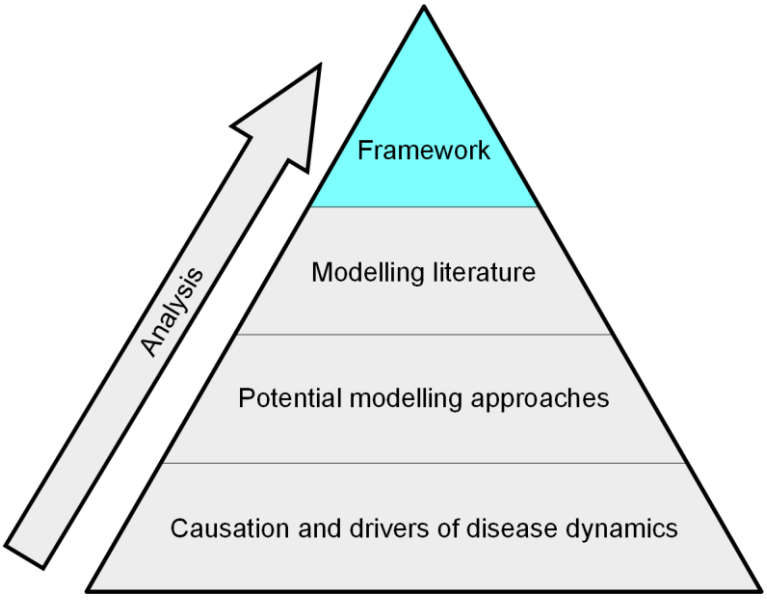

Figure 5.4: A visual summary of the content of Chapter 5.

Chapter 6 Validation

The validation strategy is designed, executed and the results thereof are discussed within this chapter. A thorough validation is necessary to state with certainty that the framework is suitable for the intended use and functions properly. The validation strategy encompasses the use of an illustrative case study combined with feedback from SMEs via semi-structured interviews.

The design considerations according to which the case study is constructed are reviewed in §6.1. The case study is then used to guide the reader through a typical application of the framework in §6.2. The approach followed as part of the SME validation process is discussed in §6.3. The results, concerns and feedback suggestions from the SMEs (as discussed in detail in §6.4) are used to guide some of the amendments and adjustments to the framework. These adjustments are made to the validation document as presented to the SMEs and are discussed in §6.5, prior to the chapter conclusion in §6.6.

6.1 Construction and design of case study

As mentioned in the introduction to this chapter, a case study is used to illustrate the typical application and use of the framework.

The application of the framework is not applied in the context of a real-life outbreak nor applied with the consideration and use of outbreak data. It is not practical to complete and implement a modelling application to verify the ability of the framework in supporting the modelling process. Furthermore, it is not advisable to perform an additional structured review on the literature in the context of one disease outbreak and validate the framework operation against the results thereof. This approach does not account for the context of the disease outbreak nor the decisions which influenced the selection of modelling considerations, which is one of the key functions of the framework.

As an alternative, an illustrative case study is used to show how a user would use the framework to assist the modelling process.

The scope of the case is limited to a narrow application of the framework. One potential concern is whether it is appropriate to use a case study with such a limited focus and theoretical application of the framework, however, case studies are often used and appropriate in situations in which a smaller selection of the whole is analysed in increased detail (Welman et al. 2005c).

The considerations which form part of the case study design process are briefly reviewed in §6.1.1. The context of the selected disease outbreak used in the case study is briefly reviewed in §6.1.2, followed in §6.1.3 with a description of the case study details as presented to the SMEs.

6.1.1 Case study design considerations

The use of case studies are appropriate for situations which do not require control of behavioural events (such as the requirement with experiments), circumstances where research questions are of the 'how' or 'why' format and situations which are concerned with contemporary (i.e. present-day) events (Yin 2014b). Five components of the research design are of importance in the design of a case study, namely (Yin 2014a):

- **Case study questions**, this concerns 'how' and 'why' questions related to the research;
- **Case study propositions**, which direct attention to a part of the scope of the study examined in the case study;
- **Unit(s) of analysis**, which relates to defining and bounding the case, in consideration of the research question;
- **Linking the data to the propositions**, this concerns the data analysis steps in the case study; and
- **Criteria for interpreting the findings**, which are specifically important if statistical analysis techniques are used for evaluation of the findings.

The first three components are particularly relevant in the design of the illustrative case study in this research project. In additional to the research design, the following four design tests are used to determine the suitability of the case research design (Welman et al. 2005a; Yin 2014a):

- **Construction validity**, concerns creating an accurate representation of the concepts in the study;
- **Internal validity**, this test is only relevant to explanatory or causal case studies, not to descriptive or exploratory studies;
- **External validity**, this test relates to the field which the study findings are generalised to and whether the findings are generalisable beyond the immediate study; and
- **Reliability**, which relates to whether a different person will arrive at the same conclusions when using the same procedural analysis.

With specific reference to the reliability test, the intention of the framework use is not that different users would select the exact same modelling approach or considerations when modelling an outbreak. Instead, the framework seeks to ensure that, regardless of whom is using the framework, that:

(i) All of the potentially relevant modelling considerations are at least considered for inclusion;

(ii) The process of selecting an appropriate modelling approach and deciding which considerations to include is executed in a consistent manner; and

(iii) The process of selecting an appropriate modelling approach and deciding which considerations to include is documented in a structured and consistent manner.

With regards to case selection, a paradigmatic case (i.e. the development of a metaphor for the domain of the case (Flyvbjerg 2006)) is selected. As the selection of modelling considerations are context-dependant, the following case types are considered not appropriate to demonstrate the framework:

- **Extreme** or **deviant cases**, typically used to obtain information with unusual cases;
- **Maximum variation case**, typically used to obtain information on the significance of circumstantially different cases; and
- **Critical cases**, typically used to achieve information which permits rigid logical deductions (i.e. hard and fast rules).

As an alternative to the aforementioned mentioned cases, the following case types are used to guide the case study design, namely (Baxter & Jack 2008):

- **Exploratory**, when the case study is used to analyse events with no particularly clear, single set of outcomes;
- **Descriptive**, when an event or phenomenon is described in the context of the real-life occurrence; and
- **Instrumental**, when the case study is of secondary interest and is used to gain insight into a problem or aid in refinement of a theory.

The aforementioned guidelines and considerations are used to guide the case study design process with a view to explore and describe the intended use of the framework. In some instances, two case studies are recommended for validation purposes (Flyvbjerg 2006). However, a single case is considered sufficient for the purpose of this validation process. An outbreak of one disease which occurs in two different geographic areas may have vastly different contextual factors which influence the modelling process, but the process of selecting an appropriate modelling approach and contextual considerations (as well as the documentation of this process) should not differ between the two outbreaks. Hence the use of an additional case study does not necessarily achieve the goal of uncovering additional insights.

6.1.2 Selection of disease outbreak for case study

An outbreak of Zika is selected as the subject of the case study. As illustrated in Figure 1.2, the relatively recent outbreak of the Zika virus strained the global health care system. The outbreak is estimated to have started in Brazil in 2015 and to date 86 countries reported vector-borne (i.e. mosquito) transmission of Zika (Goswami et al. 2018; WHO 2018). Furthermore, neurological complications are associated with Zika infection in adults and Zika infection during pregnancy contributes to various congenital disorders (i.e. a medical condition with an onset before birth).

Even though the number of new transmissions of Zika is currently not as pronounced as during the peak of the outbreak, travellers and especially pregnant couples are still advised to take precautions

when travelling to areas with known Zika prevalence (Sifferlin 2018). Additional reasons for selecting this disease include:

- Multiple transmission routes exist for the disease;
- The disease has not been modelled extensively in the past, so there isn't a well-established protocol for modelling the disease in literature; and
- The disease purposefully does not form part of the review process as performed in Chapter 3[9].

The information extracted from the GIDEON disease database to inform some of the case study considerations is included in §G.1.

6.1.3 Illustrative case study: Outbreak info

The following hypothetical situation is constructed to demonstrate the functioning of the framework in supporting the modelling process:

A major outbreak of Zika virus is in progress in Brazil, with the virus currently being transmitted beyond the country borders. There are no prophylactic vaccines available for use and no confirmed disease treatment, apart from supportive treatment. It is suspected that multiple transmission routes exist. Furthermore, the disease has not been modelled extensively in the past. Confirmed clinical case data for large cities are available to the modelling practitioner.

The modeller is tasked with selecting a modelling approach to investigate relevant factors which may suggest the prevalence of the disease in the area. As few models of Zika in Brazil have been completed in the past, the influence of relevant factors is first considered, prior to establishing a disease transmission model.

6.2 Illustrative case study: Guided framework walkthrough

In this section, the outbreak case study information is used to illustrate a high-level walkthrough of the framework steps.

Step 0: Documentation

The documentation step of the framework runs concurrently throughout the modelling process, and the user is reminded that documentation of:

- Steps 1 – 4 is done according to the template of Table 5.3; and

[9] As the disease has not been extensively modelled in the past, excluding the disease from the structured literature review on which the framework construction has been based is unlikely to have any meaningful negative impact on the quality or applicability of the framework.

- Steps 5 – 10 is done according to the template of Table 5.4.

The completed outbreak modelling contextualisation documentation and outbreak modelling selection documentation are captured to Table 6.7 and Table 6.8, respectively and are presented at the end of the section.

Step 1: Select modelling rationale

As stated in the case study, no extensive modelling has previously been completed for the Zika virus. In the context of the modelling task, which is to investigate the drivers of disease prevalence, the 'investigate causal relationships' modelling rationale is selected and noted in Table 6.7. The potential relevance of the selection of outbreak modelling considerations in the context of the selected modelling rationale is described in Table 6.1 (this is an excerpt of only the relevant information from Table 5.5) and used in Step 2 and Step 3.

Table 6.1: Selected modelling rationale and potential relevance to the outbreak contextualisation steps.

Selected modelling rationale	**Interventions (i.e. Step 2)**	**Contextual factors (i.e. Step 3)**	**Mixing patterns (i.e. Step 3)**
Investigate causal relationships	Context	Context	Strong

Step 2: Contextualisation, describe disease characteristics

As extracted from the GIDEON database, the vectors and vehicles responsible for transmission of the Zika virus are as follows:

- Vector: mosquitoes; and
- Vehicles: sexual contact, saliva, blood transfusion, breast-feeding.

Using Table 2.3, the transmission modes are determined and noted in Table 6.2. From the literature, the incubation period is also noted. The incubation period is also noted (from literature). This is used to inform potential realistic transmission parameters.

The selected modelling rationale recommends the contextual inclusion of intervention strategies, if this is a modelling requirement. Based on the case study, no vaccines are available to use against Zika infection and no treatment other than supportive treatment is available (noted in Table 6.3). In view of the modelling goal that does not require intervention strategies in the modelling approach,

Table 5.15 and Table 2.2 are not used to extract intervention strategy recommendations and the exclusion of intervention strategies from the modelling approach is noted in Table 6.7.

Table 6.2: Captured disease characteristics.

Category		Transmission modes present (✓ / ✗)	Modelling assumptions	Additional information
Incubation period (days)	Lower	N/A	3	Symptoms typically last for 2-7 days
	Upper		14	
Disease transmission mode	Direct contact	✓	Not used in model	GIDEON vehicle breast feeding, assumed very rare
	Sexual contact	✓	Not used in model	Not a model requirement
	Respiratory			
	Body fluid	✓	Not used in model	Transfusion of blood
	Food-borne			
	Water contact			
	Vector-borne	✓		Primary transmission mode investigated

Table 6.3: Consideration of intervention strategies.

Category	Accounted for (✓ / ✗)	Modelling assumptions	Additional information
Availability of vaccine	✗		No vaccine currently available. Investigation of theoretical vaccine not currently a priority
Treatment options	✗		No current treatment available

Step 3: Contextualisation, describe contextual characteristics

Based on the selected modelling rationale, contextual characteristics are a potentially strong requirement for the modelling approach, as one of the stated modelling tasks is the investigation of factors which could explain the disease prevalence. Based on the transmission mode captured and considered in Table 6.2, the relevant factors are extracted from Table 5.16. The user may select both population demographics (noted in Table 6.5) and environmental factors (noted in Table 6.4), however, only the vector-borne transmission route is studied in this modelling approach and not the other transmission routes which relate to contact between humans (i.e. sexual contact). Only environmental factors are, therefore, included in the modelling approach and noted in Table 6.7. As more information on the disease dynamics become available, future work could include detailed incorporation of population demographic factors.

Table 6.4: Consideration of environmental factors contextual factors.

Category	Accounted for (✓ / ✗)	Modelling assumptions	Additional information
Seasonality	✓		Correlation to climatic factors?
Climatic factors	✓	Temperature and rainfall	Potential drivers of disease prevalence
Additional factors	✗		

Table 6.5: Consideration of population demographic contextual factors.

Category	Accounted for (✓ / ✗)	Modelling assumptions	Additional information
Age structure	✗		No data on age related disease prevalence. Additionally not a modelling requirement
Spatial spread	✗		Not studied in detail and not a modelling requirement
Mixing	✗		
Migration	✗		
Socio-economic	✗		
Additional factors	✗		

The selected modelling rationale recommends the inclusion of alternative mixing patterns, if this is a modelling requirement. If population demographics are studied in more detail, alternative mixing patterns could form part of the modelling approach. In this modelling application, however, alternative mixing patterns are not a modelling requirement and the exclusion thereof from the modelling approach is noted in Table 6.7.

Step 4: Requirements, determine available resources

The monthly case data of reported clinical cases are available to the modeller. This is important to note, especially considering that Zika and Dengue share similar symptoms, and the availability of monthly case data therefore enables the modeller to ensure that only Zika disease instances are considered. Furthermore, monthly climate data on rainfall is documented and the availability of this data is noted by the user. The data source considerations are noted in Table 6.6.

Table 6.6: Mapping quality and source of data.

Category	Data source used (✓ / ✗)	Modelling assumptions	Additional information
Case data	✓	Monthly data on confirmed clinical cases Monthly climate data	As the incubation period of the disease is between 3-14 days, monthly data is suitable in order to investigate the effect of climatic variables on disease prevalence
Parameters from literature	✗		
Population estimates	✗		
Travel data	✗		
Assumed	✗		
None	✗		

Step 5: Select modelling scope

The information provided in Table 5.11 is used to guide the selection of the modelling scope, based on the selected modelling rationale, transmission mode, and data source. Based on the modelling rationale selection, the recommended scopes in Table 5.11 include a country, provincial and small region scope. In relation to the transmission mode (vector-borne), the recommended scope is a

provincial or small region scope. As case data is available for the modelling approach, all modelling scopes apart from a general scope are available to select. In this context, however, the data source relates to a small region. This could be aggregated to construct a provincial model, however, the modeller selects a small region scope. This selection is noted in Table 6.8, in addition to the line of reasoning for this selection.

Step 6: Select modelling approach

The information provided in Table 5.12 is used to guide the selection of a modelling approach, based on the selected modelling rationale, modelling scope, transmission mode and data source. A mathematical approach is frequently used with the selected modelling rationale and the applicable disease transmission mode. With further considerations, the simulation approach is not practical, as actors are not modelled in the approach. A similar line of reasoning eliminates the selection of network modelling. From the various mathematical approaches, regression is selected for implementation, as this is the most suitable method to investigate the effect of the climate variables. Although it is noted that a simulation approach is frequently used in the context of the selected modelling scope, Table 5.12 states that all three modelling approaches are suited for all modelling scopes. Additionally, compartmental classification is not included, as individual disease states are not modelled. The modelling approach selection is noted in Table 6.8, in addition to the line of reasoning for this selection.

Step 7: Select mixing pattern(s)

According to Table 6.7, alternative mixing patterns of individuals are not considered in this modelling approach. Individuals are assumed to mix homogenously and the selection of homogenous mixing is noted in Table 6.8, in addition to the line of reasoning for this selection.

Step 8: Select intervention strategies

According to the selection in Table 6.7, intervention strategies are not considered in this modelling approach. Therefore, the exclusion of intervention strategies from the modelling approach is noted in Table 6.8, in addition to the line of reasoning for this exclusion.

Step 9: Select contextual factors

According to the selection in Table 6.7, only environmental contextual factors are considered for inclusion in this modelling approach. Therefore, the inclusion of environmental factors in the modelling approach is noted in Table 6.8, in addition to the line of reasoning for the selection of environmental factors and the exclusion of population demographic factors as noted in Table 6.4 and Table 6.5, respectively.

Step 10: Validate model

In this step, the modeller reviews the modelling approach according to the four questions presented in the validation category in Table 6.8. In addition to addressing these questions, the fitting method used in the modelling approach to ensure that the model is a realistic representation of the disease outbreak is noted, together with the line of reasoning for the selection of the fitting method and the results of the fitting method.

Table 6.7: Outbreak modelling contextualisation documentation.

Modelling rationale	**Selected (✓ / ✗)**	**Treatment included (✓ / ✗)**	**Vaccination included (✓ / ✗)**	**Environmental factors included (✓ / ✗)**	**Demographics included (✓ / ✗)**	**Alternative mixing patterns included (✓ / ✗)**
Model disease dynamics	✗	✗	✗	✓	✗	✗
Investigate causal relationships	✓					
Investigate super spreading events	✗					
Forecast disease instance	✗					
Develop a model and analyse behaviour	✗					
Evaluate interventions	✗					

Table 6.8: Outbreak modelling selection documentation.

Category		Selection (✓)	Methods and/or categories selected	Modelling assumptions	Additional comments
Modelling scope	General		N/A		Selection based on recommendations in relation to the transmission mode and modelling rationale. Case data may be aggregated to model on a provincial scope, however, small region is selected. Additionally, the data supports the use of this modelling scope.
	Global				
	Intercountry				
	Country				
	Provincial				
	Small region	✓			
Modelling application	Mathematical	✓	Regression	Most suited approach to investigate causal relationships	Selection based on recommendations in relation to the transmission mode and modelling rationale.
	Network				
	Simulation				
	Compartmental classification		Not used	Not used	Individual disease states are not modelled
Mixing patterns	Homogeneous	✓	Homogeneous		Detailed mixing not required
	Alternative				
Intervention and control	None	✓			
	Treatment				No treatment strategies available
	Vaccination				No vaccines available, investigation of theoretical vaccine not currently a priority
Contextual factors	None				
	Environmental	✓		Correlations between factors and prevalence	Rainfall and temperature suspected to affect disease dynamics
	Demographics				Not studied in detail
Validate model	Does the model answer research question?	✓	N/A		
	Is the model comprehensible?	✓			
	Is the model believable?	✓			
	Does the model fit the data?	✓			
	Fitting methods used:	✓	Least squares	Commonly used for this mathematical approach	Correlation: 0.8 rainfall 0.4 temperature
Future work		✓	Investigate effect of population density and migration on disease prevalence		Test theoretical vaccine to prepare for availability of newly developed vaccine

6.3 Expert validation

The expert validation strategy is described within this section. As stated in the introduction to this chapter, the framework and illustrative case study are demonstrated to various SMEs, with a view to validate the proposed framework of this research project. The considerations used for the SME selection are discussed in §6.3.1. The validation data is gathered by means of semi-structured personal interviews in which an interview guide is used. This semi-structured approach combines both strengths of structured (e.g. following a directive approach in the presentation and explanation) and unstructured (e.g. allowing for explorative research discussions) interviews (Welman et al. 2005b). An overview of the structure of the validation interview is presented in §6.3.2. The criteria used to quantify the results of the validation process are briefly discussed in §6.3.3.

6.3.1 SME selection

The SMEs are selected with consideration of their background experience in both the industrial engineering and health care modelling fields as noted in Table 6.9. The highest education level obtained and academic affiliation are also noted in Table 6.9. Due to the highly specialised nature of the topic of this research, all of the SMEs that were consulted either have a PhD or are currently enrolled for one. Individuals with a diverse academic affiliation are also selected to ensure the validity of the process.

6.3.2 Structure of validation interviews

It is important that SMEs understand the context and the focus of the research project, in order to understand the context and scope of the framework. The interviews were conducted via Skype or in person and a validation document was compiled to use as a guide in the interview. The validation document consisted of the following sections:

- **Background of the research**, to adequately contextualise the problem statement, aims and the methodology followed towards construction of the framework;
- **Presentation of the framework**, to ensure a sufficient overview of the steps of the framework is obtained;
- Use of an **illustrative case study**; to highlight the typical use of the framework in the context of a disease outbreak (as presented in §6.2); and
- **Feedback**, which consists of open and close-ended questions (discussed in more detail in §6.3.3).

The validation document as presented to the SMEs is reproduced in Appendix F.

Table 6.9: SME high-level background information.

SME REF	Engineering background	Healthcare background	Highest education level obtained	Academic affiliation
A	✓	✓	M.Eng, PhD candidate	Stellenbosch University
B	✓	✓	PhD	Stanford University
C	✓	✓	M.Eng, PhD candidate	University of Twente
D	✓	✓	M.Eng, PhD candidate	University of Twente
E	✓	✓	PhD	North-West University

Table 6.10: Close-ended validation questions.

Category	Code	Questions
Purpose	PU	The framework is able to assist modelling practitioners in the context of a disease outbreak.
Function	F1	The framework is capable of informing the user of the most relevant modelling considerations.
	F2	The framework is capable of guiding selection of modelling considerations.
	F3	The most relevant steps in the modelling process are presented in the framework.
	F4	The framework steps are clear and concise.
	F5	The framework steps are easy to follow.
Performance	P1	The framework modelling steps follow each other logically.
	P2	The contextualization of the outbreak characteristics are useful to guide the modelling process.
	P3	The framework ensures thoroughness in the modelling process.
	P4	The documentation step of the framework serves as a useful checklist for the modelling process.
	P5	The documentation step of the framework is useful to assist future modelling efforts.
	P6	I would recommend the framework use in a modelling context where a rapid response is required and there are no / few previous instances where the disease has been modelled in literature.

6.3.3 Evaluation criteria

The validation questions are formulated to validate the purpose, function and the performance of the framework. The close-ended questions used in the validation questionnaire are presented in Table 6.10, designed in light of the considerations of §6.1.1. Each question is assigned a code, to simplify the analysis of feedback in the following section. A Likert scale is used to gauge the SME responses to the various aspects of the framework. With this approach, an attitudinal response is used to determine to which degree an SME agrees or disagrees with the question, typically according to a five-point scale (Welman et al. 2005b). A typical interpretation of the Likert scale responses is noted in Table 6.11.

Table 6.11: An interpretation of the Likert scale used to gauge SME responses to the close-ended validation questions.

Likert scale	Point score, with '1' being worst and '5' being best
Disagree strongly	1
Disagree moderately	2
Indifferent	3
Agree moderately	4
Agree strongly	5

Additionally, the following open-ended questions are used in the questionnaire:

- Criticism and concerns; and
- Additional feedback or comments.

The open and close-ended questions as presented in the questionnaire template to the SMEs are reproduced in §G.2. The nature of the questions also relate to the semi-structured nature of the interviews (i.e. allowing both structured and unstructured responses), as discussed in the introduction to §6.3. The questionnaire is completed by the SMEs following the interviews.

6.4 Results and feedback from validation

The results and feedback from the validation interviews are discussed in this section. The results for the purpose, function and performance questions are discussed in §6.4.1, §6.4.2 and §6.4.3, respectively, followed with a discussion of the open-ended question feedback in §6.4.4. To keep the main thesis document as brief as possible, the validation questionnaires as completed by the SMEs are produced in §G.3. The average response to each question according to the Likert scale is presented as part of the conclusion in §6.6.

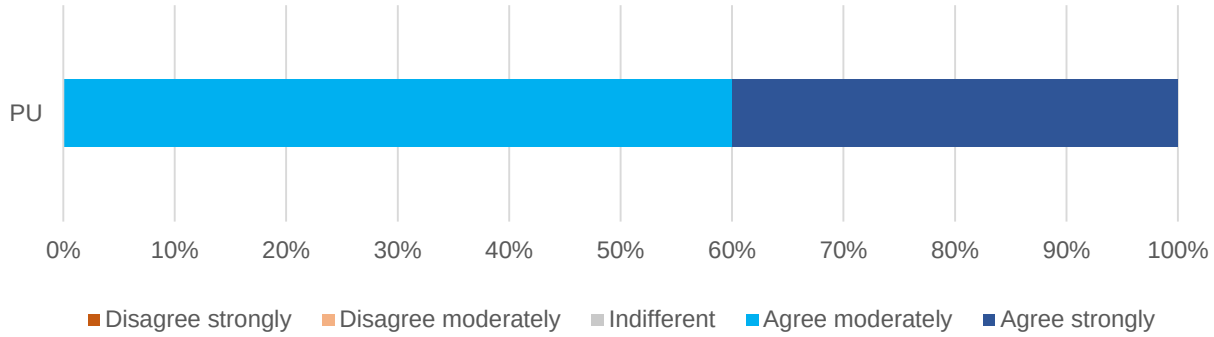

Figure 6.1: Questionnaire results for the questions pertaining to the framework purpose.

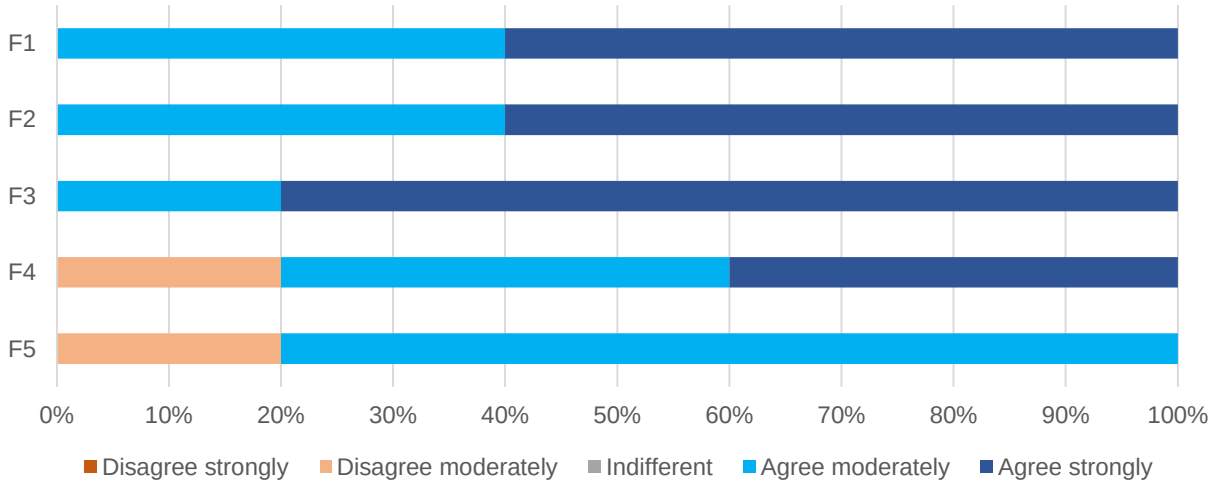

Figure 6.2: Questionnaire results for the function metric questions.

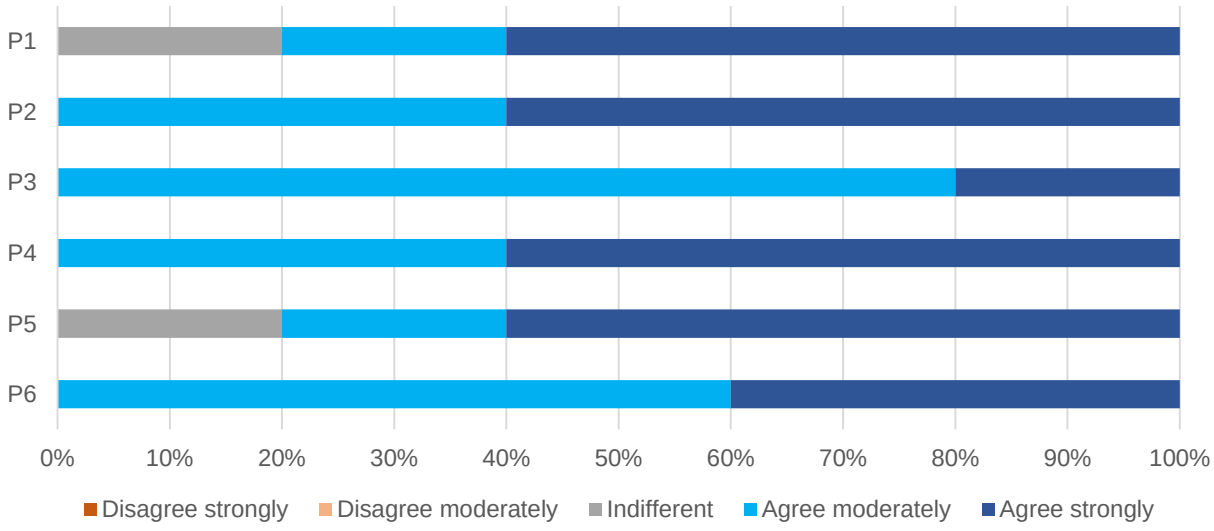

Figure 6.3: Questionnaire results for the performance metric questions.

6.4.1 Purpose

The results of the purpose question PU[10] of the framework (i.e. is the framework able to assist modelling practitioners in the context of a disease outbreak) are illustrated in Figure 6.1. The majority of the SMEs agreed moderately that the framework serves the main purpose, whilst the remainder of the SMEs agreed strongly that the framework achieves its purpose. This is a positive indication that the main goal of the framework is achieved in the research project, as no SME responded indifferently or negatively (i.e. disagree) about the purpose of the framework.[11]

6.4.2 Function

The results of the function metrics of the framework (i.e. does the framework function as intended) are illustrated in Figure 6.2. When considering the first three function questions (i.e. informing the user of relevant considerations, guiding selection of considerations and presenting the most relevant modelling steps), the majority of the SMEs agree strongly that the framework achieves the stated functions. The remaining two function questions (i.e. clarity of the steps and ease of steps) received less positive feedback from the SMEs. Both F4 and F5 had one SME which moderately disagrees with the clarity of the steps and ability of a user to follow the steps with minimal effort. Furthermore, with regards to the F5 question, which is the only close-ended question which did not have at least one SME that agrees strongly with the question, it was clear that SMEs did not always find the framework steps in the validation document easy to follow.[12] From the additional comment to F2,[13] which relates to measuring the ability of the framework in guiding consideration selection, it was clear that some experience is potentially required to properly use the framework guidance.

It is worth mentioning that, in an attempt to prevent the validation document from becoming so lengthy that SMEs may not have been able to commit the required time to read it, the framework was presented in less detail in the validation document than in the thesis document. This may have contributed to some ambiguity with regards to the framework function and execution of the steps. This concern is easily addressed by ensuring that the final stand-alone framework document (as presented in Appendix A) contains a more detailed overview of the framework steps, similar to the presentation in Chapter 5.

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[10] One SME commented that 'I agree that the modelling knowledge of a novice with suffice. However, I think some health systems knowledge (at least vocabulary will also be required),' (as indicated in Table G.5).

[11] One SME commented that it is a 'good framework for guiding a novice' (as indicated in Table G.6)

[12] One SME commented that 'the large number of tables (although very helpful) did sometimes disrupt the reading flow, making it difficult to follow' (as indicated in Table G.3). An additional comment to this question is that one SME agrees moderately with the question 'given the person has some experience, yes. For non-experience person, it may not be easy…but possible' (as indicated in Table G.6).

[13] One SME commented that 'some experience may be required, but good guidance provided' (as indicated in Table G.6).

Although the majority of the feedback is regarded as positive, it is clear that the presentation of the framework may need some adjustment to aid in the user-friendliness thereof. Considering the additional comments as mentioned in Table G.3, the development of an interactive web application could greatly assist in making the framework more user-friendly, by changing a manual selection process to a more interactive selection process. Amending the structure of the framework presentation by separating the framework tables from the framework presentation may additionally enhance the readability and clarity of the framework document for a potential user.

6.4.3 Performance

The results of the performance metrics of the framework (i.e. how well does the framework perform in support of the modelling goal) are illustrated in Figure 6.3. The P3[14] question which relates to the framework's contribution to in ensuring thoroughness in the modelling process was the question that SMEs did not agree on as strongly as the other performance questions. As mentioned in §6.4.2, this potentially resulted from the reduced detail of the framework presentation section in the validation document, as many uncertainties and ambiguities regarding the framework operation were addressed in the interviews.

Special reference is made to the P5[15] question, which concerns the usefulness of the documentation step of the framework. This is one of the proposed contributions of this research project and in light of the majority of the SMEs who agree strongly with the usefulness of the documentation approach, the attainment of this contribution is ascertained. Furthermore, all SMEs agree either moderately or strongly with the P6[16] question, which concerns recommendation of the framework for use in a novel modelling context which requires a rapid response. Additionally, one SME commented that the use of the framework may serve as a checklist for the modelling process (which indirectly relates to the documentation step which runs in parallel to all framework steps) and that the framework may therefore additionally be recommended in scenarios which do not necessarily require a rapid modelling response. The overall positive response to the performance questions of the framework, which is absent from any disagreements, confirms the appropriateness of the framework to serve as a modelling support tool in the context of an infectious disease outbreak.

[14] One SME commented that 'given the person has some experience, yes. For non-experienced person, it may not be easy…but possible' (as indicated in Table G.6).

[15] One SME commented that 'the final table provides a concise summary of what was done, assumptions made, etc., making it very useful for future work' (as indicated in Table G.3).

[16] One SME commented that they 'would even recommend the framework for use in a modelling context that does not require a "rapid response" - it could serve as a checklist to evaluate your modelling efforts and how it agrees with what is typically done in literature' (as indicated in Table G.3) An additional comment to this question is that 'it is guiding and not overly specific - this will be helpful' (as indicated in Table G.6). However, one SME commented that it is 'difficult to say if the context of the future modelling efforts are not known' (as indicated in Table G.5).

6.4.4 Open-ended question feedback

The open-ended questions allow SMEs to give feedback which is not necessarily captured through the close-ended questions. Valuable insights are gathered through these questions, as they allow the SMEs to guide the focus and scope of the responses according to their respective backgrounds and individual perception of the framework. The criticisms, concerns and additional feedback received from SMEs which have not been addressed in the previous sections, are discussed and interpreted in remainder of this section.

Nomenclature use and ambiguity of methodology and framework steps

One of the SMEs raised a concern (as indicated in the 'criticisms and concerns' row in Table G.2) that some definitions were not used consistently, in addition to some methodological steps not being clearly explained in the background to the research. The most probable explanation for the observation was the fact that the background and origin section of the validation document consisted of six pages, thus it was a very condensed overview of Chapter 1 - Chapter 4. Although great care was taken to give a sufficient overview of the background and methodology, some of the more complex and detailed considerations were not included in this condensed overview. Additionally, as mentioned previously the framework was presented in less detail in the validation document than in the thesis document, which may have contributed to some additional ambiguity with regards to the framework function. As discussed, this concern is easily addressed by ensuring that the final stand-alone framework document contains a more detailed overview of the design considerations of the framework, in addition to not condensing the explanations part of the framework presentation steps and ensuring consistent description of the nomenclature.

Lack of consideration of additional intervention strategies

One of the SMEs raised a concern (as indicated in the 'criticisms and concerns' row in Table G.2) that additional intervention strategies such as prevention and mitigation should also be considered in the context of an infectious disease outbreak (for instance, social distancing as part of prevention). Firstly, it is worth noting that the validation document did not include all the design considerations used to establish the definitions of some of the terminology and the scope of considerations which are investigated. For instance, social distancing may relate to quarantined individuals, depending on how the intervention strategy is defined, hence it is technically already included in the research project considerations. Secondly, this concern highlights the importance of using the definitions and terms appropriately and consistently, with a view to ensure universal and consistent application of the steps and terms within the framework. It is not possible to retrospectively infer new definitions to the treatment interventions in the dataset, however, future work considerations may include further distinction of the intervention strategies to include a more diversified set of options other than

treatment and vaccination strategies, in addition to more complete descriptions of the intervention strategies.

Robustness and sensitivity of framework decisions

One of the SMEs raised a concern (as indicated in the 'criticisms and concerns' row in Table G.4) that the framework is perceived to be heavily dependent on the selection of considerations by the modeller, as opposed to making recommendations on what should be included in a given case. This concern relates to the robustness of the selection and guidance process, as approached from a systems modelling perspective. During the interview with the SME, this concern was addressed by explaining that the framework use is not limited to informing the selection of considerations, but also guiding the consideration of these factors in light of the outbreak context. The SME stated that the discussion during the validation interview clarified that the main guidance of the framework is not only limited to the sections that are heavily reliant on the modelling practitioner's discretion. Only one SME voiced this specific concern and recommended that the sensitivities of the framework be evaluated. This does not reduce the importance of this concern, but, as this was only raised by one SME, it was deemed sufficient to discuss this as future work considerations in Chapter 7. In spite of this concern, the framework contribution as a valuable tool in guiding users is recognised by the SME in question (as indicated in the 'additional feedback or comments' row in Table G.4).

Merits of framework in the context of the modelling process and context uncertainty

One of the SMEs (as indicated in the 'criticisms and concerns' row in Table G.5) questioned whether the activities which are supported by the framework are truly of such a frequent and repetitive nature as to warrant the development of the proposed framework. The SME, however, also stated that the framework has potential value for both the modelling practitioner and to serve as a reference for future research projects, which indicates recognition of the contributions of this framework to the literature. Although the modelling process is not generalisable for every single modelling instance, the framework serves as a valuable departure point to ensure that the modelling process is followed systematically according to a well-researched methodology. Not all steps of the modelling process are always incorporated in every modelling approach, but allowance is made for the considerations thereof, to ensure some generalisation of the modelling process.

Additional comments

One of the SMEs had no criticism or concerns (as indicated in the 'criticisms and concerns' row in Table G.6), but gave a detailed feedback response. Some of the critiques in this feedback response relate to design considerations of the research, which was not elaborated on in detail within the validation document. As mentioned by the SME (as indicated in the 'additional feedback or

comments' row in Table G.6), however, many of these critiques were addressed as part of the validation interview. The overall response indicated that the framework is received very positively and is perceived as a 'valuable addition to the literature and practice.'

6.5 Finalised framework

The concerns and feedback suggestions from the SMEs as discussed in detail in §6.4 are used to guide some of the amendments and adjustments to the framework. The validation document that was presented to the SMEs is used as the baseline for constructing a stand-alone document that describes the framework and which may be used by any modelling practitioner. This stand-alone document is presented in Appendix A. This document as presented in Appendix A does not contain any work that has not already been presented and discussed in this thesis. It consists of the framework presentation and case study guide portions of the validation document and incorporates the small amendments and adjustments made to the framework presentation and case study guide in response to the validation feedback. The concerns raised by the SMEs which are not addressed through these adjustments are discussed as part of the future work considerations in Chapter 7.

6.6 Conclusion

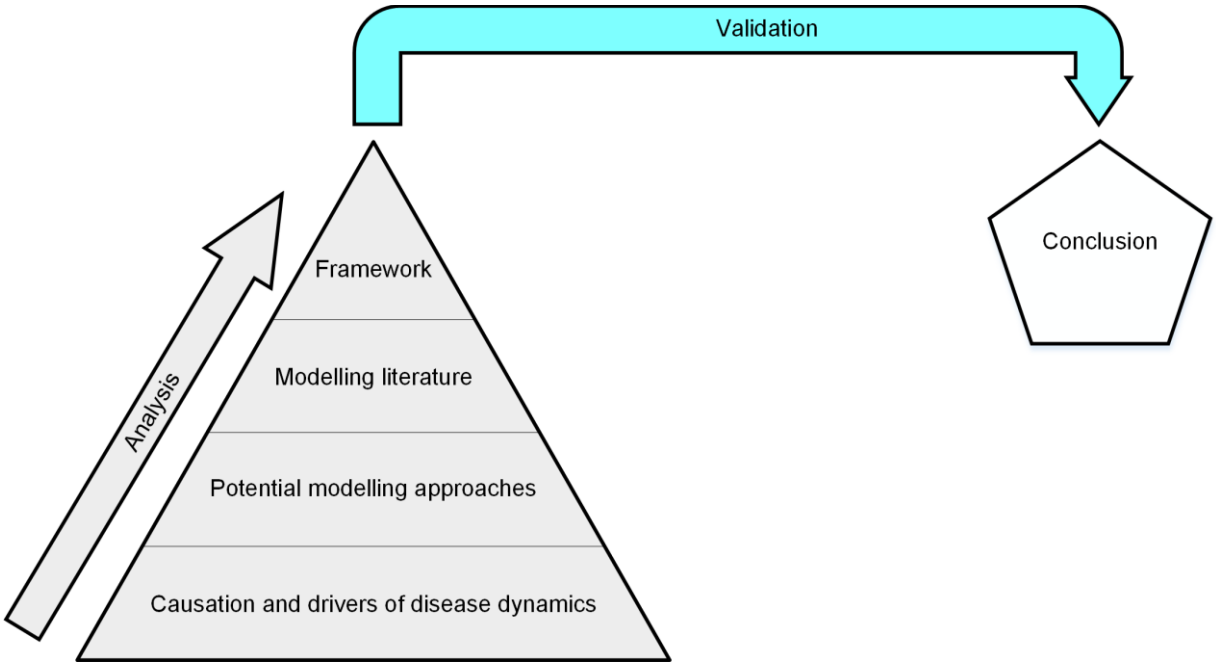

Figure 6.4: A visual summary of the content of Chapter 6.

A summary of the content of this chapter in relation to the overall document structure is illustrated in Figure 6.4. Background information on the case study design considerations is reviewed in §6.1. An illustrative case study is presented in §6.2. The validation strategy and SME selection are described

in §6.3. The results of the validation questionnaire and interviews are presented and discussed in §6.4. The stand-alone document proposed for use by modelling practitioners and included in Appendix A is introduced in §6.5.

The validation interviews allowed for the gathering of valuable insights into the framework proposed in this research project. The results for each close-ended validation question according to the average Likert scale response are illustrated in Figure 6.5. The majority of the feedback responses indicate that SMEs agree moderately and strongly with many aspects of the purpose and performance questions used to evaluate the framework. In contrast, SMEs agree less strongly on the questions which relate to the function of framework.

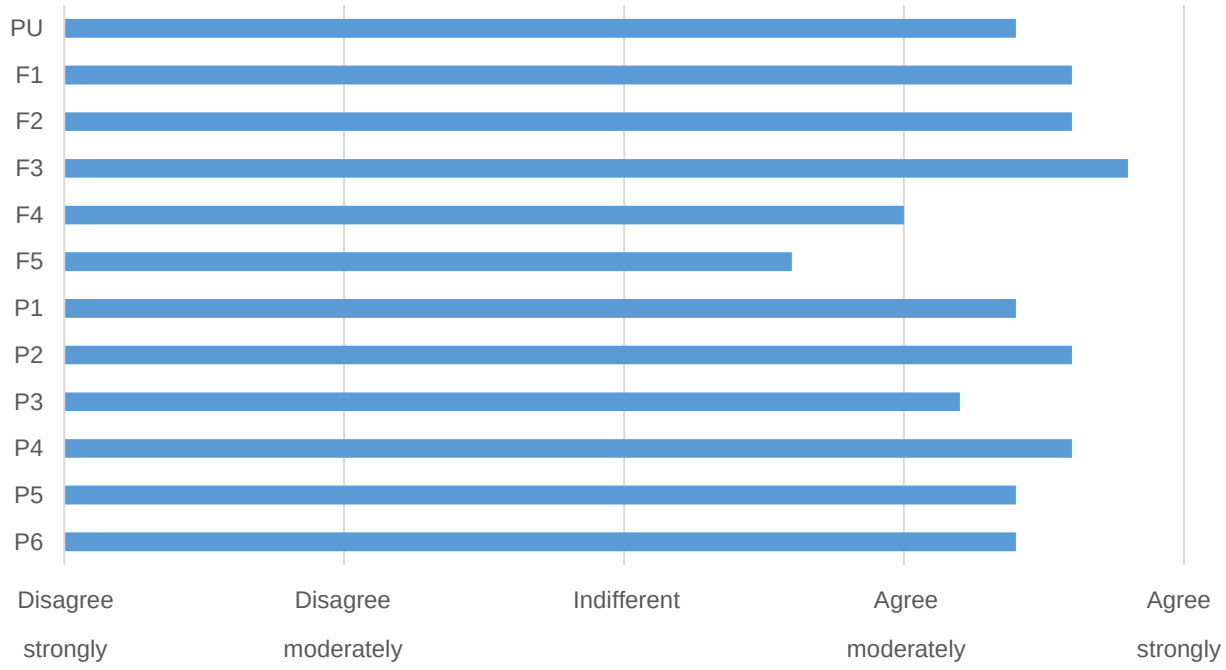

Figure 6.5: Average of the SME responses to each of the close-ended validation questions.

As discussed, the condensed presentation of the framework in the validation document, may have contributed to some ambiguity with regards to the framework function and operation as discussed in §6.4 (and especially in §6.4.2). This concern relates less to the content of the framework and more to the reduction of detail of the framework steps as presented in the validation document. This is, however, easily addressed by ensuring that the final stand-alone framework document (presented in Appendix A) contains a more detailed overview of the design considerations of the framework. Additionally the framework presentation steps are not condensed in this stand-alone document and consistent application of definitions of the nomenclature is ensured throughout the document.

This concern highlighted in the interview process also affirms the role of the validation interviews in highlighting aspects of a research project that require special attention and which may not be immediately evident from a design perspective.

Chapter 7 Conclusion

The research project concludes in this chapter. A brief summary of the thesis is presented in §7.1. The thesis contribution in relation to the research aims and objectives are critically evaluated in §7.2. A reflection on the completion of the project is also discussed in this section. Suggestions for future work are reviewed in §7.3.

7.1 Thesis summary

The background, problem statement, research aims and objectives, expected contributions and methodology were discussed in Chapter 1. The literature on infectious disease modelling was contextualised in Chapter 2. This included an overview of the chain of infection, which was used to describe the disease characteristics and contextual factors which potentially affect disease dynamics. The modelling of infectious diseases was also contextualised in Chapter 2. The structured literature review was designed and executed in Chapter 3 to construct an infectious disease modelling dataset which accurately represents the modelling approaches applied in the context of infectious disease modelling. The scope was determined, execution steps were established, and the evaluation and capturing of the data from the literature to the dataset was described. The relationships between the disease characteristics (i.e. the transmission mode), contextual factors, and modelling considerations in the dataset were analysed and interpreted in Chapter 4. Additionally, the relevance of modelling decisions and considerations which form an essential part of the modelling process was also established. One of the outcomes of the analysis was the construction of reference summary tables used to inform the development of the framework. The framework was designed and presented in Chapter 5. The framework consisted of two phases, the first phase pertained to the contextualisation of the disease outbreak considerations and the second phase pertained to the selection of modelling considerations in the modelling approach. The steps of the outbreak contextualisation and outbreak modelling selection phase of the framework were discussed in detail, which included overviews of the relevant considerations for each of the steps, links between subsequent steps and recommendations based on the analysis completed in Chapter 4. The framework validation was completed in Chapter 6. This consisted of verification of the framework function with an illustrative case study and semi-structured validation interviews with various SMEs from an engineering and healthcare modelling field. A questionnaire consisting of various close-ended and open-ended questions was completed by the SMEs following the interview. The majority of the questionnaire feedback responses were positive, which indicated that the framework was well received.

7.2 Appraisal and evaluation of thesis contributions

The thesis contributions in relation to the research aims (stated in §1.4.1) and objectives (stated in §1.4.2), as well as insights which emanated from reflection on the completion of the research project are presented within this section.

Aims

Two aims were stated in Chapter 1, summarised as the following:

1. The conceptualisation of a support tool to formalise the decisions and considerations which form part of the modelling approach implementation; and
2. The inclusion of an explicit documentation step to capture the decisions and reasoning for modelling decisions according to a documentation template.

One implicit goal of the validation strategy was the presentation of the framework to a diverse number of SMEs with a view to qualitatively test the attainment of the research aims. Selected results from the validation are used to evaluate the attainment of the aims. With special reference to the F1[17] and F3[18] questions (which relate to the first stated aim) from the questionnaire, nearly all SMEs agreed strongly with the stated questions. This is highlighted to indicate the achievement of the first research aim and one of the expected contributions[19] of this research project.

Additionally, with special reference to the P4[20] and P5[21] questions from the questionnaire, the majority of the SMEs strongly agreed with the stated questions. One SME stated that the compact documentation tables make this template potentially useful for future modelling efforts and that the documentation step (which implicitly serves as a checklist of the modelling steps) would even be useful in a modelling context which does not necessarily require a rapid modelling response. This is highlighted to indicate the achievement of the second research aim and one of the expected contributions[22] (discussed in §1.5) of this research project.

[17] The framework is capable of informing the user of the most relevant modelling considerations.

[18] The most relevant steps in the modelling process are presented in the framework.

[19] The framework may assist modellers to reduce decision fatigue with regards to modelling decisions and considerations and serve as a valuable tool to ensure that all relevant components are included in a modelling approach, as stated in §1.5.

[20] The documentation step of the framework serves as a useful checklist for the modelling process.

[21] The documentation step of the framework is useful to assist future modelling efforts.

[22] The documentation step of the framework may serve as a checklist and reference from which secondary applications are extended, as stated in §1.5.

Objectives

The chapters in which the achievement of the research objectives were implicitly attained are noted in Table 7.1.

Table 7.1: Project evaluation with special reference to each of the research objectives.

Objective	Chapter in support of objective achievement
I	Chapter 2
II	Chapter 2, particularly §2.6
III	Chapter 3
IV	Chapter 4
V	Chapter 5
VI	Chapter 6

Reflection on the expected contributions and completion of the research project

Upon reflection on the completion of this research project, the following insights and achieved contributions are presented and discussed.

The contextualisation of the literature from the realm of epidemiological modelling of disease dynamics was presented in Chapter 2. This included additional information on the chain of infection which is used as a guiding metaphor to describe the disease process and the factors which affect disease dynamics. This was completed in an attempt to summarise the most salient considerations required in the context of infectious disease modelling.

The contextualisation of the literature as presented in Chapter 2 was used towards comprehending the literature and the factors which affect disease dynamics, however, the discussion of the chapter conclusion in §2.6 particularly highlighted the link between various factors which affect disease dynamics and the process of disease propagation. Contextualising and describing the disease modelling process as a complex interaction between disease characteristics and contextual factors potentially affecting the disease dynamics, is, a far as can be ascertained, a novel approach.

The structured literature review as executed in Chapter 3 was carefully designed towards attainment of this research objective. The scope was carefully selected to minimise bias in the data gathering phase of the research project. The structured review was executed systematically and methodically to ensure that the dataset constructed from the structured literature review is an accurate

representation of the modelling approaches as applied in the literature. The 283 literature pieces which were selected through the iterative filtering process were deemed sufficient to support the findings of this research project.

The analysis of the dataset and the relationships between various disease characteristics, modelling approaches and modelling considerations was completed in Chapter 4. Different subsets were extracted from the dataset, with a view to highlight different observations and ensure adequate representation of the considered categories within the dataset. The data of the subsets were normalised appropriately to minimise inaccurate conclusion from the findings due to disproportionate representation of some data categories in the dataset. During the analysis, the observations were interpreted within the immediate context of the dataset findings and additionally in the context of a general modelling process, in order to holistically glean the findings from the analysis. The summary tables presented at the end of Chapter 4 were useful to capture the most salient findings from the dataset, in addition to establishing relationships to a selection of the informative modelling suggestions.

The framework was constructed in Chapter 5. The previous chapters and stated research aims were used to inform the design and construction considerations of the framework. The modelling contextualisation and selection steps of the framework were designed in accordance with a selection of the expected contributions.[23]

The validation strategy is designed and executed in Chapter 6. SMEs were selected from a diverse affiliation background, with the common denominator that all SMEs were required to have had exposure in both an engineering and a health care modelling context. The feedback from the validation interviews was received in the form of close-ended questionnaire responses, in addition to a selection of open-ended questions. Additionally, all concerns and feedback comments were addressed in this chapter. The overall positive response to various close-ended questions as part of the validation feedback highlights the positive reception of the framework in achieving the stated purpose, function and performance propositions. Many of the slightly less positive responses and concerns relating to the validation questions (especially with respect to the function and use of the framework) were addressed during the interview process. This highlighted that a selection of the less positive responses and concerns related less to the content of the framework, but more to the reduced level of detail in the validation document which was used as a guiding document during the validation process.

In conclusion, the proposed framework is, as far as can be ascertained, an original contribution to the literature. Additionally, the stand-alone framework document presented in Appendix A (which is

[23] The expected contributions pertained to: ensuring that the framework presents and formalises the most relevant modelling considerations; ensuring that the disease outbreak is sufficiently contextualised; and linking of the contextualisation of the disease outbreak in relation to the modelling decision selection is completed, as presented in the bullet points in §1.5.

similar to the validation document as viewed by the SMEs and is presented in Appendix F) serves as the implementation document which may be used by modelling practitioners in the field. The steps (i.e. methodology) of the framework are well suited to support the infectious disease modelling process. In this framework, much detail is afforded to the contextualisation of disease outbreaks, as the contextualisation plays an important role in the incorporation and selection of modelling considerations. Overall, a carefully designed research methodology is followed with a view to construct the proposed framework in support of the infectious disease modelling process.

7.3 Suggestions for future work

The following opportunities for future work emanated from reflection on the completion of the project.

Additional consideration of sexually transmitted diseases

As mentioned in §3.2.2, only one sexually transmissible disease was identified which satisfied the three selection criteria for inclusion in the disease dataset, namely Ebola. This excluded many diseases which are transmissible with sexual contact due to longer incubation times associated with these diseases.[24] This reduced and limited the number of recommendations which could be drawn from the dataset as a result of the very small number of inclusions of diseases which are transmissible by means of sexual contact. Future opportunities may adjust and relax the incubation period constraint employed in this research project. This adjustment will allow more inclusions of sexually transmissible modelling instances and along with additional analyses, may result in additional insights into the modelling of sexually transmissible diseases.

Additional contextual factor and modelling approach incorporation

Additional contextual factor inclusions may aid further contextualisation of the disease outbreak in the framework. The investigation and consideration of the following contextual factors and modelling approaches are suggested:

- Consideration of disease risk estimation according to geographic dispersion, with a view to predict disease prevalence in a region (e.g. the use of Google trend analysis is potentially useful to inform additional outbreak modelling contextualisation);
- Incorporation of an elementary contextualisation of human factors and the potential impact thereof on the modelling considerations; and

[24] As a reminder, one of the selection criteria for inclusion of a disease in the structured literature review were that the disease must have a relatively short incubation period (typically less than 30 days). Many sexually transmissible diseases have incubation periods which are longer than 30 days.

- Incorporation of ecological niche mapping to better describe the biotic and abiotic factors which may potentially affect the disease reservoir and susceptible host.

Theoretical models not applied to a specific transmission mode

As mentioned in §3.3.2, theoretical disease models (i.e. models which did not mention a specific disease transmission mode in the modelling application or which were not applied to a particular disease instance) were not considered within this research project. Future amendments to the modelling dataset may include the inclusion of such theoretical modelling literature instances, with a view to extend modelling approach selection guidance in the absence of disease characteristics and based more on the suitability of a particular modelling approach.

Additional validation from modelling practitioners in the private sector

The overall feedback results were positive, which highlights the positive reception of the framework from the SMEs. As mentioned in §6.3.1, the SMEs were selected according to consideration of their respective background experience in the engineering and health care modelling fields; in addition to ensuring a diverse academic affiliation. The identified SMEs from academia are well-suited to evaluate the framework purpose, function and performance, but additional validation from SMEs in the private sector would further establish and confirm the suitability of the framework in supporting the modelling approach selection process.

Lack of consideration of additional intervention strategies

As mentioned in §6.4.4, one SME stated that the entire scope of potential intervention strategies was not considered in the framework. This was the result of how treatment strategies were defined in the research project, namely that all intervention strategies other than vaccination strategies were grouped in the treatment strategy category. Additionally, as mentioned in §6.4.4, this also potentially resulted from the reduced detail of the research design considerations as presented in the validation document. Future opportunities may include better differentiation of treatment strategies, to extend the potential intervention strategies other than vaccination to differentiate between treatment, prevention and mitigation strategies. Only one SME raised this concern and it is therefore considered appropriate to include this concern as a future work recommendation.

Robustness and sensitivity of framework decisions

As mentioned in §6.4.4, one SME mentioned that there exists a potential concern on the sensitivity of the steps and to which degree the discretion of the user of the framework would influence the outcomes of the framework. After some debate and elaboration during the interview, the particular SME concluded that the steps do appear to be sufficiently robust to serve the intended purpose of

the framework. It is worth mentioning that the steps of the framework are generalised to ensure a broad application scope, which in turn requires more discretion from the framework user to select considerations in the context of a particular disease outbreak. Additional sensitivity testing of the framework operation (e.g. sensitivity of the modelling approach selection phase when more than one transmission mode is studied and included in the contextualisation phase of the framework) is suggested as part of future work opportunities. Only one SME raised this concern and it is therefore considered appropriate to include this as a future work recommendation.

Development of an interactive electronic support tool

As mentioned in §6.4.4, the development of an interactive web application could greatly assist in making the framework more user-friendly, by amending a manual selection process to a more interactive selection process. This consideration falls, however, outside the scope of this research project and is suggested as a future work opportunity.

References

Abboubakar, H., Buonomo, B. & Chitnis, N., 2016. Modelling the effects of malaria infection on mosquito biting behaviour and attractiveness of humans. *Ricerche di matematica*, (65), pp.329–346.

Abrams, J.Y. et al., 2013. Real-time modelling used for outbreak management during a cholera epidemic, Haiti, 2010-2011. *Epidemiology & Infection*, 141(6), pp.1276–1285.

Adde, A. et al., 2016. Predicting Dengue Fever Outbreaks in French Guiana Using Climate Indicators. *PLOS Neglected Tropical Diseases*, 10(e0004681), pp.1–16.

Adeola, A.M. et al., 2017. Climatic Variables and Malaria Morbidity in Mutale Local Municipality, South Africa: A 19-Year Data Analysis. *International Journal of Environmental Research and Public Health*, 14(1360), pp.1–15.

Adivar, B. & Selen, E.S., 2011. Compartmental disease transmission models for smallpox. *Discrete and Continuous Dynamical Systems*, (S2011), pp.13–21.

Ahmad, M.D. et al., 2016. Optimal control analysis of Ebola disease with control strategies of quarantine and vaccination. *Infectious Diseases of Poverty*, 5(72), pp.1–12.

Ajelli, M. et al., 2016. Spatiotemporal dynamics of the Ebola epidemic in Guinea and implications for vaccination and disease elimination: a computational modeling analysis. *BMC Medicine*, 14(130), pp.1–10.

Al-Darabsah, I. & Yuan, Y., 2016. A time-delayed epidemic model for Ebola disease transmission. *Applied Mathematics and Computation*, 290, pp.307–325.

Alexanderian, A. et al., 2011. An Age-Structured Model for the Spread of Epidemic Cholera: Analysis and Simulation. *Nonlinear Analysis: Real World Applications*, 12(6), pp.3483–3498.

Altizer, S. et al., 2006. Seasonality and the dynamics of infectious diseases. *Ecology letters*, 9(4), pp.467–484.

Amaku, M. et al., 2016. Magnitude and frequency variations of vector-borne infection outbreaks using the Ross-Macdonald model: explaining and predicting outbreaks of dengue fever. *Epidemiology & Infection*, 144, pp.3435–3450.

Andradóttir, S. et al., 2011. Reactive strategies for containing developing outbreaks of pandemic influenza. *BMC Public Health*, 11(S1), pp.1–15.

Andrews, J.R. & Basu, S., 2011. The Transmission Dynamics and Control of Cholera in Haiti: An Epidemic Model. *Lancet*, 377(9773), pp.1248–1255.

Anggraeni, W. et al., 2017. Modified Regression Approach for Predicting Number of Dengue Fever Incidents in Malang Indonesia. *Procedia Computer Science*, 124, pp.142–150.

Anno, S. et al., 2015. Space-time clustering characteristics of dengue based on ecological, socio-economic and demographic factors in northern Sri Lanka. *Geospatial Health*, 10(376), pp.215–222.

Apolloni, A., Poletto, C. & Colizza, V., 2013. Age-specific contacts and travel patterns in the spatial spread of 2009 H1N1 influenza pandemic. *BMC Infectious Diseases*, 13(176), pp.1–18.

Area, I. et al., 2017. Mathematical modeling of 2014 Ebola outbreak. *Mathematical Methods in the Applied Sciences*, 40, pp.6114–6122.

Area, I. et al., 2015. On a fractional order Ebola epidemic model. *Advances in Difference Equations*, 2015(278), pp.1–12.

Arifin, S.M.N. et al., 2015. Landscape Epidemiology Modeling Using an Agent-Based Model and a Geographic Information System. *Land*, 4, pp.378–412.

Astuti, H.N., Saputro, D.R.S. & Susanti, Y., 2017. Mixed geographically weighted regression (MGWR) model with weighted adaptive bi-square for case of dengue hemorrhagic fever (DHF) in Surakarta. *Journal of Physics: Conference Series*, 855(12007), pp.1–10.

Atique, S. et al., 2016. Meteorological influences on dengue transmission in Pakistan. *Asian Pacific Journal of Tropical Medicine*, 9(10), pp.954–961.

Augustijn, E.-W. et al., 2016. Agent-based modelling of cholera diffusion. *Stochastic Environmental Research and Risk Assessment*, 30, pp.2079–2095.

Azaele, S. et al., 2010. Stochastic dynamics of cholera epidemics. *Physical Review E*, 81(51901), pp.1–6.

Azizah, A., Widyaningsih, P. & Saputro, D.R.S., 2017. Spread of Ebola disease with susceptible exposed infected isolated recovered (SEIIhR) model. *Journal of Physics: Conference Series*, 855(12008), pp.1–6.

Bai, X., Song, W. & Chen, J., 2016. Ebola prediction with Epidemic Model. In *2nd IEEE International Conference on Computer and Communications*. pp. 847–851.

Bai, Z. & Liu, D., 2015. Modeling seasonal measles transmission in China. *Communications in Nonlinear Science and Numerical Simulation*, 25, pp.19–26.

Bakhtiar, T., 2016. Optimal intervention strategies for cholera outbreak by education and chlorination. *IOP Conference Series: Earth and Environmental Science*, 31(12022), pp.1–7.

Balcan, D. et al., 2009. Seasonal transmission potential and activity peaks of the new influenza A (H1N1): a Monte Carlo likelihood analysis based on human mobility. *BMC Infectious Diseases*, 7(45), pp.1–12.

Baracchini, T. et al., 2016. Seasonality in cholera dynamics: A rainfall-driven model explains the wide range of patterns in endemic areas. *Advances in Water Resources*, 108, pp.357–366.

Barmak, D.H., Dorso, C.O. & Otero, M., 2016. Modelling dengue epidemic spreading with human mobility. *Physica A*, 447, pp.129–140.

Baxter, P. & Jack, S., 2008. Qualitative Case Study Methodology : Study Design and Implementation for Novice Researchers Qualitative Case Study Methodology : Study Design and Implementation. *The Qualitative Report*, 13(4), pp.544–559.

Bento, A.I. & Rohani, P., 2016. Forecasting Epidemiological Consequences of Maternal Immunization. *Clinical Infectious Diseases*, 63(S4), pp.S205–S212.

Berge, T. et al., 2016. A simple mathematical model for Ebola in Africa. *Journal of Biological Dynamics*, 11(1), pp.42–74.

Berge, T., Bowong, S. & Lubuma, J.M.-S., 2017. Global stability of a two-patch cholera model with fast and slow transmissions. *Mathematics and Computers in Simulation*, 133, pp.142–164.

Bertuzzo, E. et al., 2016. On the probability of extinction of the Haiti cholera epidemic. *Stochastic Environmental Research and Risk Assessment*, 30, pp.2043–2055.

Bharti, N. et al., 2010. Measles hotspots and epidemiological connectivity. *Epidemiology & Infection*, 138(9), pp.1308–1316.

Bhattacharyya, S. & Ferrari, M.J., 2017. Age-specific mixing generates transient outbreak risk following critical-level vaccination. *Epidemiology & Infection*, 145(1), pp.12–22.

Blake, I.M. et al., 2014. The role of older children and adults in wild poliovirus transmission. *PNAS*, 111(29), pp.10604–10609.

Brauer, F., 2009. Mathematical epidemiology is not an oxymoron. *BMC Public Health*, 9(S1), pp.1–11.

Brauer, F., Shuai, Z. & Van den Driessche, P., 2013. Dynamics of an age-of-infection cholera model. *Mathematical Biosciences and Engineering*, 10(5&6), pp.1335–1349.

Brouwers, L. et al., 2010. Micro-simulation of a smallpox outbreak using official register data. *Eurosurveillance*, 15(35), pp.1–8.

Browne, C. et al., 2015. A Model of the 2014 Ebola Epidemic in West Africa with Contact Tracing. *PLOS Currents*, 7, pp.1–18.

Buonomo, B., 2011a. A simple analysis of vaccination strategies for rubella. *Mathematical Biosciences and Engineering*, 8(3), pp.677–687.

Buonomo, B., 2011b. On the optimal vaccination strategies for horizontally and vertically transmitted infectious diseases. *Journal of Biological Systems*, 19(2), pp.263–279.

Burch, M.G., Jacobsen, K.A. & Tien, J.H., Network-based analysis of a small Ebola outbreak. *Article submitted*.

Cai, L., Modnak, C. & Wang, J., 2017. An age-structured model for cholera control with vaccination. *Applied Mathematics and Computation*, 299, pp.127–140.

Camacho, A. et al., 2015. Temporal Changes in Ebola Transmission in Sierra Leone and Implications for Control Requirements: a Real-time Modelling Study. *PLOS Currents*, 7, pp.1–18.

Campbell, P.T. et al., 2016. Influence of Population Demography and Immunization History on the Impact of an Antenatal Pertussis Program. *Clinical Infectious Diseases*, 63(S4), pp.S213–S220.

Cash, B.A., Rodó, X. & Kinter, J.L., 2008. Links between Tropical Pacific SST and Cholera Incidence in Bangladesh: Role of the Eastern and Central Tropical Pacific. *Journal of Climate*, 21(18), pp.4647–4663.

CDC, 2012. *Principles of Epidemiology in Public Health Practice* 3rd ed., Atlanta, GA: CDC.

Chen, Q., 2010. The Dynamics Behavior and Immune Control Strategies of SIRs Model with Immunization on Heterogeneous Network. *International Journal of Simulation Systems, Science & Technology*, 17(46), pp.1–8.

Chen, W., 2015. A Mathematical Model of Ebola Virus Based on SIR Model. In *International Conference on Industrial Informatics-Computing Technology, Intelligent Technology, Industrial Information Integration*. pp. 213–216.

Cheng, Q. et al., 2017. The interplay of climate, intervention and imported cases as determinants of the 2014 dengue outbreak in Guangzhou. *PLOS Neglected Tropical Diseases*, 11(e0005701), pp.1–24.

Chiogna, M. & Gaetan, C., 2004. Hierarchical space-time modelling of epidemic dynamics: an application to measles outbreaks. *Statistical Methods and Applications*, 13, pp.53–69.

Chiu, R., Chang, C.-M. & Chang, Y.-C., 2008. A Forecasting Model for Deciding Annual Vaccine Demand. In *Fourth International Conference on Natural Computation*. pp. 107–111.

Chong, K.C. & Zee, B.C.Y., 2012. Modeling the impact of air, sea, and land travel restrictions supplemented by other interventions on the emergence of a new influenza pandemic virus. *BMC Infectious Diseases*, 12(309), pp.1–12.

Chowell, G. & Nishiura, H., 2014. Transmission dynamics and control of Ebola virus disease (EVD): a review. *BMC medicine*, 12(196), pp.1–16.

Codeço, C.T., 2001. Endemic and epidemic dynamics of cholera: the role of the aquatic reservoir. *BMC Infectious Diseases*, 1(1), pp.1–14.

Collins, O.C. & Duffy, K.J., 2016. Optimal control intervention strategies using an n-patch waterborne disease model. *Natural Resource Modeling*, 29(4), pp.499–519.

Collins, O.C. & Govinder, K.S., 2016. Stability analysis and optimal vaccination of a waterborne disease model with multiple water sources. *Natural Resource Modeling*, 29(3), pp.426–447.

Conrad, J.R. et al., 2016. Modeling the Impact of Behavior Change on the Spread of Ebola. In *Mathematical and Statistical Modeling for Emerging and Re-emerging Infectious Diseases*. Springer, pp. 5–23.

Coudeville, L., 2003. Measles dynamics and vaccination diffusion A model and an application. *The European Journal of Health Economics*, 4, pp.319–326.

Crooks, A. & Hailegiorgis, A., 2013. Disease modeling within refugee camps: A multi-agent systems approach. In *Proceedings of the 2013 Winter Simulation Conference*. pp. 1697–1706.

CSMG, 2010a. Chaper 12: Modelling Social Interaction. In *Modelling in Healthcare*. AMS, pp. 125–134.

CSMG, 2010b. Chapter 14: Viewing the System as a Whole. In *Modelling in Healthcare*. AMS, pp. 151–164.

CSMG, 2010c. Chapter 3: The Modelling Process. In *Modelling in Healthcare*. AMS, pp. 11–24.

CSMG, 2010d. Chapter 9: Issues in Mathematical Modelling. In *Modelling in Healthcare*. AMS, pp. 93–100.

Cui, J., Wu, Z. & Zhou, X., 2014. Mathematical Analysis of a Cholera Model with Vaccination. *Journal of Applied Mathematics*, 2014(324767), pp.1–16.

Dafilis, M.P. et al., 2014. Dynamical crises, multistability and the influence of the duration of immunity in a seasonally-forced model of disease transmission. *Theoretical Biology and Medical Modelling*, 11(43), pp.1–10.

Daley, D.J., Gani, J. & Gani, J.M., 2001. Chapter 6 - Fitting epidemic data. In *Epidemic Modelling: An Introduction*. Cambridge University Press, pp. 154–174.

Darti, I., 2016. Multiple Control Strategies for Prevention of Rotavirus Disease with Saturated Incidence Rate. *AIP Conference Proceedings*, 1746(20058), pp.1–6.

Dike, C.O., Zainuddin, Z.M. & Dike, I.J., 2016. Queueing Technique for Ebola Virus Disease Transmission and Control Analysis. *Indian Journal of Science and Technology*, 9(46), pp.1–9.

Do, T.S. & Lee, Y.S., 2016. Modeling the Spread of Ebola. *Osong Public Health and Research Perspectives*, 7(1), pp.43–48.

Dottori, M. & Fabricius, G., 2015. SIR model on a dynamical network and the endemic state of an infectious disease. *Physica A*, 434, pp.25–35.

Duan, W. et al., 2015. Mathematical and computational approaches to epidemic modeling: a comprehensive review. *Frontiers in Computers Science*, 9(5), pp.806–826.

Eames, K.T.D., 2014. The influence of school holiday timing on epidemic impact. *Epidemiology & Infection*, 142, pp.1963–1971.

Elsevier, 2017. Journal of Theoretical Biology. Available at: https://www.journals.elsevier.com/journal-of-theoretical-biology/ [Accessed June 23, 2017].

Escobar, L.E. & Craft, M., 2016. Advances and Limitations of Disease Biogeography Using Ecological Niche Modeling. *Frontiers in Microbiology*, 7(1174), pp.1–21.

Espinoza, B. et al., 2016. Assessing the Efficiency of Movement Restriction as a Control Strategy of Ebola. In *Mathematical and Statistical Modeling for Emerging and Re-emerging Infectious Diseases*. Springer, pp. 123–145.

Ferguson, N.M. et al., 2003. Planning for smallpox outbreaks. *Nature*, 425(6959), pp.681–685.

Finkenstadt, B.F. & Grenfell, B.T., 2000. Time Series Modelling of Childhood Diseases: A Dynamical Systems Approach. *Applied Statistics*, 49(2), pp.187–205.

Flahault, A., Vergu, E. & Boëlle, P.-Y., 2009. Potential for a global dynamic of Influenza A (H1N1). *BMC Infectious Diseases*, 9(129), pp.1–11.

Flyvbjerg, B., 2006. Five Misunderstandings About Case-Study Research. *Qualitative inquiry*, 12(2), pp.219–245.

Forouzannia, F. & Gumel, A., 2015. Dynamics of an age-structured two-strain model for malaria transmission. *Applied Mathematics and Computation*, 250, pp.860–886.

Fujie, R. & Odagaki, T., 2007. Effects of superspreaders in spread of epidemic. *Physica A*, 374, pp.843–852.

Van Gaalen, R.D. et al., 2017. Determinants of Rotavirus Transmission A Lag Nonlinear Time Series Analysis. *Epidemiology*, 28(4), pp.503–513.

Gani, J. & Swift, R.J., 2009. Deterministic and stochastic models for the spread of cholera. *ANZIAM*, 51(2), pp.234–240.

Gao, Z.-M., Gu, J. & Li, W., 2012. Epidemic Spreading in a Multi-compartment System. *Chinese Physics Letters*, 29(2), p.028902:1-028902:4.

Garba, S.M., Safi, M.A. & Usaini, S., 2017. Mathematical model for assessing the impact of vaccination and treatment on measles transmission dynamics. *Mathematical Methods in the Applied Sciences*, 40(18), pp.6371–6388.

Gazi, N.H. et al., 2010. A study of cholera model with environmental fluctuations. *International Journal of Mathematical Models and Methods in Applied Sciences*, 4(3), pp.150–155.

Ge, Y. et al., 2011. Agent Based Modeling for H1N1 Influenza in Artificial Campus. In *2nd IEEE International Conference on Emergency Management and Management Sciences*. pp. 464–467.

Getz, W.M. et al., 2016. An Agent-Based Model of School Closing in Under-Vacccinated Communities During Measles Outbreaks. In *Proceedings of the Agent-Directed Simulation Symposium*. pp. 1–8.

GIDEON, 2017a. GIDEON Infectious Disease. Available at: https://web.gideononline.com/web/epidemiology/# [Accessed June 30, 2017].

GIDEON, 2017b. GIDEON Web Application. Available at: https://www.gideononline.com/about/gideon/ [Accessed June 30, 2017].

Glaser, A., 2007. Dynamics and Control of Infectious Diseases. *Unpublished lecture notes. Princeton: Princeton University*.

González-Parra, G., Arenas, A.J. & Chen-Charpentier, B.M., 2014. A fractional order epidemic model for the simulation of outbreaks of influenza A(H1N1). *Mathematical Methods in the Applied Sciences*, 37, pp.2218–2226.

Goswami, N.K. et al., 2018. Mathematical modeling of zika virus disease with nonlinear incidence and optimal control. *Journal of Physics: Conference Series*, 1000(12114), pp.1–16.

Goufo, E.F.D., Noutchie, S.C.O. & Mugisha, S., 2014. A Fractional SEIR Epidemic Model for Spatial and Temporal Spread of Measles in Metapopulations. *Abstract and Applied Analysis*, 2014(781028), pp.1–6.

Goufo, E.F.D., Pene, M.K. & Mugisha, S., 2016. Stability analysis of epidemic models of Ebola hemorrhagic fever with non-linear transmission. *Journal of Nonlinear Science and Applications*, 9, pp.4191–4205.

Grais, R.F., Ellis, J.H. & Glass, G.E., 2003. Forecasting the geographical spread of smallpox cases by air travel. *Epidemiology & Infection*, 131(2), pp.849–857.

Grassly, N.C. & Fraser, C., 2008. Mathematical models of infectious disease transmission.PDF. *Nature*, 6(6), pp.477–487.

De Greeff, S.C. et al., 2009. Seasonal patterns in time series of pertussis. *Epidemiology & Infection*, 137(10), pp.1388–1395.

Grigorieva, E. & Khailov, E., 2015. Analytical Study of Optimal Control Intervention Strategies for Ebola Epidemic Model. In *Proceedings of the Conference on Control and its Applications*. pp. 392–399.

Gu, H. et al., 2016. Meteorological Factors for Dengue Fever Control and Prevention in South China. *International Journal of Environmental Research and Public Health*, 13(867), pp.1–12.

Gumel, A.B., McCluskey, C.C. & Watmough, J., 2006. An Sveir Model for Assessing Potential Impact of an Imperfect Anti-SARS Vaccine. *Mathematical Biosciences and Engineering*, 3(3), pp.485–512.

Hall, I.M. et al., 2007. Comparison of smallpox outbreak control strategies using a spatial metapopulation model. *Epidemiology & Infection*, 135(7), pp.1133–1144.

Hay, S.I. et al., 2013. Global mapping of infectious disease. *Philosophical transactions of the Royal Society of London*, 368(20120250), pp.1–11.

Hove-Musekwa, S.D. et al., 2011. Modelling and analysis of the effects of malnutrition in the spread of cholera. *Mathematical and Computer Modelling*, 53, pp.1583–1595.

Hsieh, J. et al., 2006. Teaching through Simulation: Epidemic Dynamics and Public Health Policies. *Simulation*, 82(11), pp.731–759.

Hsieh, Y. et al., 2007. Impact of quarantine on the 2003 SARS outbreak: A retrospective modeling study. *Journal of Theoretical Biology*, 244(4), pp.729–736.

Hu, K. et al., 2015. The Impact of Human Behavioral Changes in 2014 West Africa Ebola Outbreak. In *International Conference on Social Computing, Behavioral-Cultural Modeling, and Prediction*. Springer, pp. 75–84.

Hu, W. et al., 2012. Did socio-ecological factors drive the spatiotemporal patterns of pandemic in fluenza A (H1N1)? *Environment International*, 45, pp.39–43.

Huang, X. et al., 2017. Assessing the social and environmental determinants of pertussis epidemics in Queensland , Australia: a Bayesian spatio-temporal analysis. *Epidemiology & Infection*, 145(6), pp.1221–1230.

Huang, Y., 2010. Modeling the Severe Acute Respiratory Syndrome (SARS) Outbreak in Beijing – An Agent-based Approach. In *Proceedings of the 1st International Conference and Exhibition on Computing for Geospatial Research & Application*. pp. 1–4.

Huo, X., Modeling of Contact Tracing in Epidemic Populations Structured by Disease Age. *Article submitted*.

Iannelli, M. & Manfredi, P., 2007. Demographic Change and Immigration in Age-structured Epidemic Models. *Mathematical Population Studies*, 14(3), pp.169–191.

Imran, M. et al., 2016. Mathematical analysis of swine influenza epidemic model with optimal control. *Japan Journal of Industrial and Applied Mathematics*, 33, pp.269–296.

Irwan, E., Jaharuddin & Sianturi, P., 2017. Dynamical system for Ebola outbreak within vaccination treatment. *Far East Journal of Mathematical Sciences*, 102(8), pp.1711–1726.

Iwelunmor, J. et al., 2015. Toward the sustainability of health interventions implemented in sub-Saharan Africa: a systematic review and conceptual framework. In *Implementation Science*.

Chapman & Hall, pp. 1–27.

Javidi, M. & Ahmad, B., 2014. A Study of a Fractional-Order Cholera Model. *Applied Mathematics & Information Sciences*, 8(5), pp.2195–2206.

Jazbec, A., Delimar, M. & Vrzic, V.S., 2004. Simulation model of rubella - the effects of vaccination strategies. *Applied Mathematics and Computation*, 153, pp.75–96.

Jewell, N.P., 2004. Introduction. In *Statistics for Epidemiology*. pp. 1–8.

Jin, Z. et al., 2011. Modelling and analysis of influenza A (H1N1) on networks. *BMC Public Health*, 11(S1), pp.1–9.

Jinping, L. et al., 2004. Research on Mathematical Transmission Model of SARS Based on Molecular Kinematics. In *Fifth World Congress on Intelligent Control and Automation*. pp. 5530–5537.

Joubert, G., 2014. Key concepts in epidemiology. In *Epidemiology a research manual for South Africa*. Oxford University Press South Africa, pp. 13–31.

Kalyani, D. & Shankar, K., 2016. Assessment and seasonal variations of communicable diseases: 3 year study. *International Journal of Research in Medical Sciences*, 4(4), pp.1186–1192.

Kang, J. & Aldstadt, J., 2017. The Influence of Spatial Configuration of Residential Area and Vector Populations on Dengue Incidence Patterns in an Individual-Level Transmission Model. *International Journal of Environmental Research and Public Health*, 14(792), pp.1–14.

Kelly, J., 2005. *The great mortality: an intimate history of the Black Death, the most devastating plague of all time*, HarperCollins Publishers.

Kelly, M.R. et al., 2016. The impact of spatial arrangements on epidemic disease dynamics and intervention strategies. *Journal of Biological Dynamics*, 10(1), pp.222–249.

Khaleque, A. & Sen, P., 2017. An empirical analysis of the Ebola outbreak in West Africa. *Scientific Reports*, 7(42594), pp.1–8.

Khan, A. & Khan, M.A., 2016. P2P Inspired Stochastic Model for Analysis of Polio Management in Pakistan. In *First IEEE International Conference on Computer Communication and the Internet*. pp. 503–506.

Khan, M.A. et al., 2015. Dynamical Behavior of Cholera Epidemic Model with Non-linear Incidence Rate. *Applied Mathematical Sciences*, 9(20), pp.989–1002.

Koelle, K., 2009. Clinical microbiology and infection. *Clinical microbiology and infection*, 15(S1), pp.29–31.

Koepke, A.A. et al., 2016. Predictive modeling of Cholera outbreaks in Bangladesh. *Annals of Applied Statistics*, 10(2), pp.575–595.

Kong, L. et al., 2016. Modeling Heterogeneity in Direct Infectious Disease Transmission in a Compartmental Model. *International Journal of Environmental Research and Public Health*, 13(253), pp.1–13.

Kramer, A.M. et al., 2016. Spatial spread of the West Africa Ebola epidemic. *Royal Society Open Science*, 3(160294), pp.1–11.

Kretzschmar, M. et al., 2004. Ring Vaccination and Smallpox Control. *Emerging Infectious Diseases*, 10(5), pp.832–841.

Kucharski, A.J. et al., 2016. Effectiveness of Ring Vaccination as Control Strategy for Ebola Virus Disease. *Emerging Infectious Diseases*, 22(1), pp.105–108.

Kucharski, A.J. et al., 2015. Measuring the impact of Ebola control measures in Sierra Leone. *PNAS*, 112(46), pp.14366–14371.

Laguna, F. et al., 2017. Modelling malaria incidence by an autoregressive distributed lag model with

spatial component. *Spatial and Spatio-temporal Epidemiology*, 22, pp.27–37.

Lai, P.-C., Kwong, K.-H. & Wong, H.-T., 2013. Spatio-temporal and stochastic modelling of severe acute respiratory syndrome. *Geospatial Health*, 8(1), pp.183–192.

Lam, E.H.Y. et al., 2011. The feasibility of age-specific travel restrictions during influenza pandemics. *Theoretical Biology and Medical Modelling*, 8(44), pp.1–14.

Lau, M.S.Y. et al., 2017. Spatial and temporal dynamics of superspreading events in the 2014 – 2015 West Africa Ebola epidemic. *PNAS*, 114(9), pp.2337–2342.

Leander, R.N. et al., 2016. Modelling Ebola within a community. *Epidemiology & Infection*, 144(11), pp.2329–2337.

Leckebusch, G.C. & Abdussalam, A.F., 2015. Climate and socioeconomic influences on interannual variability of cholera in Nigeria. *Health & Place*, 34, pp.107–117.

Lee, H.S. et al., 2017. Seasonal patterns of dengue fever and associated climate factors in 4 provinces in Vietnam from 1994 to 2013. *BMC Infectious Diseases*, 17(218), pp.1–9.

Lee, S.D. & Kim, D.-K., 2010. Bayesian Inferences And Forecasting in Spatial Time Series Models. In *Ninth International Conference on Machine Learning and Applications*. pp. 767–770.

Legrand, J. et al., 2007. Understanding the dynamics of Ebola epidemics. *Epidemiology & Infection*, 135(4), pp.610–621.

Lemos-Paiao, A.P., Silva, C.J. & Torres, D.F.M., 2017. An epidemic model for cholera with optimal control treatment. *Journal of Computational and Applied Mathematics*, 318, pp.168–180.

Lewnard, J.A. et al., 2014. Dynamics and control of Ebola virus transmission in Montserrado, Liberia: a mathematical modelling analysis. *Lancet Infectious Disease*, 14, pp.1189–1195.

Li, C. et al., 2017. Science of the Total Environment Modeling and projection of dengue fever cases in Guangzhou based on variation of weather factors. *Science of the Total Environment*, 605, pp.867–873.

Li, M.-T. et al., 2013. Global Dynamic Behavior of a Multigroup Cholera Model with Indirect Transmission. *Discrete Dynamics in Nature and Society*, 2013(703826), pp.1–11.

Li, R. et al., 2016. The short-term association between meteorological factors and mumps in Jining, China. *Science of the Total Environment*, 568, pp.1069–1075.

Li, X. et al., 2013. Was Mandatory Quarantine Necessary in China for Controlling the 2009 H1N1 Pandemic? *International Journal of Environmental Research and Public Health*, 10, pp.4690–4700.

Li, X. & Mohebbi, S., 2015. Modeling Diffusion of Epidemic Diseases via Agent-based Simulation. In *Proceedings of the 2015 Industrial and Systems Engineering Research Conference*. pp. 2156–2163.

Lima, M., 2009. A link between the North Atlantic Oscillation and measles dynamics during the vaccination period in England and Wales. *Ecology Letters*, 12, pp.302–314.

Lingala, M.A.L., 2017. Effect of meteorological variables on Plasmodium vivax and Plasmodium falciparum malaria in outbreak prone districts of Rajasthan, India. *Journal of Infection and Public Health*, 10, pp.875–880.

Lipp, E.K., Huq, A. & Colwell, R.R., 2002. Effects of Global Climate on Infectious Disease : the Cholera Model. *Clinical Microbiology Reviews*, 15(4), pp.757–770.

Liu, F. et al., 2015. The role of vaccination coverage, individual behaviors, and the public health response in the control of measles epidemics: an agent-based simulation for California. *BMC Public Health*, 15(447), pp.1–16.

Liu, Z., Hu, J. & Wang, L., 2017. Modelling and analysis of global resurgence of mumps: A multi-group epidemic model with asymptomatic infection, general vaccinated and exposed distributions. *Nonlinear Analysis: Real World Applications*, 37, pp.137–161.

Lizarralde-Bejarano, D.P., Arboleda-Sánchez, S. & Puerta-Yepes, M.E., 2017. Understanding epidemics from mathematical models: Details of the 2010 dengue epidemic in Bello (Antioquia, Colombia). *Applied Mathematical Modelling*, 43, pp.566–578.

Lopez, L.E., Loaiza, A.M. & Tost, G.O., 2016a. A Mathematical Model for Transmission of Dengue. *Applied Mathematical Sciences*, 10(7), pp.345–355.

Lopez, L.E., Loaiza, A.M. & Tost, G.O., 2016b. Mathematical Model for the Transmission of the Dengue with Biological Control. *Applied Mathematical Sciences*, 10(30), pp.1467–1476.

Ma, Y. et al., 2017. Assessment for the impact of dust events on measles incidence in western China. *Atmospheric Environment*, 157, pp.1–9.

Maddox, M., 2014. Epidemic vs. Pandemic vs. Endemic. Available at: http://www.dailywritingtips.com/epidemic-vs-pandemic-vs-endemic/ [Accessed March 29, 2017].

Maeno, Y., 2016. Detecting a trend change in cross-border epidemic transmission. *Physica A*, 457, pp.73–81.

Maeno, Y., 2010. Discovering network behind infectious disease outbreak. *Physica A*, 389(21), pp.4755–4768.

De Magny, G.C. et al., 2008. Environmental signatures associated with cholera epidemics. *PNAS*, 105(46), pp.17676–17681.

Maitani, Y. & Ishikawa, H., 2012. Effectiveness assessment of vaccination policy against measles epidemic in Japan using an age-time two-dimensional mathematical model. *Environmental Health and Preventive Medicine*, 17, pp.34–43.

Maki, Y. & Hirose, H., 2013. Infectious Disease Spread Analysis Using Stochastic Differential Equations for SIR Model. In *4th International Conference on Intelligent Systems, Modelling and Simulation Infectious*. pp. 152–156.

Maltz, A. & Fabricius, G., 2016. SIR model with local and global infective contacts: A deterministic approach and applications. *Theoretical Population Biology*, 112, pp.70–79.

Martınez-Bello, D.A., Lopez-Quilez, A. & Torres-Prieto, A., 2017. Bayesian dynamic modeling of time series of dengue disease case counts. *PLOS Neglected Tropical Diseases*, 11(e0005696), pp.1–19.

Masuda, N., Konno, N. & Aihara, K., 2004. Transmission of severe acute respiratory syndrome in dynamical small-world networks. *Physical Review E*, 69(31917), pp.1–6.

Mathulamuthu, S.S. et al., 2016. Predicting Dengue Incidences Using Cluster Based Regression on Climate Data. In *6th IEEE International Conference on Control System, Computing and Engineering*. pp. 245–250.

Matsuda, F. et al., 2008. Prediction of epidemic cholera due to Vibrio cholerae O1 in children younger than 10 years using climate data in Bangladesh. *Epidemiology & Infection*, 136(1), pp.73–79.

Mayer, B.T. et al., 2013. Successes and Shortcomings of Polio Eradication: A Transmission Modeling Analysis. *American Journal of Epidemiology*, 177(11), pp.1236–1245.

McKinley, T.J. et al., 2013. Simulation-based Bayesian inference for epidemic models. *Computational Statistics & Data Analysis*, 71, pp.434–447.

McLeod, R.G. et al., 2006. Sensitivity and uncertainty analyses for a SARS model with time-varying inputs and outputs. *Mathematical Biosciences and Engineering*, 3(3), pp.527–544.

Merler, S. et al., 2015. Spatiotemporal spread of the 2014 outbreak of Ebola virus disease in Liberia and the effectiveness of non-pharmaceutical interventions: a computational modelling analysis. *The Lancet Infectious Diseases*, 15, pp.204–211.

Metcalf, C.J.E. et al., 2012. Structured models of infectious disease: Inference with discrete data. *Theoretical Population Biology*, 82, pp.275–282.

Meyers, L.A. et al., 2005. Network theory and SARS: predicting outbreak diversity. *Journal of Theoretical Biology*, 232, pp.71–81.

Ming, R. et al., 2016. Stochastic modelling of infectious diseases for heterogeneous populations. *Infectious Diseases of Poverty*, 5(107), pp.1–11.

Mishra, S., Fisman, D.N. & Boily, M.-C., 2011. The ABC of terms used in mathematical models of infectious diseases. *Journal of Epidemiology and Community Health*, 65(1), pp.87–94.

Mizumoto, K. et al., 2013. Vaccination and Clinical Severity: Is the Effectiveness of Contact Tracing and Case Isolation Hampered by Past Vaccination? *International Journal of Environmental Research and Public Health*, 10, pp.816–829.

Mkhatshwa, T. & Mummert, A., 2011. Modeling Super-spreading Events for Infectious Diseases: Case Study SARS. *IAENG International Journal of Applied Mathematics*, 41(2), pp.82–88.

Momoh, A.A. et al., 2013. Mathematical model for control of measles epidemiology. *International Journal of Pure and Applied Mathematics*, 87(5), pp.707–718.

Morin, C.W. et al., 2015. Meteorologically Driven Simulations of Dengue Epidemics in San Juan, PR. *PLOS Neglected Tropical Diseases*, 9(e0004002), pp.1–24.

Moss, W.J. & Griffin, D.E., 2012. Measles. *The Lancet*, 379(9811), pp.153–164.

Mostaço-Guidolin, L.C. et al., 2012. Transmissibility of the 2009 H1N1 pandemic in remote and isolated Canadian communities: a modelling study. *BMJ Open*, 2(e001614), pp.1–7.

Mukandavire, Z. et al., 2011. Modelling and Analysis of the Intrinsic Dynamics of Cholera. *Differential Equations and Dynamical Systems*, 19(3), pp.253–265.

Munoz, C.A., Montoya, J.F.A. & Loaiza, A.M., 2016. A Simulation Model with Community Structure for the Dengue Control. *Applied Mathematical Sciences*, 10(16), pp.787–794.

Naheed, A., Singh, M. & Lucy, D., 2014. Numerical study of SARS epidemic model with the inclusion of diffusion in the system. *Applied Mathematics and Computation*, 229, pp.480–498.

Ndanguza, D., Tchuenche, J.M. & Haario, H., 2013. Statistical data analysis of the 1995 Ebola outbreak in the Democratic Republic of Congo. *Afrika Matematika*, 24(1), pp.55–68.

Neal, P. & Xiang, F., 2017. Collapsing of non-centered parameterised MCMC algorithms with applications to epidemic models. *Scandinavian Journal of Statistics*, 44(1), pp.81–96.

Ngonghala, C.N., Teboh-Ewungkem, M.I. & Ngwa, G.A., 2016. Observance of period-doubling bifurcation and chaos in an autonomous ODE model for malaria with vector demography. *Theoretical Ecology*, 9, pp.337–351.

Nishiura, H. et al., 2017. Transmission dynamics of cholera in Yemen, 2017: a real time forecasting. *Theoretical Biology and Medical Modelling*, 14(14), pp.1–8.

Njagarah, J.B.H. & Nyabadza, F., 2014. A metapopulation model for cholera transmission dynamics between communities linked by migration. *Applied Mathematics and Computation*, 241, pp.317–331.

Ohtomo, K. et al., 2010. Relationship of cholera incidence to El Nino and solar activity elucidated by time-series analysis. *Epidemiology & Infection*, 138(1), pp.99–107.

Okuonghae, D., Gumel, A.B. & Safi, M.A., 2015. Dynamics of a two-strain vaccination model for

polio. *Nonlinear Analysis: Real World Applications*, 25, pp.167–189.

Omondi, O.L. et al., 2015. Modeling the effects of vaccination on rotavirus infection. *Advances in Difference Equations*, 2015(381), pp.1–12.

Ooi, E.-E. & Gubler, D.J., 2008. Dengue in Southeast Asia : epidemiological characteristics and strategic challenges in disease prevention. *Cadernos de Saúde Pública*, 25(1), pp.S115–S124.

Osei, F.B., Duker, A.A. & Stein, A., 2012. Bayesian structured additive regression modeling of epidemic data: application to cholera. *BMC Medical Research Methodology*, 12(118), pp.1–11.

Pang, L. et al., 2015. Transmission dynamics and optimal control of measles epidemics. *Applied Mathematics and Computation*, 256, pp.131–147.

Panja, P., Mondal, S.K. & Chattopadhyay, J., 2016. Dynamics of cholera outbreak with bacteriophage and periodic rate of contact. *International Journal of Dynamics and Control*, 4, pp.284–292.

Pascual, M. et al., 2008. Predicting endemic cholera: the role of climate variability and disease dynamics. *Climate Research*, 36(2), pp.131–140.

Pasetto, D. et al., 2017. Real-time projections of cholera outbreaks through data assimilation and rainfall forecasting. *Advances in Water Resources*, 108, pp.345–356.

Paynter, S., 2016. Incorporating Transmission Into Causal Models of Infectious Diseases for Improved Understanding of the Effect and Impact of Risk Factors. *American Journal of Epidemiology*, 183(6), pp.574–582.

Paz, S., 2009. Impact of Temperature Variability on Cholera Incidence in Southeastern Africa, 1971-2006. *EcoHealth*, 6(3), pp.340–345.

Pell, B. et al., 2016. Patch Models of EVD Transmission Dynamics. In *Mathematical and Statistical Modeling for Emerging and Re-emerging Infectious Diseases*. Springer, pp. 147–167.

Perez-Saez, J. et al., 2017. Climate-driven endemic cholera is modulated by human mobility in a megacity. *Advances in Water Resources*, 108, pp.367–376.

Pesco, P. et al., 2015. Assessment of pertussis vaccination strategies using a mathematical model of disease transmission using a mathematical model of disease. *Archivos Argentinos de Pediatría*, 111(5), pp.377–383.

Piot, P. et al., 2016. Addressing the growing burden of non-communicable disease by leveraging lessons from infectious disease management. *Journal of Global Health*, 6(1), pp.1–3.

Pitzer, V.E. et al., 2009. Demographic Variability, Vaccination, and the Spatiotemporal Dynamics of Rotavirus Epidemics. *Science*, 325(5938), pp.290–295.

Polgreen, P.M. et al., 2010. A spatial analysis of the spread of mumps: the importance of college students and their spring-break-associated travel. *Epidemiology & Infection*, 138(3), pp.434–441.

Ponnambalam, L. et al., 2016. A Multi-Agent Model for Adaptive Vaccination during Infectious Disease Outbreaks. In *International Conference on Computing Technologies and Intelligent Data Engineering*. pp. 1–5.

Porco, T.C. et al., 2004. Logistics of community smallpox control through contact tracing and ring vaccination: a stochastic network model. *BMC Public Health*, 4(34), pp.1–20.

Porta, M., 2014. *A Dictionary of Epidemiology* 6th ed. S. Greenland et al., eds., Oxford University Press.

Porter, A.T. & Oleson, J.J., 2016. A spatial epidemic model for disease spread over a heterogeneous spatial support. *Statistics in Medicine*, 35, pp.721–733.

Posny, D., Modnak, C. & Wang, J., 2016. A multigroup model for cholera dynamics and control. *International Journal of Biomathematics*, 9(1650001), pp.1–27.

Posny, D. & Wang, J., 2014. Modelling cholera in periodic environments. *Journal of Biological Dynamics*, 8(1), pp.1–19.

Qi, X. et al., 2015. The Effects of Socioeconomic and Environmental Factors on the Incidence of Dengue Fever in the Pearl River Delta, China, 2013. *PLOS Neglected Tropical Diseases*, 9(e0004159), pp.1–13.

Rachah, A. & Torres, D.F.M., 2016. Dynamics and Optimal Control of Ebola Transmission. *Mathematics in Computer Science*, 10, pp.331–342.

Rachah, A. & Torres, D.F.M., 2015. Mathematical Modelling, Simulation, and Optimal Control of the 2014 Ebola Outbreak in West Africa. *Discrete Dynamics in Nature and Society*, 2015, pp.1–9.

Rahmi, N., Jaharuddin & Nugrahani, E.H., 2016. Dynamics of Cholera Transmission with Hyperinfectious State of Bacteria. *Global Journal of Pure and Applied Mathematics*, 12(4), pp.3105–3121.

Rainisch, G. et al., 2015. Regional Spread of Ebola Virus, West Africa, 2014. *Emerging Infectious Diseases*, 21(3), pp.444–447.

Rathore, H., Ranwa, S. & Samant, A., 2012. Modular Network Effects on Communicable Disease Models. In *Sixth Asia Modelling Symposium*. pp. 126–131.

Rausanu, S. & Grosan, C., 2014. A hierarchical network model for epidemic spreading. Analysis of A/H1N1 virus spreading in Romania. *Applied Mathematics and Computation*, 233, pp.39–54.

Rebaudet, S. et al., 2016. Cholera spatial-temporal patterns in Gonaives, Haiti: From contributing factors to targeted recommendations. *Advances in Water Resources*, 108, pp.377–385.

Reiter, P., 2001. Climate Change and Mosquito-Borne Disease. *Environmental Health Perspectives*, 109(S1), pp.141–161.

Ren, H. et al., 2017. Exploring Determinants of Spatial Variations in the Dengue Fever Epidemic Using Geographically Weighted Regression Model: A Case Study in the Joint Guangzhou-Foshan Area, China, 2014. *International Journal of Environmental Research and Public Health*, 14(1518), pp.1–13.

Ren, Y., Ordóñez, F. & Wu, S., 2013. Optimal resource allocation response to a smallpox outbreak. *Computers & Industrial Engineering*, 66, pp.325–337.

Righetto, L. et al., 2013. Rainfall mediations in the spreading of epidemic cholera. *Advances in Water Resources*, 60, pp.34–46.

Ristic, B. & Dawson, P., 2016. Real-time forecasting of an epidemic outbreak: Ebola 2014/2015 case study. In *19th International Conference on Information Fusion*. pp. 1–8.

Roberts, M.G., 2000. Can we prevent the next epidemic? The elimination of childhood diseases by mass vaccination. *Journal of Applied Mathematics and Decision Sciences*, 4(2), pp.175–182.

Robertson, S.L., Eisenberg, M.C. & Tien, J.H., 2013. Heterogeneity in multiple transmission pathways: modelling the spread of cholera and other waterborne disease in networks with a common water source. *Journal of Biological Dynamics*, 7(1), pp.254–275.

Rocha, F. et al., 2016. Understanding dengue fever dynamics: a study of seasonality in vector-borne disease models. *International Journal of Computer Mathematics*, 93(8), pp.1405–1422.

Rohani, P., Zhong, X. & King, A.A., 2010. Contact Network Structure Explains the Changing Epidemiology of Pertussis. *Science*, 330(6006), pp.982–986.

Rostamy, D. & Mottaghi, E., 2016. Stability analysis of a fractional-order epidemics model with multiple equilibriums. *Advances in Difference Equations*, 170, pp.1–11.

Roy, P. & Upadhyay, R.K., 2017. Spatiotemporal transmission dynamics of recent Ebola outbreak in Sierra Leone, West Africa: Impact of control measures. *Journal of Biological Systems*, 25(3), pp.369–397.

Rozenbaum, M.H. et al., 2012. Modelling the impact of extended vaccination strategies on the epidemiology of pertussis. *Epidemiology & Infection*, 140(8), pp.1503–1514.

Rozhnova, G. & Nunes, A., 2010. Stochastic effects in a seasonally forced epidemic model. *Physical Review E*, 82.4(41906), pp.1–12.

Safan, M., Kretzschmar, M. & Hadeler, K.P., 2013. Vaccination based control of infections in SIRS models with reinfection: special reference to pertussis. *Journal of Mathematical Biology*, 67, pp.1083–1110.

Salem, D. & Smith, R., 2016. A Mathematical Model of Ebola Virus Disease: Using Sensitivity Analysis to Determine Effective Intervention Targets. In *Proceedings of the Summer Computer Simulation Conference*. pp. 1–8.

Samadder, A., Ghosh, K. & Chaudhuri, K., 2014. A dynamical model for the spread of cholera near an aquatic reservoir. *World Journal of Modelling and Simulation*, 10(4), pp.273–279.

Sanchez, P.J. & Sanchez, S.M., 2015. A scalable discrete event stochastic agent-based model of infectious disease propagation. In *Proceedings of the 2015 Winter Simulation Conference*. pp. 151–158.

Sanstead, E. et al., 2015. Understanding Trends in Pertussis Incidence: An Agent-Based Model Approach. *American Journal of Public Health*, 105(9), pp.e42–e48.

Sardar, T., Rana, S. & Chattopadhyay, J., 2015. A mathematical model of dengue transmission with memory. *Communications in Nonlinear Science and Numerical Simulation*, 22, pp.511–525.

Sato, A.-H. et al., 2015. An Epidemic Simulation with a Delayed Stochastic SIR Model Based on International Socioeconomic-Technological Databases. In *IEEE International Conference on Big Data*. pp. 1–10.

Sebastian, T. et al., 2015. Role of seasonality and rainfall in Vibrio cholerae infections: A time series model for 11 years surveillance data. *Clinical Epidemiology and Global Health*, 3, pp.144–148.

Sfikas, N., Greenhalgh, D. & Lewis, F., 2007. The Basic Reproduction Number and the Vaccination Coverage Required to Eliminate Rubella from England and Wales. *Mathematical Population Studies*, 14(1), pp.3–29.

Sharmin, S. et al., 2015. Interaction of Mean Temperature and Daily Fluctuation Influences Dengue Incidence in Dhaka, Bangladesh. *PLOS Neglected Tropical Diseases*, 9(e0003901), pp.1–13.

Sharmin, S. & Rayhan, I., 2012. Spatio-temporal modeling of infectious disease dynamics. *Journal of Applied Statistics*, 39(4), pp.875–882.

Shen, M., Xiao, Y. & Rong, L., 2015. Modeling the effect of comprehensive interventions on Ebola virus transmission. *Scientific Reports*, 5(15818), pp.1–14.

Shim, E. et al., 2006. An Age-structured Epidemic Model of Rotavirus with Vaccination. *Journal of Mathematical Biology*, 53(4), pp.719–746.

Shuai, Z. & Van den Driessche, P., 2013. Global stability of inffectious disease models using Lyapunov functions. *SIAM Journal on Applied Mathematics*, 73(4), pp.1513–1532.

Shuai, Z. & Van den Driessche, P., 2015. Modelling and control of cholera on networks with a common water source. *Journal of Biological Dynamics*, 9(S1), pp.90–103.

Siettos, C. et al., 2015. Modeling the 2014 Ebola Virus Epidemic – Agent - Based Simulations, Temporal Analysis and Future Predictions for Liberia and Sierra Leone. *PLOS Currents*, 7, pp.1–21.

Siettos, C.I. et al., 2016a. Estimation of the Age-Specific Per-Contact Probability of Ebola virus Transmission in Liberia using Agent-based Simulations. In *AIP Conference Proceedings*. pp. 150004–1--1150004.

Siettos, C.I. et al., 2016b. Forecasting and control policy assessment for the Ebola virus disease (EVD) epidemic in Sierra Leone using small-world networked model simulations. *BMJ Open*, 6(e008649), pp.1–8.

Sifferlin, A., 2018. Do I Still Need to Worry About Zika? *TIME Health*, pp.1–3. Available at: http://time.com/5241521/zika-virus-pregnancy/ [Accessed September 30, 2018].

Small, M., Tse, C.K. & Walker, D.M., 2006. Super-spreaders and the rate of transmission of the SARS virus. *Physica D*, 215(2), pp.146–158.

Song, Z. et al., 2015. An effective immunization strategy for airborne epidemics in modular and hierarchical social contact network. *Physica A*, 439, pp.142–149.

Sornbundit, K., Triampo, W. & Modchang, C., 2017. Mathematical modeling of diphtheria transmission in Thailand. *Computers in Biology and Medicine*, 87, pp.162–168.

Stone, L., Shulgin, B. & Agur, Z., 2000. Theoretical Examination of the Pulse Vaccination Policy in the SIR Epidemic Model. *Mathematical and Computer Modelling*, 31, pp.207–215.

Sumi, A. et al., 2017. Effect of temperature, relative humidity and rainfall on dengue fever and leptospirosis infections in Manila, the Philippines. *Epidemiology & Infection*, 145, pp.78–86.

Sun, G.-Q. et al., 2017. Transmission dynamics of cholera: Mathematical modeling and control strategies. *Communications in Nonlinear Science and Numerical Simulation*, 45, pp.235–244.

Sutradhar, B.C., 2008. On Forecasting Counts. *Journal of Forecasting*, 27, pp.109–129.

Talagala, T., 2015. Distributed Lag Nonlinear Modelling Approach to Identify Relationship between Climatic Factors and Dengue Incidence in Colombo District, Sri Lanka. *Epidemiology, Biostatistics and Public Health*, 12(e11522), pp.1–8.

Tan, X. et al., 2013. Modeling the initial transmission dynamics of influenza A H1N1 in Guangdong Province, China. *International Journal of Infectious Diseases*, 17, pp.e479–e484.

Tang, M., Liu, Z. & Li, B., 2009. Epidemic spreading by objective traveling. *Europhysics Letters*, 87(18005), pp.1–5.

Tebbens, R.J.D. et al., 2005. A Dynamic Model of Poliomyelitis Outbreaks: Learning from the Past to Help Inform the Future. *American Journal of Epidemiology*, 162(4), pp.358–372.

The American Association of Immunologists Inc., 2017. The Journal of Immunology. Available at: http://www.jimmunol.org/ [Accessed June 23, 2017].

Thiruchelvam, L. et al., 2017. K -Step Ahead Prediction Models for Dengue Occurrences. In *Proceedings of the 2017 IEEE International Conference on Signal and Image Processing Applications*. pp. 541–546.

Thompson, K.M. & Badizadegan, N.D., 2017. Modeling the Transmission of Measles and Rubella to Support Global Management Policy Analyses and Eradication Investment Cases. *Risk Analysis*, 37(6), pp.1109–1131.

Tian, J.P., Liao, S. & Wang, J., 2013. Analyzing the infection dynamics and control strategies of cholera. *Discrete and Continuous Dynamical Systems*, S2013, pp.747–757.

Tithi, S.S. & Hasan, M.S., 2015. Modeling Ebola Outbreak: A Case Study on 2014 Outbreak in Sierra Leone. In *Proceedings of the 6th ACM Conference on Bioinformatics, Computational Biology and Health Informatics*. pp. 1–2.

Toovey, S., 2010. Gideon database. *Travel Medicine and Infectious Disease*, 8, p.40.

Trentini, F. et al., 2017. Measles immunity gaps and the progress towards elimination: a multi-country modelling analysis. *Lancet Infectious Diseases*, 17, pp.1089–1097.

Trisilowati, I.D. & Fitri, S., 2014. A Nonlinear SIR with Stability. *AIP Conference Proceedings*, 1587, pp.119–122.

Tsanou, B. et al., 2017. Assessing the impact of the environmental contamination on the transmission of Ebola virus disease (EVD). *Journal of Applied Mathematics and Computing*, 55, pp.205–243.

Tse, C.K. & Small, M., 2010. Complex network models of disease propagation: Modelling, predicting and assessing the transmission of SARS. *Hong Kong Medical Journal*, 16(S4), pp.S43–S44.

Tuite, A.R. et al., 2011. Cholera Epidemic in Haiti, 2010: Using a Transmission Model to Explain Spatial Spread of Disease and Identify Optimal Control Interventions. *Annals of Internal Medicine*, 154, pp.593–601.

Tulu, T.W. & Tian, B., 2017. Mathematical Modeling, Analysis and Simulation of Ebola Epidemics. *Bulletin of the Iranian Mathematical Society*, 43(3), pp.683–693.

Tulu, T.W., Tian, B. & Wu, Z., 2017. Modeling the effect of quarantine and vaccination on Ebola disease. *Advances in Difference Equations*, 2017(178), pp.1–14.

Turner, A. et al., 2015. Comprehensive Model of Spread of Malaria in Humans and Mosquitos. In *Proceedings of the IEEE Southeast Conference*. pp. 1–6.

Upadhyay, R.K., Roy, P. & Rai, V., 2014. Deciphering Dynamics of Epidemic Spread: The Case of Influenza Virus. *International Journal of Bifurcation and Chaos*, 24(1450064), pp.1–31.

Valdez, L.D. et al., 2015. Predicting the extinction of Ebola spreading in Liberia due to mitigation strategies. *Scientific Reports*, 5(12172), pp.1–10.

Del Valle, S.Y., Hyman, J.M. & Chitnis, N., 2013. Mathematical models of contact patterns between age groups for predicting the spread of infectious diseases. *Mathematical Biosciences and Engineering*, 10, pp.1475–1497.

Verdasca, J.A. et al., 2005. Recurrent epidemics in small world networks. *Journal of Theoretical Biology*, 233(4), pp.553–561.

Vinson, J.E. et al., 2016. The potential for sexual transmission to compromise control of Ebola virus outbreaks. *Biology Letters*, 12(20151079), pp.1–4.

Walker, D.M. et al., 2010. Parameter inference in small world network disease models with approximate Bayesian Computational methods. *Physica A*, 389(3), pp.540–548.

Wang, J. & Liao, S., 2012. A generalized cholera model and epidemic-endemic analysis. *Journal of Biological Dynamics*, 6(2), pp.568–589.

Wang, J. & Modnak, C., 2011. Modeling cholera dynamics with controls. *Canadian Applied Mathematics Quaterly*, 19(3), pp.255–273.

Wang, L. et al., 2017. Modeling the transmission and control of Zika in Brazil. *Scientific Reports*, 7(1), pp.1–14.

Wang, W. & Ruan, S., 2004. Simulating the SARS outbreak in Beijing with limited data Simulating the SARS outbreak in Beijing with limited data. *Journal of Theoretical Biology*, 227, pp.369–379.

Wang, X., Posny, D. & Wang, J., 2016. A reaction-convection-diffusion model for cholera spatial dynamics. *Discrete and Continuous Dynamical Systems - Series B*, 21, pp.2785–2809.

Wang, X. & Wang, J., 2017. Disease dynamics in a coupled cholera model linking within-host and between-host interactions. *Journal of Biological Dynamics*, 11(S1), pp.238–262.

Wang, Y. & Cao, J., 2015. Global stability of general cholera models with nonlinear incidence and removal rates. *Journal of the Franklin Institute*, 352, pp.2464–2485.

Wang, Y. & Wei, J., 2013. Global dynamics of a cholera model with time delay. *International Journal of Biomathematics*, 6(1250070), pp.1–18.

Wanying, C., Alain, G. & Angel, R., 2016. Modeling the logistics response to a bioterrorist anthrax attack. *European Journal of Operational Research*, 254(2), pp.458–471.

Webb, G.F. & Browne, C.J., 2016. A model of the Ebola epidemics in West Africa incorporating age of infection. *Journal of Biological Dynamics*, 10(1), pp.18–30.

Welman, C., Kruger, F. & Mitchell, B., 2005a. Chapter 6: Validity of conclusions. In *Research methodology*. pp. 105–132.

Welman, C., Kruger, F. & Mitchell, B., 2005b. Chapter 7: Data-collecting methods and measuring instruments in quantitative research. In *Research methodology*. Oxford University Press, pp. 133–186.

Welman, C., Kruger, F. & Mitchell, B., 2005c. Chapter 8: Qualitative research designs. In 3rd, ed. *Research methodology*. Oxford University Press, pp. 187–208.

Weng, W. & Ni, S., 2015. Evaluation of containment and mitigation strategies for an influenza A pandemic in China. *Medical Simulation*, 91(5), pp.407–416.

WHO, 2017a. Communicable diseases: feature stories, fact files and Q&As. Available at: http://www.who.int/features/infectious_diseases/en/ [Accessed May 23, 2017].

WHO, 2002. Guidelines for estimating costs of introducing new vaccines into the national immunization system. , pp.1–20.

WHO, 2017b. Noncommunicable diseases. Available at: http://www.who.int/mediacentre/factsheets/fs355/en/ [Accessed April 25, 2017].

WHO, 2016a. The Expanded Programme on Immunization. Available at: http://www.who.int/immunization/programmes_systems/supply_chain/benefits_of_immunization/en/ [Accessed May 31, 2016].

WHO, 2016b. What is hepatitis? Available at: http://www.who.int/features/qa/76/en/ [Accessed August 17, 2017].

WHO, 2008. WHO Recommendations for Routine Immunization: A User's Guide to the Summary Tables. , pp.1–19.

WHO, 2018. Zika virus. Available at: http://www.who.int/news-room/fact-sheets/detail/zika-virus [Accessed September 30, 2018].

Wilder-Smith, A. et al., 2015. Potential for international spread of wild poliovirus via travelers. *BMC Medicine*, 13(133), pp.1–11.

Word, D.P. et al., 2010. Estimating seasonal drivers in childhood infectious diseases with continuous time and discrete-time models. In *American Control Conference*. pp. 5137–5142.

Wu, C. & Wong, P.J.Y., 2017. Estimating reproduction number of dengue transmission in 2013 and 2014. *Southeast Asian Journal of Tropical Medicine and Public Health*, 48(4), pp.809–818.

Xia, Y., Bjørnstad, O.N. & Grenfell, B.T., 2004. Measles Metapopulation Dynamics: A Gravity Model for Epidemiological Coupling and Dynamics. *The American Naturalist*, 164(2), pp.267–281.

Xia, Z.-Q. et al., 2015. Modeling the transmission dynamics of Ebola virus disease in Liberia. *Scientific Reports*, 5(13857), pp.1–13.

Xu, C. et al., 2014. Spatial pattern of severe acute respiratory syndrome in-out flow in 2003 in Mainland China. *BMC Infectious Diseases*, 14(721), pp.1–10.

Xu, L. et al., 2017. Climate variation drives dengue dynamics. *PNAS*, 114(1), pp.113–118.

Xue, L. & Scoglio, C., 2015. The network-level reproduction number and extinction threshold for vector-borne diseases. *Mathematical Biosciences and Engineering*, 12(3), pp.565–584.

Yaari, R. et al., 2016. Modeling the spread of polio in an IPV-vaccinated population: lessons learned from the 2013 silent outbreak in southern Israel. *BMC Medicine*, 14(95), pp.1–12.

Yan, S., 2015. The Model of Ebola Disease Control and Optimization Algorithm of Pharmaceutical Logistics Path. In *8th International Conference on BioMedical Engineering and Informatics*. pp. 826–831.

Yang, J. & Qiu, Z., 2014. Global stability of an age-structured cholera model. *Mathematical Biosciences and Engineering*, 11(3), pp.641–665.

Yarmand, H., Ivy, J.S. & Roberts, S.D., 2013. Identifying optimal mitigation strategies for responding to a mild influenza epidemic. *Simulation*, 89(11), pp.1400–1415.

Yeung, K.H.T. et al., 2017. An update of the global burden of pertussis in children younger than 5 years: a modelling study. *Lancet Infectious Diseases*, 17, pp.974–980.

Yin, R.K., 2014a. Designing case studies: Identifying your case(s) and establishing the logic of your case study. In *Case study research design and methods*. pp. 27–69.

Yin, R.K., 2014b. Getting started: How to know whether and when to use the case study as a research method. In *Case study research design and methods*. pp. 3–25.

Yoneyama, T., Das, S. & Krishnamoorthy, M., 2010. A Hybrid Model for Disease Spread and an Application to the SARS Pandemic. *Journal of Artificial Societies and Social Simulation*, 15(1), pp.1–12.

Zekri, N. & Clerc, J.P., 2002. Monte Carlo simulation of the transmission of measles: Beyond the mass action principle. *Physical Review E*, 65(46108), pp.1–6.

Zeng, Q. et al., 2016. Time series analysis of temporal trends in the pertussis incidence in Mainland China from 2005 to 2016. *Scientific Reports*, 6(32367), pp.1–8.

Zhang, L. et al., 2015. Partial Differential Equation Optimation for Infectious Disease Model. In *8th International Conference on Intelligent Computation Technology and Automation*. pp. 630–633.

Zhang, Y. et al., 2016. Developing a Time Series Predictive Model for Dengue in Zhongshan, China Based on Weather and Guangzhou Dengue Surveillance Data. *PLOS Neglected Tropical Diseases*, 10(e0004473), pp.1–17.

Zhong, W., 2017. Simulating influenza pandemic dynamics with public risk communication and individual responsive behavior. *Computational and Mathematical Organization Theory*, 23, pp.475–495.

Zhou, X.-Y. & Cui, J., 2013. Threshold dynamics for a cholera epidemic model with periodic transmission rate. *Applied Mathematical Modelling*, 37, pp.3093–3101.

Zhou, X. & Cui, J., 2011. Modeling and stability analysis for a cholera model with vaccination. *Mathematical Methods in the Applied Sciences*, 34, pp.1711–1724.

Zhou, X., Shi, X. & Cui, J., 2017. Stability and backward bifurcation on a cholera epidemic model with saturated recovery rate. *Mathematical Methods in the Applied Sciences*, 40, pp.1288–1306.

Zhou, Y., Ma, Z. & Brauer, F., 2004. A Discrete Epidemic Model for SARS Transmission and Control in China. *Mathematical and Computer Modelling*, 40, pp.1491–1506.

Zhu, L. & Zhou, Y., 2008. The Dynamics of an SIQS Epidemic Model with Pulse Quarantine. In *Chinese Control and Decision Conference*. pp. 1–6.

Appendix A (Framework document)

The framework document as would be used by a modelling practitioner in industry is presented in this appendix. This appendix is the result of the amendments to the validation document used in the validation interview following the incorporation of the suggested amendments and feedback from the SMEs.

A framework to support the decision-making process for modelling of communicable diseases

The document is structured as follows:

- In Section 1 an introduction to the framework development is presented;
- In Section 2, the aim and intended use of the framework is discussed;
- In Section 3, the framework is presented;
- In Section 4, an illustrative case study is used to describe the use of the framework, and
- In Section 5, a brief conclusion of the document is presented.

Author: Bernie Cronje, Study leader: Louzanne Bam

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Section 1. Background of framework development

1.1. Background and origin of the problem

Mathematical modelling of infectious disease is used to describe the prevalence and incidence of disease in humans. A flowchart of the relationship between infectious disease and mathematical models is illustrated in Figure A.1. The modelling process starts with identifying a disease outbreak. Assumptions which characterise the disease outbreak are used to describe the biological problem mathematically. Analysis of the mathematical model is used to identify solutions to the disease outbreak. This subsequently allows the testing of different conditions and scenarios in the model, to estimate predicted outcomes. Comparing the outcome of the model to the real data is considered an indication of the suitability of the model in describing the biological problem mathematically.

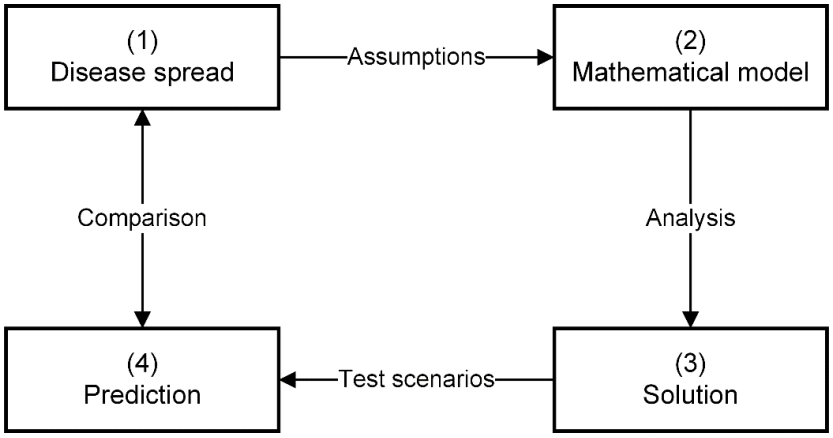

Figure A.1: Flowchart of mathematical modelling of infectious disease.

1.2. Problem background

As illustrated in Figure A.2, during the past two decades the following major disease outbreaks strained the global health system. Disease outbreaks such as the illustrated examples often require rapid responses and frequently result in global collaboration between various health care professionals and modellers. The literature on available disease modelling approaches is well established, but the factors which affect the selection and the application of one approach above another are not always clear. Analysts who frequently model infectious disease are likely to be very well acquainted with the process of modelling approach selection and which modelling considerations to include, but individuals who are not well acquainted with the field might not always know which considerations and incorporations are necessarily required in a particular modelling application.

Furthermore, no single response strategy is the most efficient and effective strategy for all epidemics; rather, the best strategy depends on the circumstances of the particular epidemic. This further

highlights the importance of accurately describing the context in which a disease outbreak occurs in order to construct a realistic mathematical model of the disease outbreak.

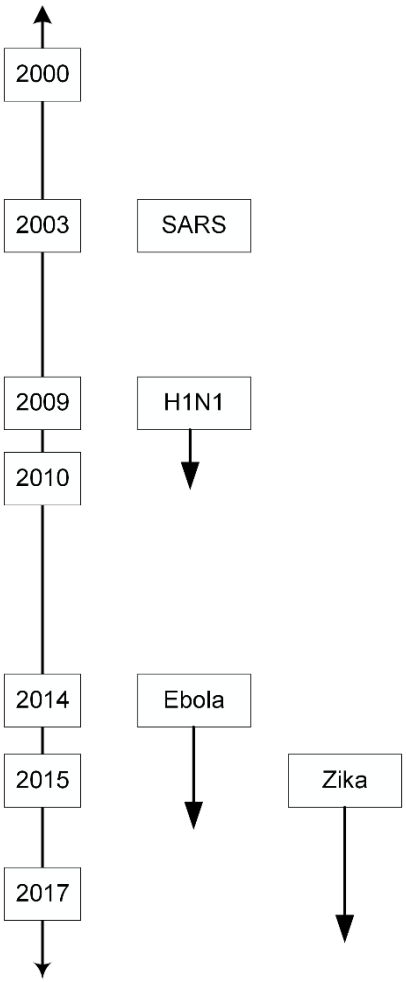

Figure A.2: Timeline of major disease outbreaks.

1.3. Problem statement

The problem statement is visualised in Figure A.3. Given the rapid response required for disease outbreaks, modellers and decision makers would benefit from a holistic framework capable of assisting the selection of modelling approaches and the incorporation of relevant modelling considerations. The numerous drivers of disease dynamics, such as the disease characteristics and the contextual factors of the disease outbreak, are expected to play a role in the selection of modelling approaches. Many potential approaches are available in literature, but the factors which influence the selection of a particular approach are not always evident from the literature. A structured review of the modelling literature, in the context of disease dynamics and the available modelling approaches, can be performed to construct a dataset of existing modelling approaches. This dataset is then analysed to construct the proposed modelling support framework. The

framework is used to assist the modeller with developing the model, as illustrated in Figure A.1 and considering the appropriate modelling factors in the modelling approach.

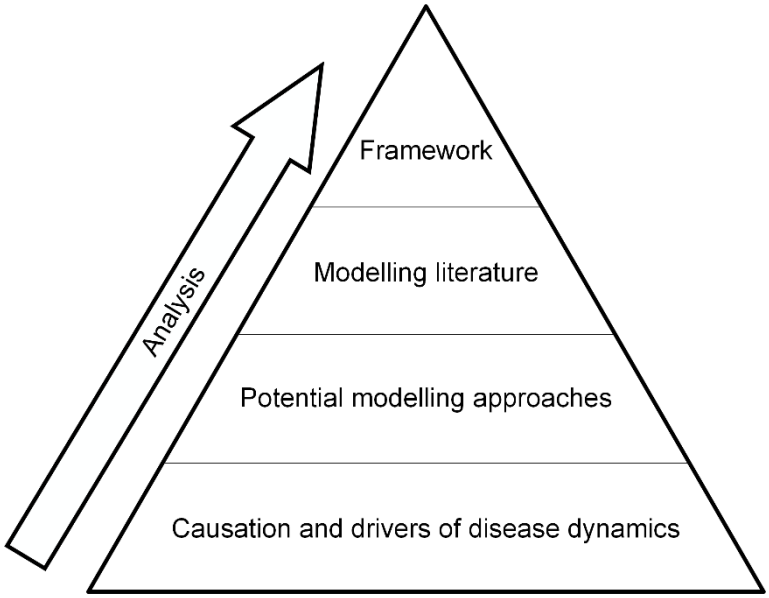

Figure A.3: A visualisation of the problem statement.

Section 2. Aim and intended use of the framework

2.1. Aim

The aim of the document is to present a support tool which formalises the decisions and considerations which form part of modelling approach implementation. The framework consists of two modules. The first module is used to contextualise the modelling aims and considerations which relate to the context of the disease outbreak and establish relationships to the second module of the framework, which relates to modelling approach selection.

An additional aim of the framework is the inclusion of an explicit documentation step which captures the relevant decisions and the reasoning for modelling decisions according to a documentation template. This is used to guide the modeller to systematically document the modelling approach selection process, thus creating a paper trail of factors that were taken into account when selecting the model approach and developing the model. Additionally, the systematic documentation of inclusions and exclusions contributes to ensuring that the most relevant modelling considerations are incorporated in the modelling approach, with specific consideration of the contextual circumstances of the given disease outbreak.

2.2. Intended use

The intention of the framework use is not that different user would select the exact same modelling approach or considerations when modelling an outbreak. Instead, the framework seeks to ensure that, regardless of whom is using the framework, that:

(i) All of the potentially relevant modelling considerations are at least considered for inclusion;

(ii) The process of selecting an appropriate modelling approach and deciding which considerations to include is executed in a consistent manner; and

(iii) The process of selecting an appropriate modelling approach and deciding which considerations to include is documented in a structured and consistent manner.

Section 3. Framework presentation

The comprehensive steps of the framework are illustrated in Figure A.4. Within the remainder of this section, the framework steps are defined and briefly explained.

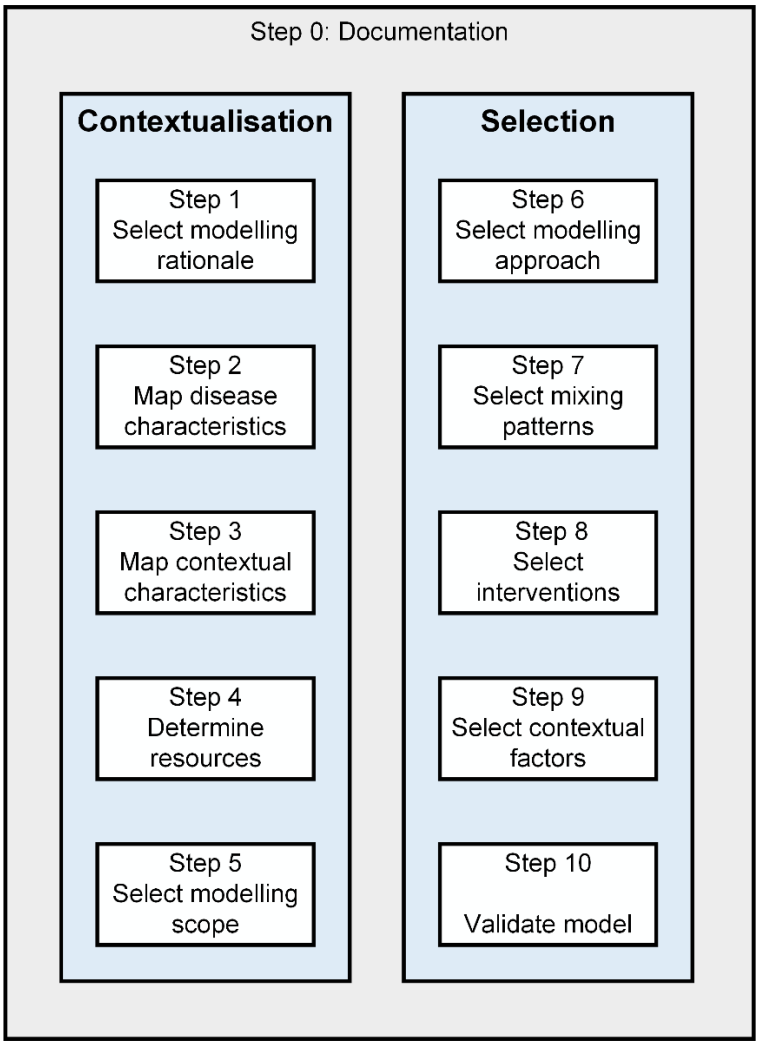

Figure A.4: High-level overview of framework.

3.1. Step 0: Documentation

The documentation of the modelling approach is a step that runs concurrently through each of the steps of the framework. This step serves the purpose of documenting both the aspects of the outbreak modelling contextualisation (i.e. modelling preparation) and the outbreak modelling selection phase, analogous to creating a roadmap of the modelling process. The main reasons for incorporating this step in the framework are as follows:

- Modelling assumptions and selections are captured clearly and concisely.
- Assurance is provided to the modeller that all relevant factors were considered in the modelling process, in addition to describing why some considerations were omitted and how the outbreak context relates to the selection of the modelling application.
- The ability to extend or clarify aspects of the modelling application in future work is assisted, in the sense of indicating which modelling considerations are incorporated or explicitly omitted from the modelling application.

The steps of the outbreak modelling contextualisation are documented according to the steps in Table A.1, whereas the decisions pertaining to the outbreak modelling selection are documented according to the steps in Table A.2. Table A.3 serves as a checklist in the outbreak modelling contextualisation phase of the framework and is used to capture the high-level modelling considerations which are considered for inclusion within the modelling application. Table A.4 is used as the main documentation table of the framework, which is used to capture the selection of modelling decisions during the modelling selection process. The modelling assumptions and any additional details (i.e. additional comments) which are considered part of the modelling selection process are also captured to Table A.4.

Table A.1: Outbreak modelling contextualisation documentation steps.

Step(s)	Framework step	Section	Documentation table
1	Select modelling rationale	§3.2	Table A.3
2	Describe disease characteristics	§3.3.1	Table A.6
2	Describe disease interventions	§3.3.2	Table A.8
3	Describe environmental contextual factors	§3.4.1	Table A.9
3	Describe population demographic contextual factors	§3.4.2	Table A.10
3	Describe mixing pattern consideration	§3.4.3	Table A.10
4	Determine resources	§3.5	Table A.11
1 – 4	Document high-level outbreak modelling consideration	§3.2 – §3.5	Table A.3 (p.175)

Table A.2: Outbreak modelling selection documentation steps.

Step(s)	Framework step	Section	Documentation table
5	Select modelling scope	§3.6	Table A.4 (p.176)
6	Select modelling approach	§3.7.1	
6	Select compartmental classification	§3.7.2	
7	Select mixing pattern(s)	§3.8	
8	Select intervention strategies	§3.9	
9	Select contextual factors	§3.10	
10	Validate model	§3.11	
1-10	Future work considerations	§3.1 – §3.11	

Table A.3: Reference table to capture decisions of the outbreak modelling contextualisation phase.

Modelling rationale	**Selected (✓ / ✗)**	**Treatment included (✓ / ✗)**	**Vaccination included (✓ / ✗)**	**Environmental factors included (✓ / ✗)**	**Demographics included (✓ / ✗)**	**Alternative mixing patterns included (✓ / ✗)**
Model disease dynamics						
Investigate causal relationships						
Investigate super spreading events						
Forecast disease instance						
Develop a model and analyse behaviour						
Evaluate interventions						

Table A.4: Reference table to capture decisions of the outbreak modelling selection phase.

CAT		Selection (✓)	Methods and/or categories selected	Modelling assumptions	Additional comments
Modelling scope	General		N/A		
	Global				
	Intercountry				
	Country				
	Provincial				
	Small region				
Modelling application	Mathematical				
	Network				
	Simulation				
	Compartmental classification				
Mixing patterns	Homogeneous		Homogeneous		
	Alternative				
Intervention and control	None		N/A		
	Treatment				
	Vaccination				
Contextual factors	None		N/A		
	Environmental				
	Demographics				
Validate model	Does the model answer research question?		N/A		
	Is the model comprehensible?				
	Is the model believable?				
	Does the model fit the data?				
	Fitting methods used:				
Future work					
Documentation completed	Outbreak modelling contextualisation	Table A.3	Table A.6 – Table A.11		
	Outbreak modelling selection	Table A.4	Table A.12 – Table A.18		

Steps 1 – 5: Outbreak modelling contextualisation

In order to holistically approach the disease modelling process, the context-specific characteristics of the disease are characterised prior to any modelling approach selection and implementation. The steps which form part of the outbreak contextualisation are illustrated in Figure A.4, namely:

- Select the modelling rationale in §3.2;
- Capture and describe disease characteristics and interventions in §3.3;
- Capture and describe (contextual) environmental factors in §3.4.1;
- Capture and describe (contextual) population demographics in §3.4.2;
- Capture and describe available resources (i.e. data sources) in §3.5; and
- Consideration and selection of the modelling scope in §3.6.

The steps of the outbreak modelling selection are documented according to the steps in Table A.1.

3.2. Step 1: Select modelling rationale

The first and most important step of the modelling contextualisation is the selection of the rationale of the modelling approach. Setting the rationale (i.e. modelling goal) of the modelling application as part of the modelling contextualisation will guide the modelling process and aid in identifying and incorporating relevant outbreak modelling considerations. The set of potential modelling rationales that can be selected are presented below, namely:

- **Model disease transmission dynamics** (develop a model to study disease transmission dynamics);
- **Investigate causal relationships** (develop a model to investigate the effect of factors which affect the chain of infection and correlates to changes in disease propagation or prevalence);
- **Investigate super spreading events** (develop a model to analyse instances of unusually high secondary infections emanating from a few individuals);
- **Forecast disease instance** (develop a model to not only fit data or parameters, but to explicitly forecast future disease prevalence from the model);
- **Develop a model and analyse behaviour** (develop a theoretical model of disease transmission and investigate behaviour of the model in the context of varying parameter values); and
- **Evaluate interventions** (develop a model to evaluate one or more of the treatment strategies or vaccination strategies).

Following the modelling rationale selection (which is noted in Table A.3), the relationships to a select number of outbreak modelling considerations are produced in Table A.5. The strength of the relationships are characterised according to the following guidelines, namely:

- **Strong**, the modelling consideration has a significant relevance in the context of the selected modelling rationale;
- **Potentially**, the modelling consideration is typically included in the context of the selected modelling rationale, however, the inclusion thereof is not a set requirement; and
- **Context**, the context of the modelling application will determine the potential inclusion of the modelling consideration (i.e. the modelling consideration is not explicitly related to the modelling rationale).

As mentioned previously, more than one modelling rationale may be selected for a modelling approach. The above mentioned guidelines serve as prompts to inform the potential relevance of modelling considerations of Step 2 and Step 3 in the context of the selected modelling rationale. For each rationale, the modeller may choose to incorporate or leave out modelling considerations depending on the context-specific requirements of the modelling application.

Table A.5: Relevance of the selection of the modelling rationale on the outbreak modelling contextualisation steps.

Selected modelling rationale	**Interventions (i.e. Step 2)**	**Contextual factors (i.e. Step 3)**	**Mixing patterns (i.e. Step 3)**
Model disease dynamics	Potentially	Potentially	Potentially
Investigate causal relationships	Context	Strong	Context
Investigate super spreading events	Potentially	Strong	Strong
Forecast disease instance	Context	Potentially	Potentially
Develop a model and analyse behaviour	Potentially	Context	Context
Evaluate interventions	Strong	Potentially	Potentially

3.3. Step 2: Contextualisation, describe disease characteristics

The chain of infection is used as the reference to describe the disease characteristics as illustrated in the conceptual diagram in Figure A.5. The disease characteristics which relate to the transmission mode, incubation period and intervention strategies are captured within this section. The captured disease transmission modes are used in the steps that follow to inform the selection of the modelling considerations.

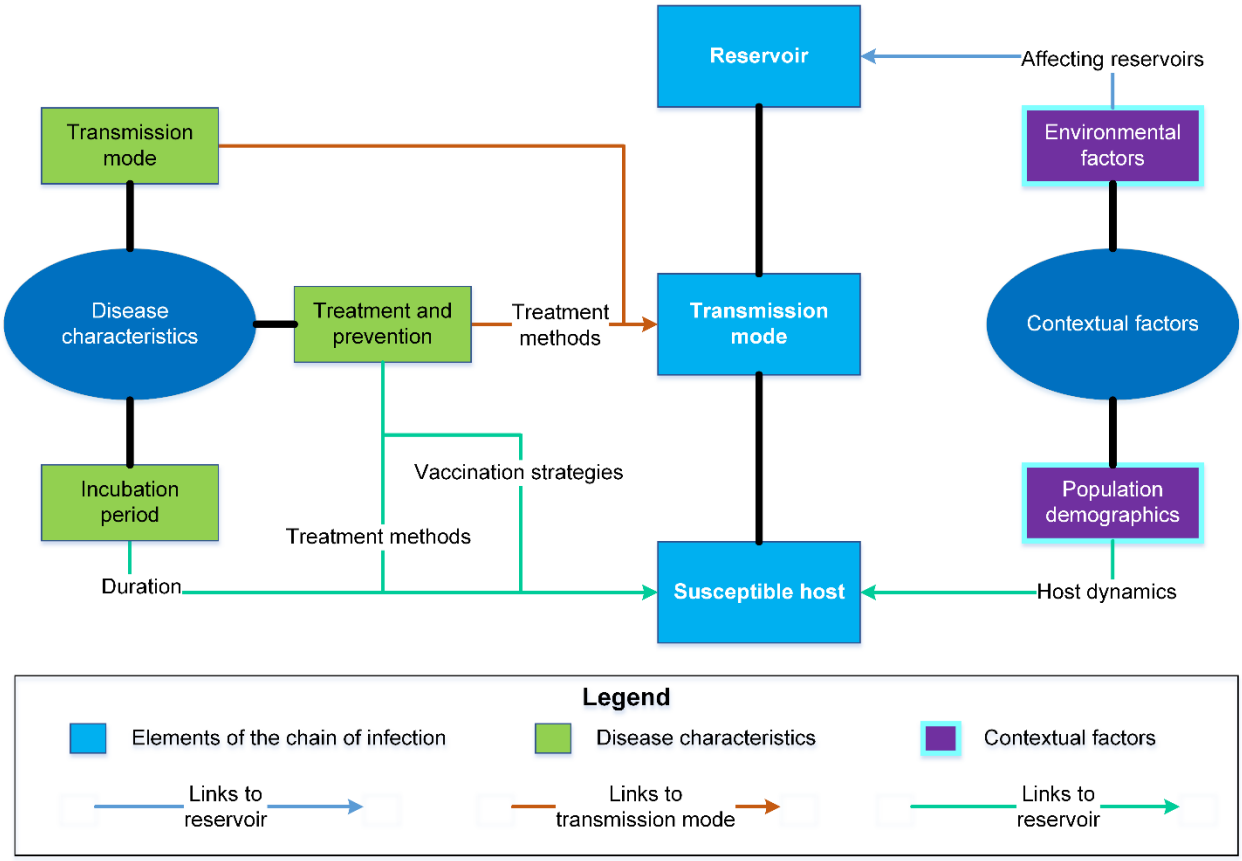

Figure A.5: The chain of infection as linked to the disease characteristics and contextual factors.

Table A.6: Mapping disease characteristics.

CAT		Transmission modes present (✓ / ✗)	Modelling assumptions	Additional information
Incubation period	Lower	N/A		
	Upper			
Disease transmission mode	Direct contact			
	Sexual contact			
	Respiratory			
	Body fluid			
	Food-borne			
	Water contact			
	Vector-borne			

Table A.7: A classification of vehicles and vectors according to 9 disease transmission categories.

Animal contact	**Direct contact**	**Sexual contact**	**Respiratory / droplet**	**Blood / body fluid**	**Food-borne**	**Soil contact**	**Water contact**	**Vector-borne**
Amphibian Reptile Animal bite Snail Earthworm Slug	Physical contact	Sexual contact	Droplet Dust Aerosol Respiratory Pharyngeal acquisition	Breastfeeding Fecal-oral Secretion Blood Tissue	Dairy products Eaten insect Fish Food Meat or poultry Shellfish Vegetable Fruit	Soil contact Vegetable matter	Water Fecal-oral	Fly Mosquito

3.3.1. Transmission mode

The disease characteristics which relate to the incubation period and the transmission mode are captured and described according to Table A.6. The upper and lower duration of the incubation period is noted, which may indicate how fast a disease leads to expression of symptoms and is able to transmit between individuals. Additionally, the information on the vehicles and vectors which are responsible for disease transmission are noted according to available clinical knowledge of the disease, or retrieved from the literature. The transmission mode is then determined using Table A.7. This is performed to ensure a consistent approach to determining the transmission mode categories. All potential disease transmission modes are then captured to Table A.6. With the goal to capture additional information or modelling assumptions of these categories (such as the most prominent transmission mode or additional details pertaining to the transmission vehicles), columns for modelling assumptions and additional information are available.

Table A.8: Mapping disease intervention strategies and modelling assumptions.

CAT	Accounted for (✓ / ✗)	Modelling assumptions	Additional information
Availability of vaccine			
Treatment options			

3.3.2. Intervention strategies

In addition to the transmission mode, the consideration of different intervention strategies also forms part of the disease characteristics. This describes aspects of both the transmission mode and the susceptible host of the chain of infection as illustrated in Figure A.5. The following data is captured and described in Table A.8 according to available clinical knowledge of the disease, or retrieved from the literature, namely:

- **Vaccines** which are available; and
- **Treatments** which can be used.

This will give background on interventions which are typically incorporated in the context of the disease management and which may be considered for incorporation within the modelling approach.

To inform the potential relevance of the inclusion of intervention strategies when modelling a given disease, the following guidelines are used, namely:

- Potential relevance of intervention strategies in relation to the transmission mode in in Table A.17; and
- Relevance of intervention strategies in the context of the selected modelling rationale as described in Table A.5.

Additional columns for modelling assumptions and additional information are available to capture any additional information relevant to the consideration and selection of intervention strategies in Table A.8.

Following the considerations of this step of the framework, the inclusion or exclusion of

- treatment; and
- vaccination;

in the proposed modelling approach are noted in Table A.3.

3.4. Step 3: Contextualisation, describe contextual characteristics

The chain of infection is used as the reference to describe the contextual characteristics which relate to the disease outbreak as illustrated in Figure A.5. The contextual factors which relate to the reservoir (i.e. typically environmental contextual factors) and the susceptible host (i.e. typically population demographic contextual factors and mixing pattern selection) are captured within this section. Following the considerations of this step of the framework, the inclusion or exclusion of:

- environmental factors;
- population demographics; and
- alternative mixing patterns;

in the proposed modelling approach are noted in Table A.3.

3.4.1. Environmental factors

The environmental factors which are considered within the disease modelling approach are described and captured in Table A.9. The suggested factors to consider include the following:

- **Seasonality** of disease dynamics;
- **Climate**, which may include rainfall and temperature; and
- **Additional factors**, which are determined at the discretion of the modeller.

To inform the potential relevance of the inclusion of environmental contextual factors when modelling a given disease, the following guidelines are used, namely

- Potential relevance of environmental factors in relation to the transmission mode in Table A.18; and

- Relevance of contextual factors in the context of the modelling rationale as described in Table A.5.

During the process of describing the environmental factors in increased detail, additional columns for modelling assumptions and additional information are available to capture any additional information relevant to the considered factors in Table A.9.

3.4.2. Population demographics

The population demographic factors which are considered within the disease modelling approach are described and captured in Table A.10. The suggested factors to consider include the following:

- **Population structure**, which relates to the age structure of the population;
- **Spatial spread**, how the population is dispersed geographically;
- **Mixing and migration** of the population, directly affecting the manner in which individuals move, interact and create potential contacts which may facilitate disease transmission;
- **Socio-economic** profile, which may indirectly affect the susceptibility of individuals; and
- **Additional factors**, which are determined at the discretion of the modeller.

To inform the potential relevance of the inclusion of population demographic contextual factors when modelling a given disease, the following guidelines are used, namely:

- Potential relevance of population demographic factors in relation to the transmission mode in Table A.18; and
- Relevance of contextual factors in the context of the modelling rationale as described in Table A.5.

During the process of describing the population demographics factors in increased detail, additional columns for modelling assumptions and additional information are available to capture any additional information relevant to the considered factors in Table A.10.

3.4.3. Mixing pattern selection

In addition to the population demographics, the mixing pattern consideration is also part of the ‘mixing and migration’ population demographic factor. The default mixing pattern in modelling approaches is homogenous mixing of contacts.

To inform the potential relevance of the inclusion of alternative mixing patterns when modelling a given disease, the following guidelines are used, namely:

- Transmission mode in Table A.15; and
- Relevance of alternative mixing patterns in the context of the modelling rationale as described in Table A.5.

Any additional detail regarding the mixing assumptions or considerations of the population are subsequently captured to the 'mixing and migration' row of Table A.10.

Table A.9: Mapping environmental contextual factors.

CAT	Accounted for (✓ / ✗)	Modelling assumptions	Additional information
Seasonality			
Climatic factors			
Additional factors			

Table A.10: Mapping population demographic contextual factors.

CAT	Accounted for (✓ / ✗)	Modelling assumptions	Additional information
Age structure			
Spatial spread			
Mixing			
Migration			
Socio-economic			
Additional factors			

3.5. Step 4: Requirements, determine available resources

3.5.1. Data source selection

Following the contextualisation of the chain of infection of the outbreak, the next contextualisation step is describing the available data sources in Table A.11. The data source categories typically employed in modelling approaches are reproduced below:

- **Case data** (e.g. data on confirmed cases of disease infection);
- **Parameters from literature** (e.g. data on transmission parameters previously formalised in the literature);
- **Population estimates** (e.g. census data);
- **Travel data** (e.g. data on movement of individuals);
- **Assumed** (e.g. data which assumes important transmission characteristics); and

- **None** (no data source used).

The data source does not necessarily imply or limit modelling considerations such as the modelling scope, modelling approach or incorporation of mixing patterns, but merely the resolution at which the disease outbreak may be described within the population. For instance, some data source categories may describe contextual factors such as population age structure or climate data on a country level, whereas other data sources relate to clinical instances of the disease on a provincial level. In order to better describe and capture the use of the data source, additional columns for modelling assumptions and additional information are available to capture any additional information relevant to the data source in Table A.11.

Table A.11: Mapping quality and source of data.

CAT	Data source used (✓ / ✗)	Modelling assumptions	Additional information
Case data			
Parameters from literature			
Population estimates			
Travel data			
Assumed			
None			

3.5.2. Previous modelling applications

Another resource apart from data which may prove useful is the availability of previous modelling applications. This may serve as a starting point for the current modelling application or enable the use of a previous modelling application following small extensions and alterations of the model. This would be context-specific for each modelling application and require sufficient research of the modelling literature. This would ideally be used to guide the selection and mapping of disease characteristics within the following phase. It is not possible to generalise this aspect of the resources available to the modeller, nonetheless, it is useful to take note of the option of considering previous modelling applications with a view to inform the current modelling application.

3.6. Step 5: Select modelling scope

Although the modelling scope selection is presented as part of the outbreak contextualisation phase, the selection of the modelling scope is also viewed as a one of the outbreak modelling selection steps. The options for selecting the scope of the modelling application are the following:

- General (i.e. a general modelling application with no indication of the scale of the application, typically a theoretical model for a specific disease instance);
- Global (i.e. disease transmission between more than two countries);
- Intercountry (i.e. disease transmission between two countries);
- Country (i.e. disease transmission within a single country);
- Provincial (i.e. disease transmission within a province); and
- Small region (i.e. disease transmission in a small region, such as a city or small village).

The modelling scope selection relates to the resolution of the area which the modelling application should model. To aid the modeller in the selection of the modelling scope, the selections of the following modelling considerations are used in Table A.12:

- Modelling rationale (captured in Table A.3);
- Transmission mode (captured in Table A.6); and
- Data source (captured in Table A.11).

The aforementioned three categories (completed as part of the outbreak contextualisation) guide and recommend the selection of the modelling scope in Table A.12. The selection of the modelling scope does not, however, relate solely to these three modelling considerations and the modeller has the freedom to select a different modelling scope regardless of the recommendations, should this be a modelling application requirement. In short, any modelling scope requirement is selectable, as long as the modelling approach and the data source are implemented so as to realistically and verifiably model the selected modelling scope. Following the considerations and recommendations, the modelling scope selection is noted in Table A.4.

Table A.12: Scope consideration and selection guidance within the framework.

CAT	Effect on incorporation		Modelling scope					
			General	Global	Intercountry	Country	Provincial	Small region
General observation	Scope most frequently observed:		✓			✓		
Modelling rationale	Most modelling scopes are used and suitable in the context of all modelling rationales, however, the three modelling scopes which are most frequently employed for each modelling rationale are:	Investigate causal relationships			✓		✓	✓
		Model disease transmission dynamics	✓			✓		✓
		Develop a model and analyse behaviour	✓	✓				✓
		Forecast disease instance				✓	✓	✓
		Evaluate interventions	✓	✓		✓		
		Investigate super spreading events				✓	✓	✓
Transmission mode	The most diverse modelling scope is applied to respiratory transmission modes, followed by direct contact and water contact transmission modes. Frequently observed modelling scopes in relation to the transmission mode are:	Direct contact	✓	✓	✓	✓		
		Sexual contact	✓			✓		
		Respiratory	✓	✓	✓		✓	✓
		Body fluid	✓		✓	✓		
		Food-borne	✓					✓
		Water contact	✓			✓	✓	
		Vector-borne	✓				✓	✓
Data source	Not all data sources are observed in the context of the modelling scope. The recommended scope for each data source category is:	Case data		✓	✓	✓	✓	✓
		Parameters from literature	✓			✓	✓	✓
		Population estimates		✓	✓	✓		
		Travel data		✓	✓	✓		
		Assumed	✓			✓		
		None	✓					

Steps 5 – 10: Outbreak modelling selection

Following the description of the background information (i.e. outbreak contextualisation) of the disease outbreak, the next phase of the framework entails the steps in the outbreak modelling selection phase. The steps which form part of the outbreak modelling contextualisation are as follows:

- Modelling approach selection in §3.7;
- Mixing pattern selection in §3.8;
- Selection of interventions strategies in §3.9;
- Selection of contextual factors in §3.10; and
- Model validation in §3.11.

The steps of the outbreak modelling selection are documented according to the steps in Table A.2. Not all steps of the outbreak modelling selection phase are necessarily required within all modelling applications. It is worth noting that the steps of the outbreak modelling selection phase that should always be included are the selection of a modelling approach (i.e. Step 6), model validation (i.e. Step 10) and documentation of the modelling process (i.e. Step 0). The inclusion of the remaining steps described in §3.8, §3.9, and §3.10 relate to the context-specific modelling goals, in addition to the following:

- Resources (§3.5); and
- Context-specific choices of the modeller.

In conclusion, the selections within the outbreak modelling selection phase of the framework depend on the interaction of numerous factors that are not necessarily generalisable to a single factor. Based on the suggestions of this section, however, the modeller may select the steps for inclusion based on the context and the modelling requirements.

3.7. Step 6: Select modelling approach

3.7.1. Modelling approach selection

The modelling approach selection is the first step of the outbreak modelling phase. In the framework, three broad modelling approach categories are available for selection, namely:

- Mathematical;
- Network; and
- Simulation.

.

Table A.13: Modelling approach consideration and selection guidance within the framework.

CAT	Effect on decision		Modelling approach categories		
			Mathematical	**Network**	**Simulation**
Methods observed most frequently	Numerous modelling approaches exist for the three categories, however, the following approaches are observed the most frequently:		DE Regression	Small world Metapopulation	ABS
Modelling rationale	All three modelling approaches are used and suitable in the context of all modelling rationales, however, the modelling approach which is used the most frequently per modelling approach category is:	Investigate causal relationships	✓		
		Model disease transmission dynamics			✓
		Develop a model and analyse behaviour		✓	
		Forecast disease instance	✓		
		Evaluate interventions			✓
		Investigate super spreading events			✓
Transmission mode	All three modelling approaches are used and suitable in the context of all transmission modes, however, the modelling approach(es) which are used the most frequently per transmission mode category are:	Direct contact		✓	✓
		Sexual contact	✓		
		Respiratory		✓	✓
		Body fluid		✓	✓
		Food-borne	✓		
		Water contact	✓		
		Vector-borne	✓		
Data source	All three modelling approaches are used and suitable in the context of all types of data sources, however, the modelling approaches which are used the most frequently per data source category are:	Case data			✓
		Parameters from literature	✓		
		Population estimates			✓
		Travel data		✓	
		Assumed		✓	
		None			✓
Modelling scope	All three modelling approaches are used and suitable in the context of all modelling scopes, however, when selecting a modelling approach, the modelling approach which is most frequently used for a given scope is:	General	✓		
		Global		✓	
		Intercountry		✓	
		Country	✓	✓	✓
		Provincial		✓	✓
		Small region			✓

Table A.14: Compartmental classification consideration and selection guidance within the framework.

CAT	Effect on decision		Transmission mode						
			Direct contact	**Sexual contact**	**Respiratory**	**Body fluid**	**Food-borne**	**Water contact**	**Vector-borne**
Compartmental categories in relation to the transmission mode	Modelling delay or exposure to disease	E	✓		✓	✓			✓
	Isolation from population	Q	✓		✓	✓			
	Prevent transmission with safe burial	F	✓			✓			
	Dependant on availability of (theoretical) vaccine	V	✓	✓	✓	✓		✓	
	Water-bodies are studied in relation to human populations	B W						✓	
	Mosquito populations are studied in relation to human populations	M							✓
General observation	It is not possible to recommend incorporation of compartmental classification based solely on the disease characteristics or contextual factors. Furthermore, all three broad modelling approaches are suitable to incorporate compartmental classification.								

To aid in the modeller in the selection of a modelling approach category, the previous selections of the following modelling considerations are used in Table A.13 to gather modelling suggestions, namely:

- Modelling rationale (captured in Table A.3);
- Transmission mode (captured in Table A.6);
- Data source (captured in Table A.11); and
- Modelling scope (selected in Step 5).

Similar to the section in which the modelling scope selection is described, the modeller has the freedom to select any modelling approach regardless of the recommendations, especially if a particular modelling approach is a requirement.

Following the considerations and recommendations of this modelling step, the modelling approach selection is noted in Table A.4.

3.7.2. Select (optional) compartmental classification

The choice of incorporating compartmental classification of individuals is an additional step of the modelling approach selection. It is not possible to generalise the inclusion of compartmental classification, however, recommendations on the selection of disease states are produced in Table A.14 in the context of the transmission mode of the disease. It is worth noting that some intervention strategies such as vaccination, quarantine and hospitalisation are occasionally incorporated as part of the compartmental classification.

Following the considerations and recommendations, if compartmental classification is incorporated, the selected compartmental categories are noted in Table A.4.

3.8. Step 7: Select mixing pattern(s)

Depending on the mapping completed relating to the contextualisation steps, the inclusion of alternative mixing patterns may form part of the outbreak modelling phase. The default mixing pattern in modelling approaches is homogenous mixing of contacts. Although alternative mixing patterns reflect the interactions between contacts more realistically, it is more difficult to incorporate these mixing patterns in modelling applications.

The selection in Table A.3 which relates to the incorporation of alternative mixing patterns is used to guide the mixing pattern selection. If alternative mixing patterns are not deemed necessary at this stage of the modelling application, the default mixing pattern of homogeneous mixing is selected. If alternative mixing patterns are required, the previous selections of the following modelling considerations are used in Table A.15 to gather modelling suggestions, namely:

- Transmission mode (captured in Table A.6);

- Modelling scope (selected in Step 5);
- Population demographics (captured in Table A.10); and
- Modelling approach (selected in Step 6).

It is worth noting that the following population demographic factors play an important role in mixing patterns:

- Age distribution and age related susceptibility;
- Population density; and
- Spatial spread of contacts.

If additional detail is required at this stage of the modelling process, the modeller may amend the details of the population demographics (Table A.10) or the data source (Table A.11) in order to realistically incorporate the alternative mixing patterns.

Following the considerations and recommendations, the mixing pattern selection is noted in Table A.4.

3.9. Step 8: Select intervention strategies

Depending on the mapping completed relating to the contextualisation steps, intervention strategies may form part of the outbreak modelling phase. These intervention strategies relate to treatment or vaccination of individuals. The selection in Table A.3 which relates to the inclusion of treatment and vaccination are used to guide the inclusion of treatment and vaccination strategies, respectively. If intervention strategies are required, the previous selections of the following modelling considerations are used in in Table A.17 to gather modelling suggestions, namely:

- Recommended strategies in relation to the transmission mode (captured in Table A.6);
- Data source (captured in Table A.11); and
- Modelling approach (selected in Step 6).

3.9.1. Treatment strategies

The transmission modes captured in Table A.6 are used to find potentially appropriate treatment methods in Table A.17. It is useful to note that the most frequently modelled treatment strategies relate to the reduction of contact between individuals (i.e. quarantine and hospitalisation). Similarly to previous modelling considerations, the modeller has the freedom to select different or additional treatment strategies regardless of the recommendations if these are a modelling requirement and the strategies are modelled realistically.

Following the considerations and recommendations, the treatment strategy inclusion and selection is noted in Table A.4.

Table A.15: Alternative mixing pattern consideration and selection guidance within the framework.

CAT	Effect on decision		Mixing incorporated	Occurrence of inclusion
Mixing methods observed most frequently	Of alternative mixing patterns included in modelling approaches, age and social mixing are the most frequently modelled. WAIFW matrices to model probability of disease transmission between different age groups or compartmental groups are also utilised to model alternative mixing patterns		N/A	
Transmission mode	When considering the inclusion of alternative mixing patterns in relation to the transmission mode, the following recommendations are made:	Direct contact	✓	High
		Sexual contact		N/A
		Respiratory	✓	High
		Body fluid	✓	High
		Food-borne		N/A
		Water contact	✓	Moderate
		Vector-borne	✓	Moderate
Modelling scope	Alternative mixing patterns are applied in the context of all modelling scopes, however, not all modelling scopes have equal proportions of inclusion of alternative mixing patterns. The occurrence of alternative mixing patterns in the context of the modelling scope guide the following recommendations:	General	✓	High
		Global	✓	Moderate
		Intercountry	✓	Moderate
		Country	✓	High
		Provincial	✓	Moderate
		Small region	✓	Very high
Population demographics	The following population demographic contextual factors are typically present in modelling approaches when alternative mixing patterns are included in the modelling approach:	Age and spatial spread Potentially population density	N/A	N/A
Modelling approach	Alternative mixing patterns are included in all three modelling approaches, however, based on the most frequent inclusion of age and social mixing in the context of the modelling approach, the following modelling approaches are recommended for usage of alternative mixing patterns:	Mathematical	✓	N/A
		Network		
		Simulation	✓	

Table A.16: A high-level overview of commonly used vaccination strategies.

Name of strategy	Strategy	Advantages	Disadvantages
Ring	Identify individuals with disease infection, then trace contacts for vaccination.	Minimises the required amount of vaccine doses.	Highly effective contact tracing required to limit disease transmission.
Targeted	Vaccination of an entire population within a specific city or district.	Effective strategy if used in an eradication campaign to contain geographically localised disease transmission.	Only effective in the context of prior high levels of herd immunity.
Mass (similar to RI)	Vaccination of an entire population in a country.	Effective at preventing and protecting against disease transmission across large areas.	Quick vaccination of large quantities of individuals are required to be effective.
Prophylactic	Preventative vaccination before disease outbreak.	Very effective at stopping spread of disease when used for an entire population.	High long term cost when used to protect an entire population.
Pulse	Repeated intervals of vaccination targeting a specific age range or a group of susceptible individuals.	Relative low levels of vaccination are required to ensure disease eradication.	Timing of pulses critical in the effectiveness of the strategy.

Table A.17: Intervention strategy consideration and selection guidance within the framework.

CAT	Effect on decision		Treatment	Vaccination
Potential relevance of intervention strategies in relation to the transmission mode	When considering the inclusion of intervention strategies, the relevance of the treatment and intervention strategies in relation to the transmission mode are:	Direct contact	High	High
		Sexual contact	High	High
		Respiratory	High	High
		Body fluid	High	High
		Food-borne	Moderate	Low
		Water contact	Moderate	High
		Vector-borne	Low	Low
Intervention strategies in relation to the transmission mode: Recommended strategies	The intervention strategies which are observed the most frequently in relation to the transmission mode are:	Direct contact	Quarantine Hospitalisation	A proportion of susceptible Ring
		Sexual contact	Quarantine	A proportion of susceptible
		Respiratory	Quarantine Hospitalisation	A proportion of susceptible Ring
		Body fluid	Quarantine Hospitalisation	A proportion of susceptible Ring
		Food-borne	Disinfection	N/A
		Water contact	Disinfection Drug usage	A proportion of susceptible
		Vector-borne	Drug usage	N/A
Data source	All six data sources are suitable in the context of intervention strategies, and the data source is not expected to play a role in the inclusion of intervention strategies. However, the ‘case data’ and ‘parameters from the literature’ data sources are observed in the highest proportion of modelling approaches which include treatment and vaccination strategies.			
Modelling approach	All three modelling approaches are suitable in the context of intervention strategy inclusion and the selection of a modelling approach is not expected to play a role in the inclusion of intervention strategies.			

3.9.2. Vaccination strategies

The transmission modes captured in Table A.6 are used to find vaccination strategies relevant to the transmission modes in Table A.17. It is useful to note that the most frequently incorporated vaccination strategies are ring vaccination and a general vaccination of a portion of the susceptible population. Additional vaccination strategies which are also available for incorporation are summarised in Table A.16. Similarly to previous modelling considerations, the modeller has the freedom to select different or additional vaccination strategies regardless of the recommendations if this is a modelling requirement and the strategies are modelled realistically.

Following the considerations and recommendations, the vaccination strategy inclusion and selection is noted in Table A.4.

3.10. Step 9: Select contextual factors

Depending on the decisions captured as part of the modelling contextualisation phase, contextual factors may form part of the outbreak modelling selection phase. These contextual factors relate to environmental or population demographic factors. The selection in Table A.3 which relates to the inclusion of environmental contextual factors and demographics is used to guide the inclusion of environmental and population demographic factors, respectively. If contextual factors are required, the previous selections of the following modelling considerations are used in Table A.18 to gather modelling suggestions, namely:

- Recommended environmental factors in relation to the transmission mode (captured in Table A.6);
- Recommended population demographic factors in relation to the transmission mode (captured in Table A.6); and
- Data source (captured in Table A.11).

3.10.1. Environmental factors

The transmission modes captured in Table A.6 are used to find potentially relevant environmental contextual factors in relation to the transmission modes in Table A.18. Similarly to previous modelling considerations, the modeller has the freedom to include or model different or additional environmental factors regardless of the recommendations if this is a modelling application requirement and it is modelled realistically.

Following the considerations and recommendations, the environmental factor inclusion and selection is noted in Table A.4.

Table A.18: Contextual factor consideration and selection guidance within the framework.

CAT	Effect on decision		Contextual factors	
			Linked to disease propagation	**Modelled**
Potential relevance of environmental factors in relation to the transmission mode	When considering the inclusion of environmental contextual factors, the relevance to the transmission mode are:	Direct contact	Low	
		Sexual contact	Low	
		Respiratory	Moderate	
		Body fluid	High	
		Food-borne	High	
		Water contact	High	
		Vector-borne	Very high	
Environmental factors in relation to the transmission mode: Recommended factors to consider	The environmental contextual factors which are observed the most frequently in relation to the transmission mode are:	Direct contact	N/A	Seasonality
		Sexual contact	N/A	
		Respiratory	Climate & seasonality & rainfall	Seasonality
		Body fluid	N/A	Seasonality
		Food-borne	Climate & rainfall	
		Water contact	Climate & temperature & rainfall	
		Vector-borne	Climate & temperature & rainfall	
Potential relevance of demographic factors in relation to the transmission mode	When considering the inclusion of population demographic contextual factors, the relevance of the to the transmission mode are:	Direct contact	Very high	
		Sexual contact	Low	
		Respiratory	Very high	
		Body fluid	High	
		Food-borne	Moderate	
		Water contact	Very high	
		Vector-borne	Moderate	
Population demographic factors in relation to the transmission mode: Recommended factors to consider	The population demographic contextual factors which are observed the most frequently in relation to the transmission mode are:	Direct contact	Age & population density & migration & spatial spread	
		Sexual contact	N/A	
		Respiratory	Age & population density & migration & spatial spread	
		Body fluid	Age & population density & migration & spatial spread	
		Food-borne	Spatial spread & socio economic	
		Water contact	Spatial spread & socio economic	
		Vector-borne	Spatial spread & socio economic	Age & spatial spread
Data source	The only two data sources which were used in the context of all contextual factors were case data and parameters from the literature. Population estimates and travel data are only used in the context of population demographic factors.			

3.10.2. Population demographic factors

The transmission modes captured in Table A.6 are used to find potentially relevant population demographic contextual factors in relation to the transmission modes in Table A.18. Similarly to previous modelling considerations, the modeller has the freedom to include or model different or additional population demographic factors regardless of the recommendations if it is a modelling application requirement and is modelled realistically. It is useful to note that the most frequently included demographic factors are the spatial spread of individuals, population density, migration and age stratification of individuals within the population.

Following the considerations, the population demographic factor inclusion and selection is noted in Table A.4.

3.11. Step 10: Validate model

Following the modelling application selection and implementation, the model is validated to ensure that the modelling application and modelling results accurately reflect the disease outbreak. The challenges when developing models are formulated as questions to guide the validation process:

- Does the model answer the research question (i.e. modelling rationale and modelling goals)?
- Is the model comprehensible (i.e. ability to analyse and examine the model)?
- Is the model believable (i.e. an accurate reflection of reality)?
- Does the model fit the data (i.e. verify the model operation)?

It is not possible to generalise the methods used to fit the modelling data to a modelling application. This does not reduce the importance of fitting the data to a model or the validation thereof, but the selection of a fitting method is left to the discretion of the modeller. A checklist is available for use in Table A.4 to ensure the validation questions are considered as part of the validation, in addition to noting the selection of a fitting method.

Section 4. Illustrative case study: Guided framework walkthrough

The fairly recent global Zika outbreak is used as the studied disease in the case study. The following hypothetical situation is constructed to demonstrate the functioning of the framework in supporting the modelling process:

A major outbreak of Zika virus is in progress in Brazil, with the virus currently being transmitted beyond the country borders. There are no prophylactic vaccines available for use and no confirmed disease treatment, apart from supportive treatment. It is suspected that multiple transmission routes exist. Furthermore, the disease has not been modelled extensively in the past.

The modeller is tasked with selecting a modelling approach to investigate relevant factors which may suggest the prevalence of the disease in the area. As few modelling approaches are completed in the past, the influence of relevant factors are first considered, prior to establishing a disease transmission model. Confirmed clinical case data for large cities are available to the modeller.

In this section, the outbreak case study information is used to illustrate a high-level walkthrough of the framework steps.

4.1. Step 0: Documentation

The documentation step of the framework runs concurrently throughout the modelling process, and the user is reminded that documentation of:

- Steps 1 – 4 is done according to the template of Table A.3; and
- Steps 5 – 10 is done according to the template of Table A.4.

The completed outbreak modelling contextualisation documentation and outbreak modelling selection documentation are captured to Table A.25 and Table A.26, respectively and are presented at the end of the section.

4.2. Step 1: Select modelling rationale

As stated in the case study, no extensive modelling has previously been completed for the Zika virus. In the context of the modelling task, which is to investigate the drivers of disease prevalence, the ‘investigate causal relationships’ modelling rationale is selected and noted in Table A.25. The potential relevance of the selection of outbreak modelling considerations in the context of the selected modelling rationale is described in Table A.19 (this is an excerpt of only the relevant information from Table A.5) and used in Step 2 and Step 3.

Table A.19: Selected modelling rationale and potential relevance to the outbreak contextualisation steps.

Selected modelling rationale	**Interventions (i.e. Step 2)**	**Contextual factors (i.e. Step 3)**	**Mixing patterns (i.e. Step 3)**
Investigate causal relationships	Context	Context	Strong

Table A.20: Captured disease characteristics.

Category		**Transmission modes present (✓ / ✗)**	**Modelling assumptions**	**Additional information**
Incubation period (days)	Lower	N/A	3	Symptoms typically last for 2-7 days
	Upper		14	
Disease transmission mode	Direct contact	✓	Not used in model	GIDEON vehicle breast feeding, assumed very rare
	Sexual contact	✓	Not used in model	Not a model requirement
	Respiratory			
	Body fluid	✓	Not used in model	Transfusion of blood
	Food-borne			
	Water contact			
	Vector-borne	✓		Primary transmission mode investigated

Table A.21: Consideration of intervention strategies.

Category	**Accounted for (✓ / ✗)**	**Modelling assumptions**	**Additional information**
Availability of vaccine	✗		No vaccine currently available. Investigation of theoretical vaccine not currently a priority
Treatment options	✗		No current treatment available

4.3. Step 2: Contextualisation, describe disease characteristics

As extracted from the literature, the vectors and vehicles responsible for transmission of the Zika virus are as follows:

- Vector: mosquitoes; and
- Vehicles: sexual contact, saliva, blood transfusion, breast-feeding.

Using Table A.7, the transmission modes are determined and noted in Table A.20. From the literature, the incubation period is also noted. The incubation period is also noted (from literature). This is used to inform potential realistic transmission parameters.

The selected modelling rationale recommends the contextual inclusion of intervention strategies, if this is a modelling requirement. Based on the case study, no vaccines are available to use against Zika infection and no treatment other than supportive treatment is available (noted in Table A.21). In view of the modelling goal that does not require intervention strategies in the modelling approach, Table A.16 and Table A.17 are not used to extract intervention strategy recommendations and the exclusion of intervention strategies from the modelling approach is noted in Table A.25.

4.4. Step 3: Contextualisation, describe contextual characteristics

Based on the selected modelling rationale, contextual characteristics are a potentially strong requirement for the modelling approach, as one of the stated modelling tasks is the investigation of factors which could explain the disease prevalence. Based on the transmission mode captured and considered in Table A.20, the relevant factors are extracted from Table A.18. The user may select both population demographics (noted in Table A.23) and environmental factors (noted in Table A.22), however, only the vector-borne transmission route is studied in this modelling approach and not the other transmission routes which relate to contact between humans (i.e. sexual contact). Only environmental factors are, therefore, included in the modelling approach and noted in Table A.25. As more information on the disease dynamics become available, future work could include detailed incorporation of population demographic factors.

The selected modelling rationale recommends the inclusion of alternative mixing patterns, if this is a modelling requirement. If population demographics are studied in more detail, alternative mixing patterns could form part of the modelling approach. In this modelling application, however, alternative mixing patterns are not a modelling requirement and the exclusion thereof from the modelling approach is noted in Table A.25.

Table A.22: Consideration of environmental factors contextual factors.

Category	Accounted for (✓ / ✗)	Modelling assumptions	Additional information
Seasonality	✓		Correlation to climatic factors?
Climatic factors	✓	Temperature and rainfall	Potential drivers of disease prevalence
Additional factors	✗		

Table A.23: Consideration of population demographic contextual factors.

Category	Accounted for (✓ / ✗)	Modelling assumptions	Additional information
Age structure	✗		No data on age related disease prevalence. Additionally not a modelling requirement
Spatial spread	✗		Not studied in detail and not a modelling requirement
Mixing	✗		
Migration	✗		
Socio-economic	✗		
Additional factors	✗		

4.5. Step 4: Requirements, determine available resources

The monthly case data of reported clinical cases are available to the modeller. This is important to note, especially considering that Zika and Dengue share similar symptoms, and the availability of monthly case data therefore enables the modeller to ensure that only Zika disease instances are considered. Furthermore, monthly climate data on rainfall is documented and the availability of this data is noted by the user. The data source considerations are noted in Table A.24.

4.6. Step 5: Select modelling scope

The information provided in Table A.12 is used to guide the selection of the modelling scope, based on the selected modelling rationale, transmission mode, and data source. Based on the modelling rationale selection, the recommended scopes in Table A.12 include a country, provincial and small region scope. In relation to the transmission mode (vector-borne), the recommended scope is a

provincial or small region scope. As case data is available for the modelling approach, all modelling scopes apart from a general scope are available to select. In this context, however, the data source relates to a small region. This could be aggregated to construct a provincial model, however, the modeller selects a small region scope. This selection is noted in Table A.26, in addition to the line of reasoning for this selection.

Table A.24: Mapping quality and source of data.

Category	Data source used (✓ / ✗)	Modelling assumptions	Additional information
Case data	✓	Monthly data on confirmed clinical cases Monthly climate data	As the incubation period of the disease is between 3-14 days, monthly data is suitable in order to investigate the effect of climatic variables on disease prevalence
Parameters from literature	✗		
Population estimates	✗		
Travel data	✗		
Assumed	✗		
None	✗		

4.7. Step 6: Select modelling approach

The information provided in Table A.13 is used to guide the selection of a modelling approach, based on the selected modelling rationale, modelling scope, transmission mode and data source. A mathematical approach is frequently used with the selected modelling rationale and the applicable disease transmission mode. With further considerations, the simulation approach is not practical, as actors are not modelled in the approach. A similar line of reasoning eliminates the selection of network modelling. From the various mathematical approaches, regression is selected for implementation, as this is the most suitable method to investigate the effect of the climate variables. Although it is noted that a simulation approach is frequently used in the context of the selected modelling scope, Table A.13 states that all three modelling approaches are suited for all modelling scopes. Additionally, compartmental classification is not included, as individual disease states are not modelled. The modelling approach selection is noted in Table A.26, in addition to the line of reasoning for this selection.

4.8. Step 7: Select mixing pattern(s)

According to Table A.25, alternative mixing patterns of individuals are not considered in this modelling approach. Individuals are assumed to mix homogenously and the selection of homogenous mixing is noted in Table A.26, in addition to the line of reasoning for this selection.

4.9. Step 8: Select intervention strategies

According to the selection in Table A.25, intervention strategies are not considered in this modelling approach. Therefore, the exclusion of intervention strategies from the modelling approach is noted in Table A.26, in addition to the line of reasoning for this exclusion.

4.10. Step 9: Select contextual factors

According to the selection in Table A.25, only environmental contextual factors are considered for inclusion in this modelling approach. Therefore, the inclusion of environmental factors in the modelling approach is noted in Table A.26, in addition to the line of reasoning for the selection of environmental factors and the exclusion of population demographic factors as noted in Table A.22 and Table A.23, respectively.

4.11. Step 10: Validate model

In this step, the modeller reviews the modelling approach according to the four questions presented in the validation category in Table A.26. In addition to addressing these questions, the fitting method used in the modelling approach to ensure that the model is a realistic representation of the disease outbreak is noted, together with the line of reasoning for the selection of the fitting method and the results of the fitting method.

Table A.25: Outbreak modelling contextualisation documentation.

Modelling rationale	**Selected (✓ / ✗)**	**Treatment included (✓ / ✗)**	**Vaccination included (✓ / ✗)**	**Environmental factors included (✓ / ✗)**	**Demographics included (✓ / ✗)**	**Alternative mixing patterns included (✓ / ✗)**
Model disease dynamics	✗	✗	✗	✓	✗	✗
Investigate causal relationships	✓					
Investigate super spreading events	✗					
Forecast disease instance	✗					
Develop a model and analyse behaviour	✗					
Evaluate interventions	✗					

Table A.26: Outbreak modelling selection documentation.

Category		Selection (✓)	Methods and/or categories selected	Modelling assumptions	Additional comments
Modelling scope	General		N/A		Selection based on recommendations in relation to the transmission mode and modelling rationale. Case data may be aggregated to model on a provincial scope, however, small region is selected. Additionally, the data supports the use of this modelling scope.
	Global				
	Intercountry				
	Country				
	Provincial				
	Small region	✓			
Modelling application	Mathematical	✓	Regression	Most suited approach to investigate causal relationships	Selection based on recommendations in relation to the transmission mode and modelling rationale.
	Network				
	Simulation				
	Compartmental classification		Not used	Not used	Individual disease states are not modelled
Mixing patterns	Homogeneous	✓	Homogeneous		Detailed mixing not required
	Alternative				
Intervention and control	None	✓			
	Treatment				No treatment strategies available
	Vaccination				No vaccines available, investigation of theoretical vaccine not currently a priority
Contextual factors	None				
	Environmental	✓		Correlations between factors and prevalence	Rainfall and temperature suspected to affect disease dynamics
	Demographics				Not studied in detail
Validate model	Does the model answer research question?	✓	N/A		
	Is the model comprehensible?	✓			
	Is the model believable?	✓			
	Does the model fit the data?	✓			
	Fitting methods used:	✓	Least squares	Commonly used for this mathematical approach	Correlation: 0.8 rainfall 0.4 temperature
Future work		✓	Investigate effect of population density and migration on disease prevalence		Test theoretical vaccine to prepare for availability of newly developed vaccine

Section 5. Conclusion

Modelling approach selection is a complex endeavour and decisions are not reducible to a single factor or consideration. The goal of the framework is not to establish fixed rules which are universal in all instances or to suggest every single potential theoretical modelling approach. This is infeasible due to the interaction of various factors and considerations which influence the selection of a modelling approach, in addition to the difficulty in generalising the context of a disease outbreak. Instead, the framework is used to prompt the modelling practitioner to ensure that all relevant modelling considerations are taken into account, and guides the modelling approach selection by proposing options based on analysis of observed relationships in the literature. Furthermore, the framework steps guide the modeller to systematically document the approach selection process, thus creating a paper trail of factors that were taken into account when selecting the model approach and developing the model.

Appendix B (Chapter 2)

A figure omitted from Chapter 2 is presented in this appendix.

B.1 Figure

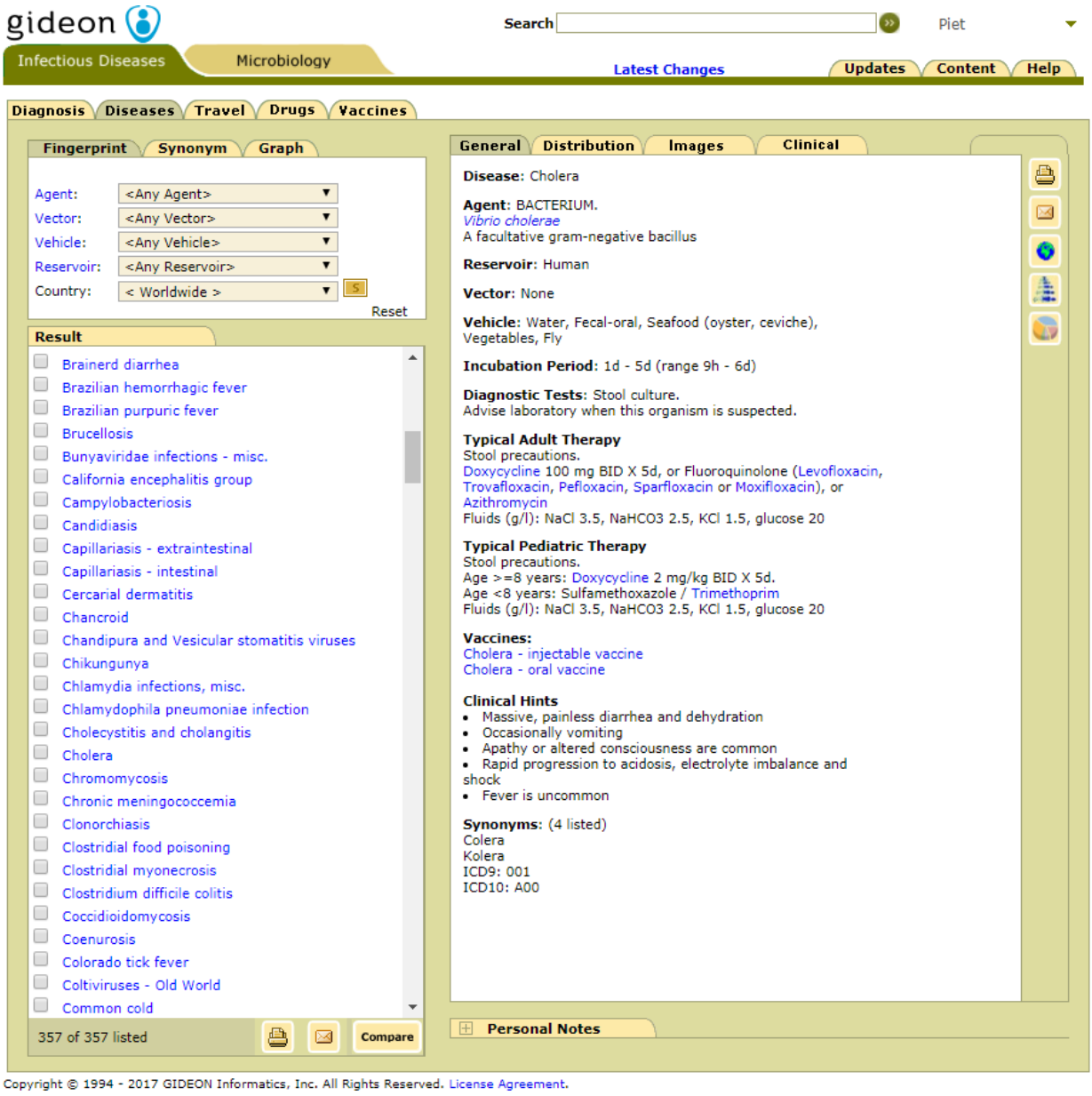

Figure B.1: Screenshot of GIDEON database.

Appendix C (Chapter 3)

A number of sections in support of Chapter 3 is presented in this appendix. Information pertaining to a selection of the structured literature review steps and omissions are presented, in addition to the descriptive analysis of the dataset (i.e. REF A analysis).

C.1 Scopus search protocols

C.1.1 Diphtheria

TITLE-ABS-KEY (diphtheria AND model) AND (LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (PUBYEAR , 2009) OR LIMIT-TO (PUBYEAR , 2008) OR LIMIT-TO (PUBYEAR , 2007) OR LIMIT-TO (PUBYEAR , 2006) OR LIMIT-TO (PUBYEAR , 2005) OR LIMIT-TO (PUBYEAR , 2004) OR LIMIT-TO (PUBYEAR , 2003) OR LIMIT-TO (PUBYEAR , 2002) OR LIMIT-TO (PUBYEAR , 2001) OR LIMIT-TO (PUBYEAR , 2000)) AND (EXCLUDE (SUBJAREA , "BIOC") OR EXCLUDE (SUBJAREA , "IMMU") OR EXCLUDE (SUBJAREA , "PHAR") OR EXCLUDE (SUBJAREA , "NEUR") OR EXCLUDE (SUBJAREA , "CHEM") OR EXCLUDE (SUBJAREA , "SOCI") OR EXCLUDE (SUBJAREA , "ARTS") OR EXCLUDE (SUBJAREA , "MATE") OR EXCLUDE (SUBJAREA , "PSYC"))

C.1.2 Measles

TITLE-ABS-KEY (measles AND model) AND (LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (PUBYEAR , 2009) OR LIMIT-TO (PUBYEAR , 2008) OR LIMIT-TO (PUBYEAR , 2007) OR LIMIT-TO (PUBYEAR , 2006) OR LIMIT-TO (PUBYEAR , 2005) OR LIMIT-TO (PUBYEAR , 2004) OR LIMIT-TO (PUBYEAR , 2003) OR LIMIT-TO (PUBYEAR , 2002) OR LIMIT-TO (PUBYEAR , 2001) OR LIMIT-TO (PUBYEAR , 2000)) AND (EXCLUDE (SUBJAREA , "IMMU") OR EXCLUDE (SUBJAREA , "BIOC") OR EXCLUDE (SUBJAREA , "PHAR") OR EXCLUDE (SUBJAREA , "NEUR") OR EXCLUDE (SUBJAREA , "MATE") OR EXCLUDE (SUBJAREA , "CHEM") OR EXCLUDE (

SUBJAREA , "ARTS") OR EXCLUDE (SUBJAREA , "PSYC") OR EXCLUDE (SUBJAREA , "DENT"))

C.1.3 Mumps

TITLE-ABS-KEY (mumps AND model) AND (LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (PUBYEAR , 2009) OR LIMIT-TO (PUBYEAR , 2008) OR LIMIT-TO (PUBYEAR , 2007) OR LIMIT-TO (PUBYEAR , 2006) OR LIMIT-TO (PUBYEAR , 2005) OR LIMIT-TO (PUBYEAR , 2004) OR LIMIT-TO (PUBYEAR , 2003) OR LIMIT-TO (PUBYEAR , 2002) OR LIMIT-TO (PUBYEAR , 2001) OR LIMIT-TO (PUBYEAR , 2000)) AND (EXCLUDE (SUBJAREA , "IMMU") OR EXCLUDE (SUBJAREA , "BIOC") OR EXCLUDE (SUBJAREA , "PHAR") OR EXCLUDE (SUBJAREA , "MATE") OR EXCLUDE (SUBJAREA , "NEUR") OR EXCLUDE (SUBJAREA , "ARTS") OR EXCLUDE (SUBJAREA , "PSYC") OR EXCLUDE (SUBJAREA , "CHEM") OR EXCLUDE (SUBJAREA , "DENT"))

C.1.4 Pertussis

TITLE-ABS-KEY (pertussis AND model) AND (LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (PUBYEAR , 2009) OR LIMIT-TO (PUBYEAR , 2008) OR LIMIT-TO (PUBYEAR , 2007) OR LIMIT-TO (PUBYEAR , 2006) OR LIMIT-TO (PUBYEAR , 2005) OR LIMIT-TO (PUBYEAR , 2004) OR LIMIT-TO (PUBYEAR , 2003) OR LIMIT-TO (PUBYEAR , 2002) OR LIMIT-TO (PUBYEAR , 2001) OR LIMIT-TO (PUBYEAR , 2000)) AND (EXCLUDE (SUBJAREA , "BIOC") OR EXCLUDE (SUBJAREA , "IMMU") OR EXCLUDE (SUBJAREA , "PHAR") OR EXCLUDE (SUBJAREA , "NEUR") OR EXCLUDE (SUBJAREA , "CHEM") OR EXCLUDE (SUBJAREA , "ARTS") OR EXCLUDE (SUBJAREA , "MATE") OR EXCLUDE (SUBJAREA , "PSYC"))

C.1.5 Polio

TITLE-ABS-KEY (polio AND model) AND (LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (PUBYEAR , 2009) OR LIMIT-TO (PUBYEAR , 2008) OR LIMIT-TO (PUBYEAR , 2007) OR LIMIT-TO (PUBYEAR , 2006) OR LIMIT-TO (PUBYEAR , 2005) OR LIMIT-TO (PUBYEAR , 2004) OR LIMIT-TO (PUBYEAR ,

2003) OR LIMIT-TO (PUBYEAR , 2002) OR LIMIT-TO (PUBYEAR , 2001) OR LIMIT-TO (PUBYEAR , 2000)) AND (EXCLUDE (SUBJAREA , "BIOC") OR EXCLUDE (SUBJAREA , "IMMU") OR EXCLUDE (SUBJAREA , "PHAR") OR EXCLUDE (SUBJAREA , "NEUR") OR EXCLUDE (SUBJAREA , "ARTS") OR EXCLUDE (SUBJAREA , "CHEM") OR EXCLUDE (SUBJAREA , "PSYC") OR EXCLUDE (SUBJAREA , "DENT") OR EXCLUDE (SUBJAREA , "MATE"))

C.1.6 Rotavirus

TITLE-ABS-KEY (rotavirus AND model) AND (LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (PUBYEAR , 2009) OR LIMIT-TO (PUBYEAR , 2008) OR LIMIT-TO (PUBYEAR , 2007) OR LIMIT-TO (PUBYEAR , 2006) OR LIMIT-TO (PUBYEAR , 2005) OR LIMIT-TO (PUBYEAR , 2004) OR LIMIT-TO (PUBYEAR , 2003) OR LIMIT-TO (PUBYEAR , 2002) OR LIMIT-TO (PUBYEAR , 2001) OR LIMIT-TO (PUBYEAR , 2000)) AND (EXCLUDE (SUBJAREA , "IMMU") OR EXCLUDE (SUBJAREA , "BIOC") OR EXCLUDE (SUBJAREA , "PHAR") OR EXCLUDE (SUBJAREA , "CHEM") OR EXCLUDE (SUBJAREA , "MATE") OR EXCLUDE (SUBJAREA , "NEUR") OR EXCLUDE (SUBJAREA , "ARTS") OR EXCLUDE (SUBJAREA , "PSYC"))

C.1.7 Rubella

TITLE-ABS-KEY (rubella AND model) AND (LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (PUBYEAR , 2009) OR LIMIT-TO (PUBYEAR , 2008) OR LIMIT-TO (PUBYEAR , 2007) OR LIMIT-TO (PUBYEAR , 2006) OR LIMIT-TO (PUBYEAR , 2005) OR LIMIT-TO (PUBYEAR , 2004) OR LIMIT-TO (PUBYEAR , 2003) OR LIMIT-TO (PUBYEAR , 2002) OR LIMIT-TO (PUBYEAR , 2001) OR LIMIT-TO (PUBYEAR , 2000)) AND (EXCLUDE (SUBJAREA , "IMMU") OR EXCLUDE (SUBJAREA , "BIOC") OR EXCLUDE (SUBJAREA , "PHAR") OR EXCLUDE (SUBJAREA , "NEUR") OR EXCLUDE (SUBJAREA , "ARTS") OR EXCLUDE (SUBJAREA , "PSYC") OR EXCLUDE (SUBJAREA , "MATE") OR EXCLUDE (SUBJAREA , "CHEM") OR EXCLUDE (SUBJAREA , "DENT"))

C.1.8 Cholera

TITLE-ABS-KEY (cholera AND model) AND (LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR

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C.1.9 Dengue

TITLE-ABS-KEY (dengue AND model) AND (LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (PUBYEAR , 2009) OR LIMIT-TO (PUBYEAR , 2008) OR LIMIT-TO (PUBYEAR , 2007) OR LIMIT-TO (PUBYEAR , 2006) OR LIMIT-TO (PUBYEAR , 2005) OR LIMIT-TO (PUBYEAR , 2004) OR LIMIT-TO (PUBYEAR , 2003) OR LIMIT-TO (PUBYEAR , 2002) OR LIMIT-TO (PUBYEAR , 2001) OR LIMIT-TO (PUBYEAR , 2000)) AND (EXCLUDE (SUBJAREA , "IMMU") OR EXCLUDE (SUBJAREA , "BIOC") OR EXCLUDE (SUBJAREA , "PHAR") OR EXCLUDE (SUBJAREA , "CHEM") OR EXCLUDE (SUBJAREA , "NEUR") OR EXCLUDE (SUBJAREA , "MATE") OR EXCLUDE (SUBJAREA , "ARTS") OR EXCLUDE (SUBJAREA , "ENER") OR EXCLUDE (SUBJAREA , "PSYC")) AND (EXCLUDE (PUBYEAR , 2018)) AND (LIMIT-TO (EXACTKEYWORD , "Disease Transmission") OR LIMIT-TO (EXACTKEYWORD , "Statistical Model") OR LIMIT-TO (EXACTKEYWORD , "Disease Outbreaks") OR LIMIT-TO (EXACTKEYWORD , "Transmission") OR LIMIT-TO (EXACTKEYWORD , "Risk Assessment") OR LIMIT-TO (EXACTKEYWORD , "Risk Factor") OR LIMIT-TO (EXACTKEYWORD , "Mathematical Model") OR LIMIT-TO (EXACTKEYWORD , "Climate") OR LIMIT-TO (EXACTKEYWORD , "Climate Change") OR LIMIT-TO (EXACTKEYWORD , "Forecasting") OR LIMIT-TO (EXACTKEYWORD , "Temperature") OR LIMIT-TO (EXACTKEYWORD , "Models, Statistical") OR LIMIT-TO (EXACTKEYWORD , "Models, Biological") OR LIMIT-TO (EXACTKEYWORD , "Theoretical Model") OR LIMIT-TO (EXACTKEYWORD , "Regression Analysis") OR LIMIT-TO (EXACTKEYWORD , "Seasonal Variation") OR LIMIT-TO (EXACTKEYWORD , "Time Factors") OR LIMIT-TO (EXACTKEYWORD , "Infection Risk") OR LIMIT-TO (EXACTKEYWORD , "Population Density") OR LIMIT-TO (EXACTKEYWORD , "Population Dynamics") OR LIMIT-TO (EXACTKEYWORD , "Epidemics") OR LIMIT-TO (EXACTKEYWORD , "Geographic Distribution") OR LIMIT-TO (EXACTKEYWORD , "Vaccination"

) OR LIMIT-TO (EXACTKEYWORD , "Biological Model") OR LIMIT-TO (EXACTKEYWORD , "Prevalence") OR LIMIT-TO (EXACTKEYWORD , "Socioeconomics") OR LIMIT-TO (EXACTKEYWORD , "Disease Model") OR LIMIT-TO (EXACTKEYWORD , "Mathematical Models") OR LIMIT-TO (EXACTKEYWORD , "Humidity") OR LIMIT-TO (EXACTKEYWORD , "Statistics And Numerical Data") OR LIMIT-TO (EXACTKEYWORD , "Demography") OR LIMIT-TO (EXACTKEYWORD , "Computer Simulation") OR LIMIT-TO (EXACTKEYWORD , "Environmental Factor") OR LIMIT-TO (EXACTKEYWORD , "Weather") OR LIMIT-TO (EXACTKEYWORD , "Environmental Temperature") OR LIMIT-TO (EXACTKEYWORD , "Geographic Information Systems") OR LIMIT-TO (EXACTKEYWORD , "Travel") OR LIMIT-TO (EXACTKEYWORD , "Spatial Analysis") OR LIMIT-TO (EXACTKEYWORD , "Spatiotemporal Analysis") OR LIMIT-TO (EXACTKEYWORD , "Socioeconomic Factors")) AND (EXCLUDE (PUBYEAR , 2012) OR EXCLUDE (PUBYEAR , 2011) OR EXCLUDE (PUBYEAR , 2010) OR EXCLUDE (PUBYEAR , 2009) OR EXCLUDE (PUBYEAR , 2008) OR EXCLUDE (PUBYEAR , 2007) OR EXCLUDE (PUBYEAR , 2006) OR EXCLUDE (PUBYEAR , 2005) OR EXCLUDE (PUBYEAR , 2004) OR EXCLUDE (PUBYEAR , 2003) OR EXCLUDE (PUBYEAR , 2002) OR EXCLUDE (PUBYEAR , 2001) OR EXCLUDE (PUBYEAR , 2000)) AND (EXCLUDE (PUBYEAR , 2013)) AND (EXCLUDE (PUBYEAR , 2014))

C.1.10 Ebola

TITLE-ABS-KEY (ebola AND model) AND (LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (PUBYEAR , 2009) OR LIMIT-TO (PUBYEAR , 2008) OR LIMIT-TO (PUBYEAR , 2007) OR LIMIT-TO (PUBYEAR , 2006) OR LIMIT-TO (PUBYEAR , 2005) OR LIMIT-TO (PUBYEAR , 2004) OR LIMIT-TO (PUBYEAR , 2003) OR LIMIT-TO (PUBYEAR , 2002) OR LIMIT-TO (PUBYEAR , 2001) OR LIMIT-TO (PUBYEAR , 2000)) AND (EXCLUDE (SUBJAREA , "IMMU") OR EXCLUDE (SUBJAREA , "BIOC") OR EXCLUDE (SUBJAREA , "PHAR") OR EXCLUDE (SUBJAREA , "CHEM") OR EXCLUDE (SUBJAREA , "NEUR") OR EXCLUDE (SUBJAREA , "MATE") OR EXCLUDE (SUBJAREA , "ARTS") OR EXCLUDE (SUBJAREA , "ENER") OR EXCLUDE (SUBJAREA , "PSYC") OR EXCLUDE (SUBJAREA , "DENT"))

C.1.11 H1N1

TITLE-ABS-KEY (h1n1 AND model) AND (LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (PUBYEAR , 2009) OR LIMIT-TO (PUBYEAR , 2008) OR LIMIT-TO (PUBYEAR , 2007) OR LIMIT-TO (PUBYEAR , 2006) OR

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C.1.12 Malaria

TITLE-ABS-KEY (malaria AND model) AND (LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (

PUBYEAR , 2009) OR LIMIT-TO (PUBYEAR , 2008) OR LIMIT-TO (PUBYEAR , 2007) OR LIMIT-TO (PUBYEAR , 2006) OR LIMIT-TO (PUBYEAR , 2005) OR LIMIT-TO (PUBYEAR , 2004) OR LIMIT-TO (PUBYEAR , 2003) OR LIMIT-TO (PUBYEAR , 2002) OR LIMIT-TO (PUBYEAR , 2001) OR LIMIT-TO (PUBYEAR , 2000)) AND (EXCLUDE (SUBJAREA , "IMMU") OR EXCLUDE (SUBJAREA , "BIOC") OR EXCLUDE (SUBJAREA , "PHAR") OR EXCLUDE (SUBJAREA , "CHEM") OR EXCLUDE (SUBJAREA , "NEUR") OR EXCLUDE (SUBJAREA , "MATE") OR EXCLUDE (SUBJAREA , "ARTS") OR EXCLUDE (SUBJAREA , "PSYC") OR EXCLUDE (SUBJAREA , "ENER") OR EXCLUDE (SUBJAREA , "DENT")) AND (EXCLUDE (PUBYEAR , 2018)) AND (LIMIT-TO (EXACTKEYWORD , "Disease Transmission") OR LIMIT-TO (EXACTKEYWORD , "Statistical Model") OR LIMIT-TO (EXACTKEYWORD , "Prevalence") OR LIMIT-TO (EXACTKEYWORD , "Models, Biological") OR LIMIT-TO (EXACTKEYWORD , "Risk Factor") OR LIMIT-TO (EXACTKEYWORD , "Risk Factors") OR LIMIT-TO (EXACTKEYWORD , "Biological Model") OR LIMIT-TO (EXACTKEYWORD , "Mathematical Model") OR LIMIT-TO (EXACTKEYWORD , "Disease Model") OR LIMIT-TO (EXACTKEYWORD , "Malaria Vaccine") OR LIMIT-TO (EXACTKEYWORD , "Climate Change") OR LIMIT-TO (EXACTKEYWORD , "Models, Theoretical") OR LIMIT-TO (EXACTKEYWORD , "Models, Statistical") OR LIMIT-TO (EXACTKEYWORD , "Computer Simulation") OR LIMIT-TO (EXACTKEYWORD , "Transmission") OR LIMIT-TO (EXACTKEYWORD , "Infection Risk") OR LIMIT-TO (EXACTKEYWORD , "Time Factors") OR LIMIT-TO (EXACTKEYWORD , "Malaria Vaccines") OR LIMIT-TO (EXACTKEYWORD , "Theoretical Model") OR LIMIT-TO (EXACTKEYWORD , "Regression Analysis") OR LIMIT-TO (EXACTKEYWORD , "Epidemic") OR LIMIT-TO (EXACTKEYWORD , "Vaccination") OR LIMIT-TO (EXACTKEYWORD , "Climate") OR LIMIT-TO (EXACTKEYWORD , "Demography") OR LIMIT-TO (EXACTKEYWORD , "Statistics And Numerical Data") OR LIMIT-TO (EXACTKEYWORD , "Temperature")) AND (EXCLUDE (PUBYEAR , 2012) OR EXCLUDE (PUBYEAR , 2011) OR EXCLUDE (PUBYEAR , 2010) OR EXCLUDE (PUBYEAR , 2009) OR EXCLUDE (PUBYEAR , 2008) OR EXCLUDE (PUBYEAR , 2007) OR EXCLUDE (PUBYEAR , 2006) OR EXCLUDE (PUBYEAR , 2005) OR EXCLUDE (PUBYEAR , 2004) OR EXCLUDE (PUBYEAR , 2003) OR EXCLUDE (PUBYEAR , 2002) OR EXCLUDE (PUBYEAR , 2001) OR EXCLUDE (PUBYEAR , 2000)) AND (EXCLUDE (PUBYEAR , 2013)) AND (EXCLUDE (PUBYEAR , 2014))

C.1.13 SARS

TITLE-ABS-KEY (sars AND model) AND (LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (PUBYEAR , 2009) OR LIMIT-TO (PUBYEAR , 2008) OR LIMIT-TO (PUBYEAR , 2007) OR LIMIT-TO (PUBYEAR , 2006) OR LIMIT-TO (PUBYEAR , 2005) OR LIMIT-TO (PUBYEAR , 2004) OR LIMIT-TO (PUBYEAR ,

2003) OR LIMIT-TO (PUBYEAR , 2002) OR LIMIT-TO (PUBYEAR , 2001) OR LIMIT-TO (PUBYEAR , 2000)) AND (EXCLUDE (SUBJAREA , "BIOC") OR EXCLUDE (SUBJAREA , "IMMU") OR EXCLUDE (SUBJAREA , "PHAR") OR EXCLUDE (SUBJAREA , "CHEM") OR EXCLUDE (SUBJAREA , "MATE") OR EXCLUDE (SUBJAREA , "NEUR") OR EXCLUDE (SUBJAREA , "ARTS") OR EXCLUDE (SUBJAREA , "ENER") OR EXCLUDE (SUBJAREA , "PSYC") OR EXCLUDE (SUBJAREA , "DENT"))

C.1.14 Smallpox

TITLE-ABS-KEY (smallpox AND model) AND (LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (PUBYEAR , 2009) OR LIMIT-TO (PUBYEAR , 2008) OR LIMIT-TO (PUBYEAR , 2007) OR LIMIT-TO (PUBYEAR , 2006) OR LIMIT-TO (PUBYEAR , 2005) OR LIMIT-TO (PUBYEAR , 2004) OR LIMIT-TO (PUBYEAR , 2003) OR LIMIT-TO (PUBYEAR , 2002) OR LIMIT-TO (PUBYEAR , 2001) OR LIMIT-TO (PUBYEAR , 2000)) AND (EXCLUDE (SUBJAREA , "IMMU") OR EXCLUDE (SUBJAREA , "BIOC") OR EXCLUDE (SUBJAREA , "PHAR") OR EXCLUDE (SUBJAREA , "ARTS") OR EXCLUDE (SUBJAREA , "CHEM") OR EXCLUDE (SUBJAREA , "NEUR") OR EXCLUDE (SUBJAREA , "MATE") OR EXCLUDE (SUBJAREA , "DENT") OR EXCLUDE (SUBJAREA , "PSYC"))

C.2 Pay per view articles

The number of pay-per-view articles for each disease is produced in Table C.1.

Table C.1: The number of pay-per-view articles for each disease in comparison to the potentially relevant articles.

Disease	Potential abstracts	Available abstracts	Articles not available freely	Unavailable articles (%)
Diphtheria	4	4	0	0
Measles	59	54	5	8.5
Mumps	10	8	2	20.0
Pertussis	28	26	2	7.1
Polio	25	22	3	12.0
Rotavirus	18	16	2	11.1
Rubella	18	16	2	11.1
Cholera	109	92	17	15.6
Dengue	58	56	2	3.4
Ebola	86	78	8	9.3
Influenza (H1N1)	61	60	1	1.6
Malaria	29	26	3	10.3
SARS	75	62	13	17.3
Smallpox	31	26	5	16.1
Total	**611**	**546**	**65**	**11.9**

C.3 Results of the iterative filtering process

A few of the high-level observations which characterise the dataset are discussed within this section. The number of literature instances in the dataset is discussed in §C.3.1. The observed modelling approaches are broadly discussed in §C.3.2, followed by a broad overview of the type of data used in the modelling approaches and modelling scopes used in the modelling applications in §C.3.3. The consideration and inclusion of contextual factors within the dataset is discussed in §C.3.4. Intervention strategies included in modelling approaches are discussed in §C.3.5, followed by a few general observations in §C.3.6.

C.3.1 Number of diseases instances in the dataset

The results of the iterative filtering process are tabulated in Table C.4 (p.222). The first seven diseases form part of RI and the following seven are not part of RI. The complete overview of the number of literature instances considered for each disease as part of the iterative filtering process is produced in Table C.4.[25]

RI diseases

The total number of literature pieces in the dataset for RI diseases are noted in Table C.2. The disease with the largest number of literature pieces is measles, followed by pertussis. Diphtheria had the fewest results, however, it is a disease with few associated outbreaks. Pertussis, rotavirus, rubella and polio are diseases for which the symptoms and death rates are more severe, which may explain more modelling instances thereof than the other disease.

One of the criteria for including literature in the dataset was modelling of disease dynamics between individuals on the population level. Diseases that form part of RI programmes are typically more endemic in nature and the transmission dynamics are typically well understood. This may explain the observation that potential literature and models of these diseases focus more on qualitative factors affecting vaccination uptake, pharmacological effects of vaccine usage and supply chain optimisation, rather than on population-level transmission modelling.

Table C.2: Number of disease instances part of RI included in the dataset.

Diphtheria	Measles	Mumps	Pertussis	Polio	Rotavirus	Rubella
2	25	5	15	8	6	7

[25] It is worth noting that some literature pieces incorporated more than one disease in the modelling approach, hence the numbers with an asterisk (the totals in the 'available abstracts' and 'relevant abstracts' columns) in Table C.4 refer to the actual number of literature pieces reviewed in these steps.

Non-RI diseases

The total number of literature pieces in the dataset for non-RI diseases are noted in Table C.3. The disease with the largest number of literature pieces is cholera, potentially attributed to numerous instances of contextual factor analysis, in addition to retrospective analysis of cholera prevalence. Another disease with a very large number of literature pieces is Ebola, which is likely explained by the scale of the recent outbreak thereof as illustrated in Figure 1.2. The disease with the least modelling instances is malaria. As malaria is an endemic disease in many areas, the transmission modelling thereof might not be regarded as a top priority. Additionally, transmission modelling might focus more on mosquitoes (vectors) and contextual factors affecting vector dynamics, which does not explicitly relate to transmission modelling of the malaria between humans. Smallpox also has few instances, as the disease is not currently in circulation and almost eradicated entirely, apart from feared potential bioterror attacks of weaponised smallpox.

Table C.3: Number of disease instances not part of RI included in the dataset.

Cholera	Dengue	Ebola	H1N1	Malaria	SARS	Smallpox
63	29	54	26	9	27	11

Table C.4: Number of literature instances considered during each step of the iterative filtering process in the structured literature review.

Disease	Search protocol	Date exclusion	Categorical exclusion	Keyword exclusion	Year exclusion	Potential titles	Potential abstracts	Available abstracts	Relevant abstracts
Diphtheria	2735	2095	781	781	781	8	4	4	2
Measles	2889	2087	906	906	906	106	59	54	25
Mumps	1020	745	419	419	419	19	10	8	5
Pertussis	4625	2990	841	841	841	44	28	26	16
Polio	665	511	256	256	256	44	25	22	8
Rotavirus	1792	1419	556	556	556	38	18	16	6
Rubella	995	719	380	380	380	30	18	16	8
Cholera	4804	3218	761	761	761	145	109	92	63
Dengue	3544	3377	1399	818	339	92	58	56	29
Ebola	1440	1392	667	667	667	122	86	78	54
H1N1	4292	4201	1489	1331	1331	112	61	60	26
Malaria	14994	12103	3131	1581	414	63	29	26	9
SARS	2840	2648	1094	1094	1094	108	75	62	27
Smallpox	1031	933	306	306	306	49	31	26	11
Total	**47666**	**38438**	**12986**	**10697**	**9051**	**980**	**611**	**546 (522)***	**289 (283)***

C.3.2 Modelling approach

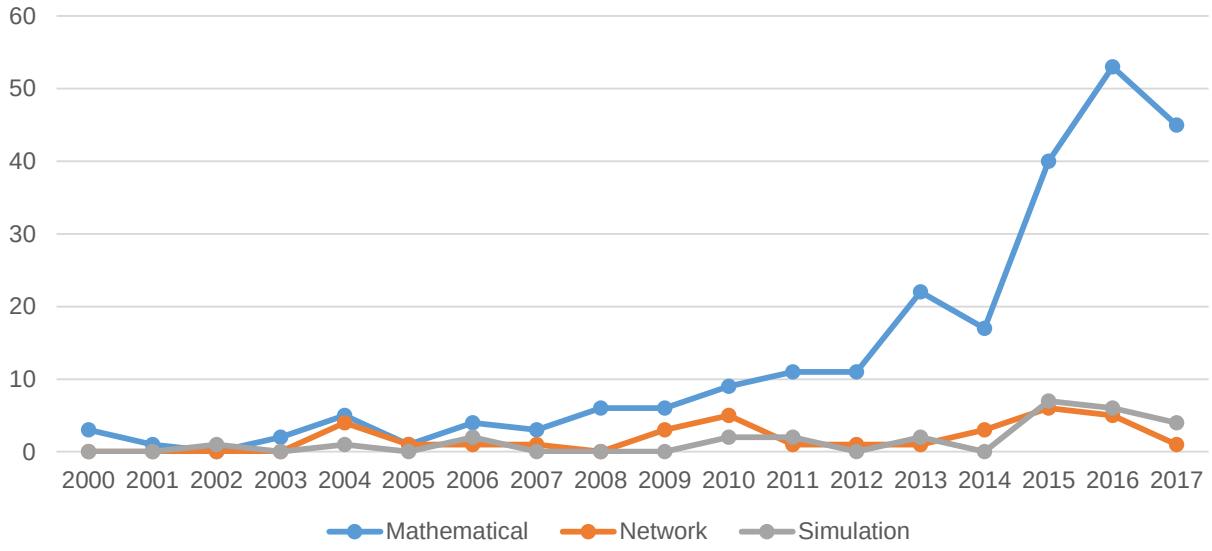

Figure C.1: Annual comparison of the number of modelling instances for mathematical, network and simulation approaches within the dataset.

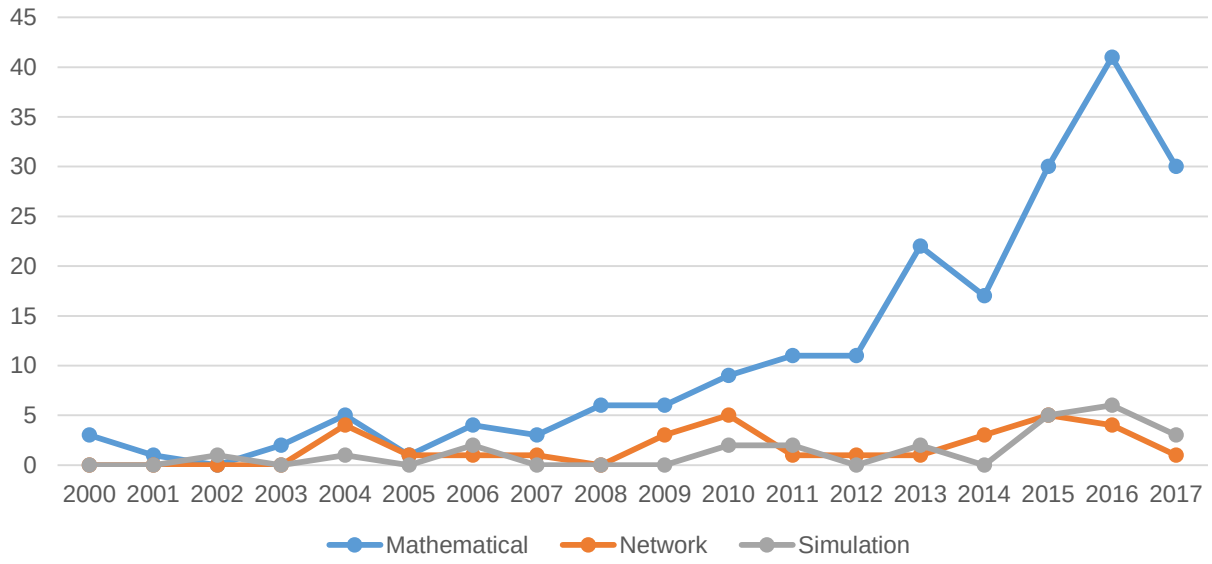

Figure C.2: Annual occurrence of the number of modelling instances for mathematical, network and simulation approaches within the dataset without inclusion of vector-borne diseases.

It is clear that mathematical modelling instances were used the most frequently within the dataset, as illustrated in Figure C.1. In total there were five more instances of network modelling applications than simulation applications in the dataset. A notable increase in mathematical modelling applications are observed from 2010 onwards. This could potentially be attributed to the outbreak of H1N1 in 2009, in addition to the Ebola outbreak in 2014. In comparison to Figure C.1, the deviant timeframe used for the vector-borne diseases (as discussed in §3.4.2) did not create a noticeable

bias in the results, as illustrated in Figure C.2 without vector-borne disease instances. A brief overview of the results for the mathematical, network and simulation modelling categories is provided below.

Mathematical models

The most diverse set of sub-categories occur within the mathematical approach category as illustrated in Figure C.3. The applications which occur the most frequently in the dataset are DE models, followed by regression models. If a specific mathematical method only occurred once within the dataset, it was clustered under the 'other' category, unless it was clear that it may be regarded as one of the existing categories.

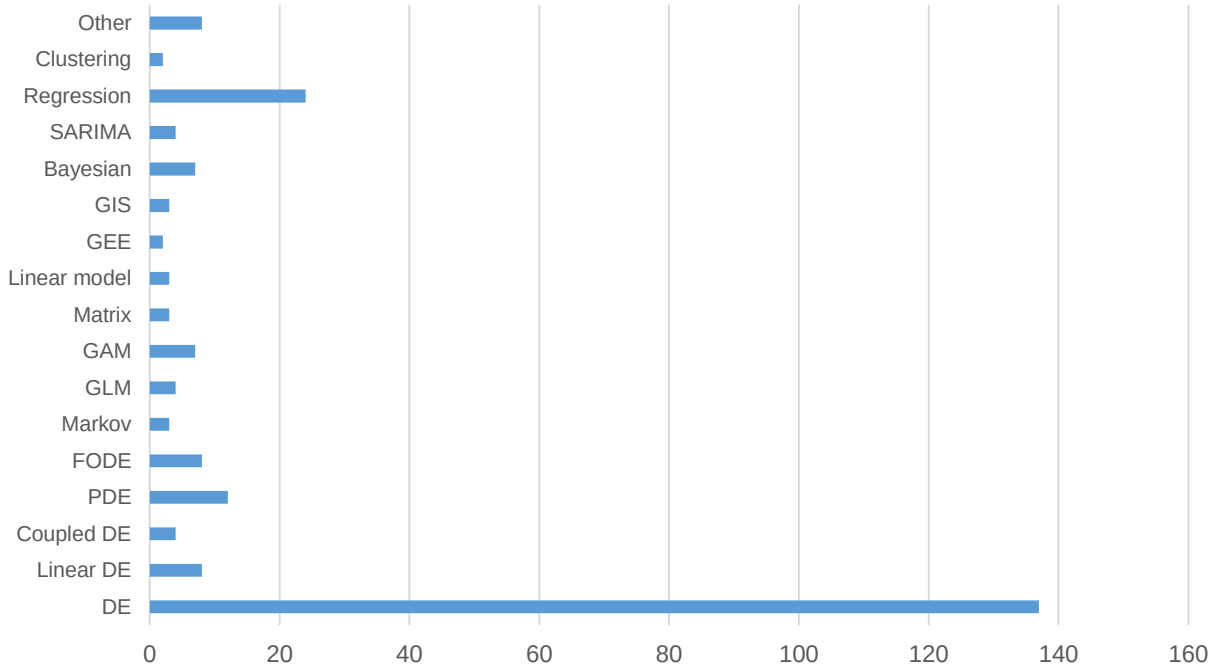

Figure C.3: Number of mathematical model approaches in the dataset.

Network models

The network model approaches which occur the most frequently in the dataset are the metapopulation network models, followed by small world network models as illustrated in Figure C.4. Other approaches which had two occurrences include the hierarchical-, gravity- and general network models. All other approaches only had one occurrence in the dataset.

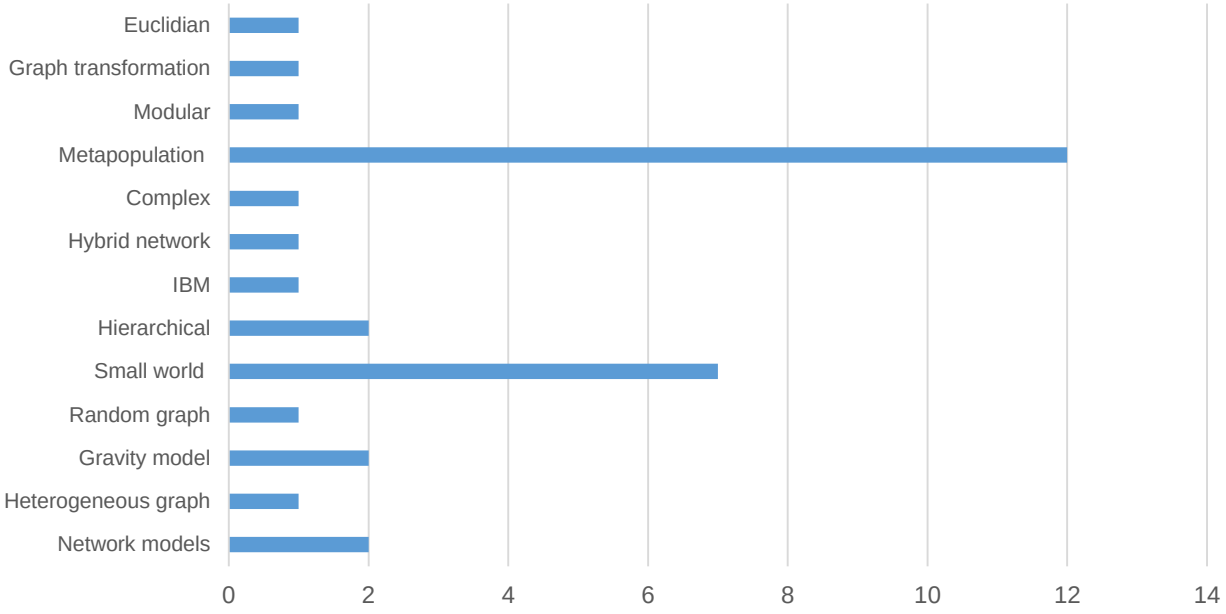

Figure C.4: Number of network model approaches in the dataset.

Simulation models

The simulation modelling category occurs the most infrequently in the dataset and contains the least number of alternative approaches as illustrated in Figure C.5. It is clear that ABS models are the most frequently occurring simulation approach, with a marginally higher occurrence of Monte Carlo simulation approaches than the remaining non-ABS approaches. As simulation models are the most data intensive and complex modelling approach (as discussed previously in §3.1.3), it is as expected to find that this modelling approach is used the most infrequently.

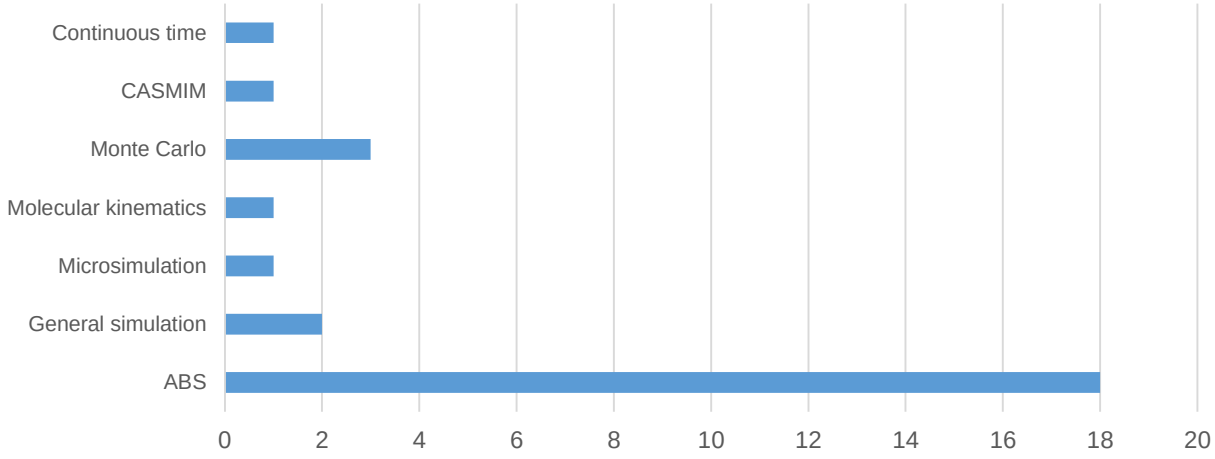

Figure C.5: Number of simulation model approaches in the dataset.

C.3.3 Data source and modelling scope

As tabulated in Table C.5, it is clear that case data is most commonly used to fit models within the dataset, followed by using parameters from literature. The ‘no data source’ and ‘assumed data source’ categories which are present in the dataset are typically used for theoretical disease models. Population estimates and travel data are rarely used within models, as a result of the required detail associated with these data sources, in addition to difficulty in calibrating model parameters to these sources.

Table C.5: Number of data source instances in the dataset.

None	Case data	Travel data	Parameters from literature	Population estimates	Assumed
34	151	5	89	11	30

The annual breakdown of data source occurrences in the dataset is illustrated in Figure C.6. A notable increase in the use of case data was observed from 2014 onwards. This could potentially be ascribed to the outbreak of the Ebola epidemic and the use of case data in initial models to understand the underlying dynamics of this disease.

The deviant timeframe used for the vector-borne diseases (as discussed in §3.4.2) did not create a noticeable bias in the results (illustrated without vector-borne disease in Figure C.7) when compared to Figure C.6, apart from a few less instances of case data in 2017.

With regards to the modelling scope (tabulated in Table C.6), the general transmission scope occurs the most frequently, followed by country and small region scope. The high occurrence of the general scope is ascribed to the initial need to model the dynamics of a particular disease, followed closely by country scope as this is the typical scope of data and modelling approaches. The small region scope also is used frequently. The global and intercountry scope occur the least in the dataset, as it is difficult to obtain enough data to realistically calibrate models of this scope.

Table C.6: Number of modelling scope instances in the dataset.

General	Global	Intercountry	Country	Provincial	Small region
99	8	10	85	26	55

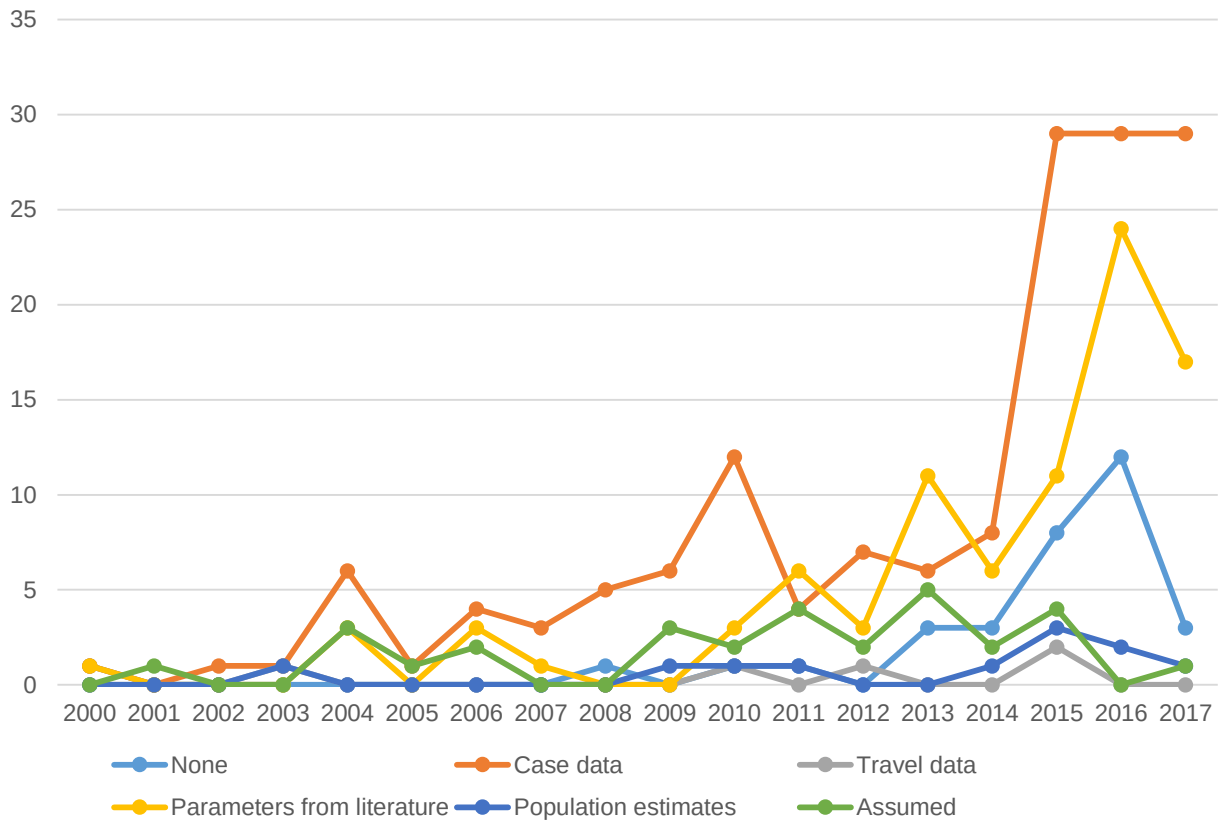

Figure C.6: Annual breakdown of the number of data source occurrences within the dataset.

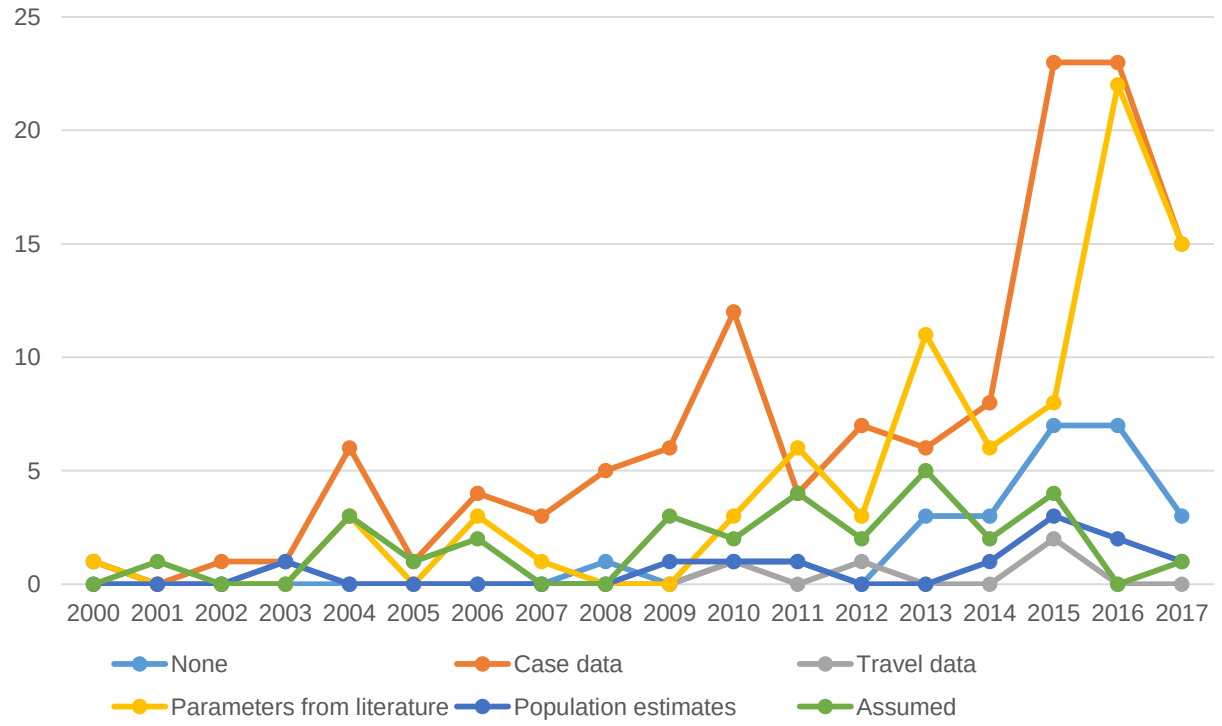

Figure C.7: Annual breakdown of the number of data source occurrences within the dataset without inclusion of vector-borne diseases.

The annual breakdown of modelling scope occurrences in the dataset is illustrated in Figure C.8. The deviant timeframe used for the vector-borne diseases (as discussed in §3.4.2) did not create a noticeable bias in the results (illustrated without vector-borne diseases in Figure C.9) when compared to Figure C.8, apart from a few less general scope inclusions in 2015.

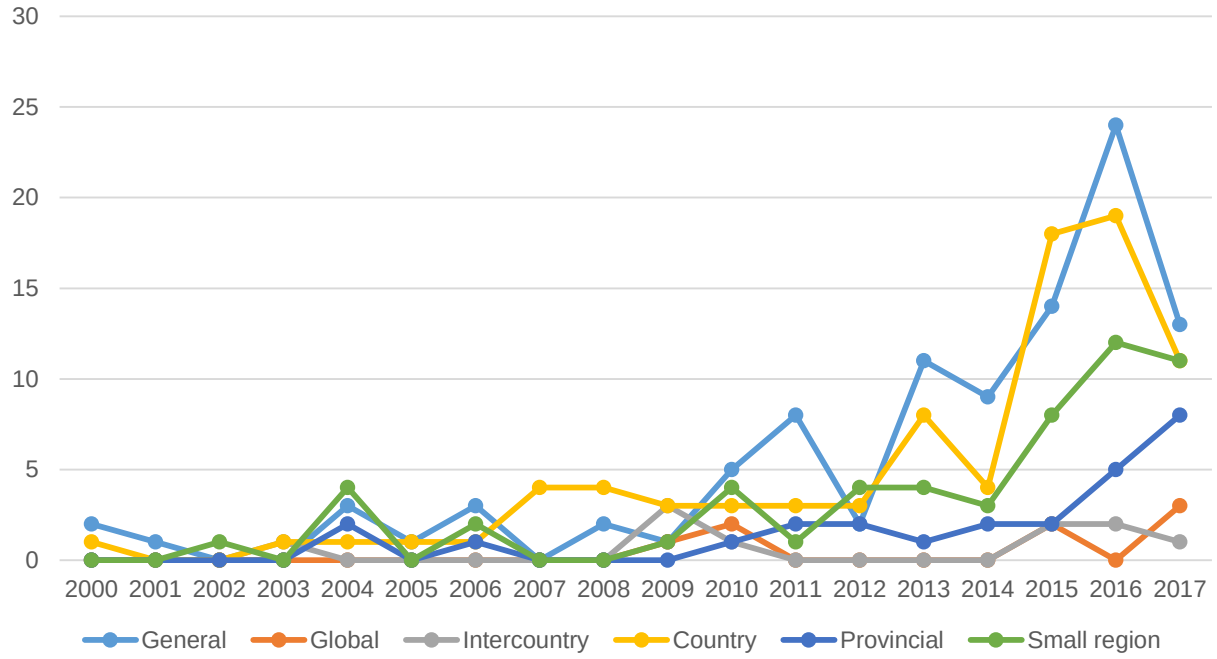

Figure C.8: Annual breakdown of modelling scope occurrences within the dataset.

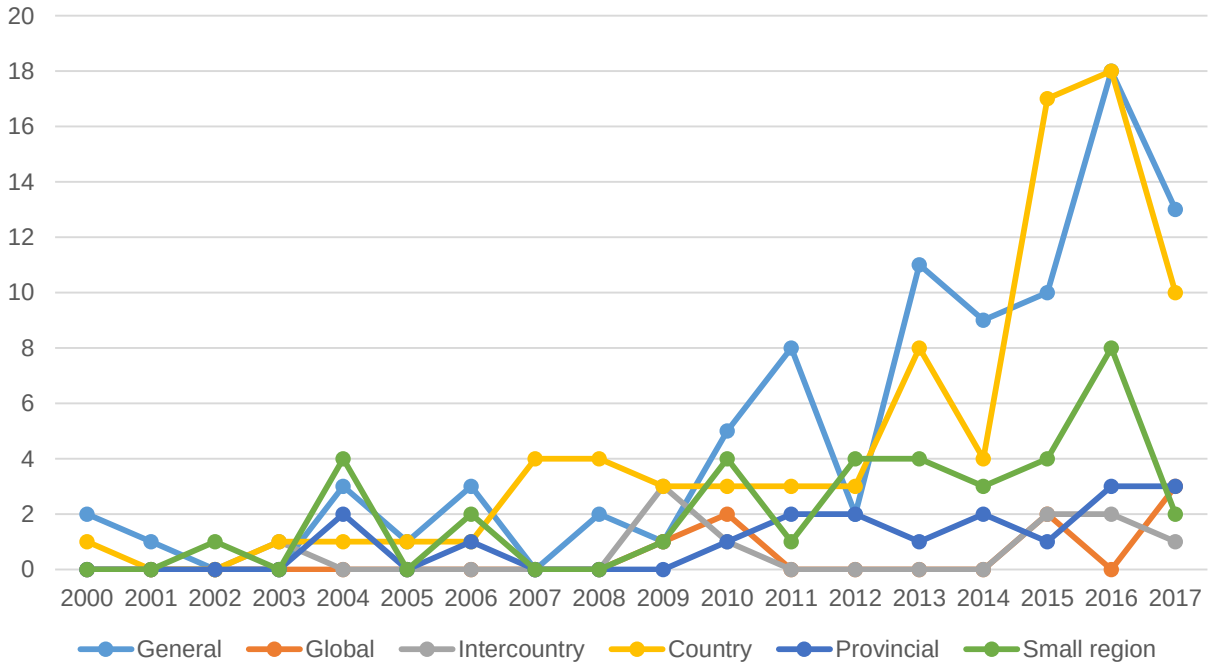

Figure C.9: Annual breakdown of modelling scope occurrences within the dataset without inclusion of vector-borne diseases.

C.3.4 Contextual factors

Of the 283 modelling instances in the dataset, 60% incorporate contextual factors within the modelling approach, as tabulated in Table C.7. Additionally, 42% of the literature pieces in the dataset incorporated contextual factors in the modelling approaches, with 20% of the literature pieces linking contextual factors to disease propagation. Population demographics were included in 127 literature pieces of the dataset and environmental factors were included in 57 literature pieces of the dataset.

Table C.7: Nature of contextual factors deduced from the dataset.

Modelling instances	Mentioned	Modelled	Linked to disease propagation
Number	169	120	57
Percentage	60%	42%	20%

C.3.5 Intervention strategies

Intervention strategies are used in 120 of the literature inclusions, categorised either as treatment strategies or vaccination strategies, as illustrated in Figure C.10. It is clear that there is not a large difference between the annual usage of treatment and vaccination strategies within modelling approaches. In comparison to Figure C.10, the deviant timeframe used for the vector-borne diseases (as discussed in §3.4.2) did not create a noticeable bias in the results, as illustrated Figure C.11 without vector-borne disease instances.

It is interesting to note that of the 56 vector-borne disease inclusions, only 4 instances made use of vector control in the modelling approach and only a single instance assumed the use of a theoretical vaccine for malaria, as there are currently no vaccines available for vector-borne diseases. Furthermore, the vaccination strategies over networks only amounted to three instances and were, along with vector control, not included in further analysis of the intervention strategies.

C.3.6 General observations

Alternative mixing patterns were mentioned in 41 literature pieces of the set, which amount to 14% of the dataset. The transmission mode is mentioned explicitly in 187 of the literature pieces, which amounts to 66% of the dataset (a discussion on mentioned transmission modes in comparison to all theoretical transmission modes is completed in §4.1.1).

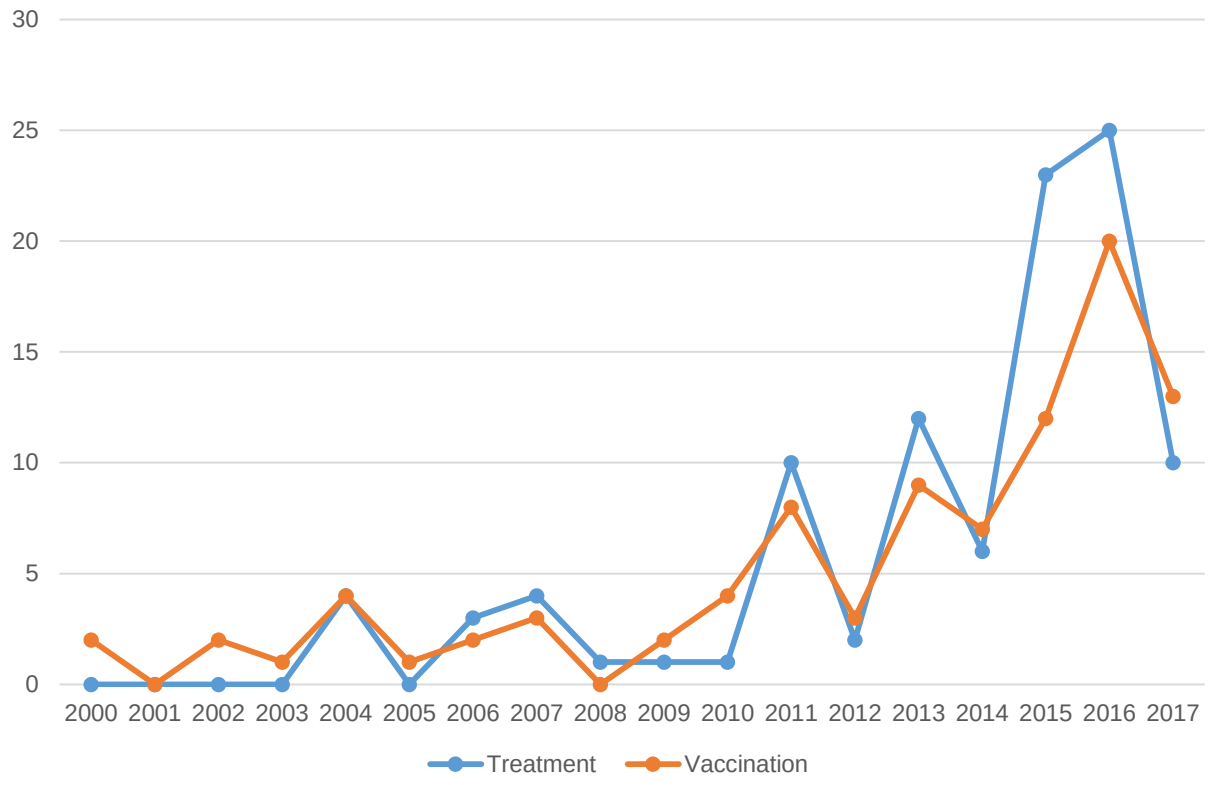

Figure C.10: Annual occurrence of the number of treatment and vaccination occurrences within the dataset.

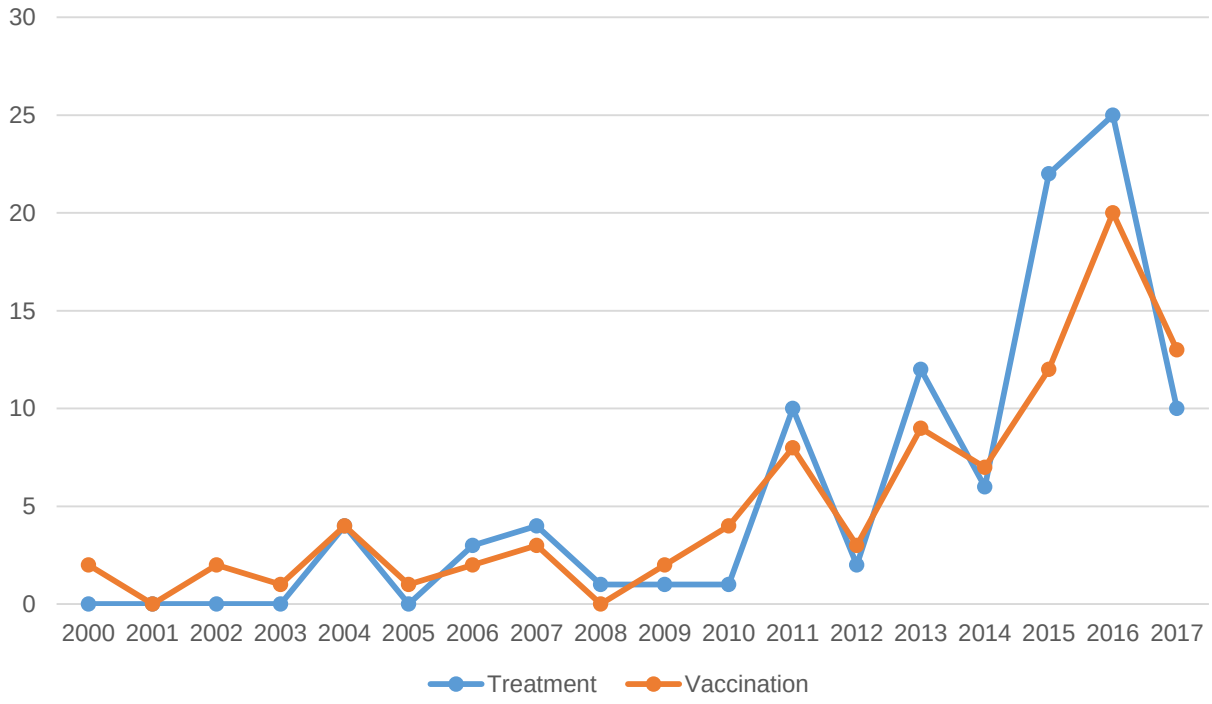

Figure C.11: Annual occurrence of the number of treatment and vaccination strategies within the dataset without vector-borne diseases.

Appendix D (Chapter 4)

A number of sections in support of Chapter 4 is presented in this appendix. This includes the data extracted from the dataset and the data used to normalise the extracted subsets. Additionally, the REF B and REF C analysis categories are also presented in this appendix.

D.1 Normalisation tables

Table D.1: Data used to normalise subset 1 and subset 2.

Subset	Transmission modes						
	Direct contact	Sexual contact	Respiratory	Body fluid	Food-borne	Water contact	Vector-borne
S1N	100	54	171	156	73	77	38
S2N	37	5	46	30	3	62	37
S1**N	81	46	128	111	57	60	17
S2**N	33	5	29	28	2	50	17

Table D.2: Data used to normalise subset 3.

Subset	Modelling approaches		
	Mathematical	Network	Simulation
S3N	234	33	27

Table D.3: Data used to normalise subset 4.

Subset	Disease classification	
	Part of RI	Not part of RI (i.e. non-RI)
S4N	66	217

Table D.4: Data used to normalise subset 5.

Subset	Modelling rationales					
	Investigate causal relationships	**Model disease transmission dynamics**	**Develop a model and analyse behaviour**	**Forecast disease instance**	**Evaluate interventions**	**Investigate super spreading events**
S5N	70	205	115	22	120	7

Table D.5: Data used to normalise subset 6.

Subset	Data sources					
	None	**Case data**	**Travel data**	**Parameters from literature**	**Population estimates**	**Assumed**
S6N	33	152	5	89	11	30

Table D.6: Data used to normalise subset 7.

Subset	Modelling scopes					
	General	**Global**	**Intercountry**	**Country**	**Provincial**	**Small region**
S7N	99	8	10	85	26	55

Table D.7: Data used to normalise subset 8.

Subset	Intervention strategies	
	Treatment	**Vaccination**
S8N	67	75

Table D.8: Data used to normalise subset 9.

Subset	Contextual factors	
	Linked to disease propagation	**Modelled**
S9N	57	120

D.2 Data prior to normalisation, subset 1

Table D.9: Data extracted from dataset prior to normalisation, subset 1.

REF	CAT	Transmission modes						
		Direct contact	Sexual contact	Respira-tory	Body fluid	Food-borne	Water contact	Vector-borne
B1	Mentioned	37	5	46	30	3	62	37
B2.1	General	31	18	49	47	38	40	10
	Global	4	1	8	6	1	1	0
	Intercountry	6	4	7	7	1	2	0
	Country	38	26	63	50	20	22	3
	Provincial	3	0	13	13	6	5	8
	Small region	18	5	31	33	7	7	17
B2.2	Contextual factors investigated	8	5	19	30	17	19	18
	Contextual factors modelled	36	16	75	57	32	33	12
B2.3	Alternative mixing patterns	27	3	47	36	5	6	1
B3.1	Mathematical	75	46	127	125	70	74	35
	Network	17	6	30	20	2	2	2
	Simulation	13	7	22	16	2	2	3
B3.2	DE	55	37	81	73	43	45	13
	Linear DE	2	0	7	5	4	4	0
	Coupled DE	0	0	1	1	3	3	0
	PDE	4	1	6	5	5	6	0
	FODE	3	3	6	5	1	1	1
	Markov	0	0	1	0	1	1	0
	GLM	0	0	0	1	2	2	1
	GAM	0	0	2	3	2	2	2
	Matrix	2	0	3	2	0	0	0
	Linear model	2	1	3	3	0	0	0
	GEE	0	0	1	2	0	0	1
	GIS	1	0	1	2	0	0	2
	Bayesian	2	1	3	4	1	1	2
	SARIMA	0	0	0	1	2	2	2

REF	CAT	Transmission modes						
		Direct contact	Sexual contact	Respira-tory	Body fluid	Food-borne	Water contact	Vector-borne
B3.2	Regression	2	2	9	15	5	6	10
	Clustering	1	0	1	2	0	0	1
	Other	3	2	4	5	2	2	2
B3.3	Network models	1	0	2	1	0	0	0
	Heterogeneous graph model	0	0	1	0	0	0	0
	Gravity model	1	1	2	1	0	0	0
	Configuration model random graph	1	1	1	1	0	0	0
	Small world network model	6	2	7	7	0	0	0
	Hierarchical model	0	0	2	0	0	0	0
	IBM	0	0	0	1	0	0	1
	Hybrid network model	1	0	1	1	0	0	0
	Complex network models	1	0	1	1	0	0	0
	Metapopulation network model	5	1	10	5	1	1	1
	modular network	0	0	1	0	0	0	0
	Graph transformation	0	0	1	1	1	1	0
	Euclidian	1	1	1	1	0	0	0
B3.4	ABS	8	7	14	10	2	2	2
	General simulation	1	0	2	1	0	0	0
	Microsimulation	1	0	1	1	0	0	0
	Molecular kinematics	1	0	1	1	0	0	0
	Monte Carlo	1	0	2	2	0	0	1
	CASMIM	1	0	1	1	0	0	0
	Continuous time	0	0	1	0	0	0	0

REF	CAT	Transmission modes						
		Direct contact	Sexual contact	Respira-tory	Body fluid	Food-borne	Water contact	Vector-borne
B4	Treatment	38	24	53	40	11	13	1
	Vaccination	25	9	55	41	23	25	0
B4.1	Contact tracing	7	2	8	7	0	0	0
	Quarantine / Isolation	22	10	27	22	1	1	0
	Hospitalisation	15	13	16	15	0	0	0
	Drug / Pharmaceutical	1	1	5	1	1	1	1
	Safe burial	8	8	8	8	0	0	0
	Reduce contact	2	2	2	3	1	2	0
	Reduce contact	0	0	2	0	0	0	0
	Disinfection / sanitation	0	0	0	2	10	12	0
	General	1	1	5	1	4	4	0
	Treatment kits	1	1	1	1	0	0	0
	School closure	0	0	3	0	0	0	0
	Education	2	2	2	3	1	2	0
B4.2	Ring	7	2	7	7	0	0	0
	Target	1	0	2	1	0	0	0
	Mass	5	0	5	5	0	0	0
	Prophylactic	5	0	11	9	3	2	0
	Post exposure	0	0	1	0	0	0	0
	Booster	1	0	4	2	2	1	0
	Pulse	0	0	1	0	0	0	0
	Age	1	0	1	1	0	0	0
	Maternal immunisation	0	0	2	2	0	0	0
	Proportion of susceptible	10	7	21	17	17	20	0
	Vaccination rate	3	2	7	5	4	3	0
	Starting dates	1	1	1	1	0	0	0
	Coverage levels	2	0	8	3	0	0	0
	Cost and age	0	0	1	0	0	0	0

REF	CAT	Transmission modes						
		Direct contact	**Sexual contact**	**Respira-tory**	**Body fluid**	**Food-borne**	**Water contact**	**Vector-borne**
B5.1	Linked to disease propagation	8	5	19	30	17	19	18
	Modelled	36	16	75	57	32	33	12
B5.2[26]	Climate	0	0	4	11	6	7	10
	Temperature	0	0	3	15	6	7	16
	Rainfall	0	0	2	14	12	13	16
	Seasonality	0	0	7	4	3	4	1
B5.2[27]	Climate	0	0	1	2	3	3	2
	Temperature	0	0	0	4	2	2	5
	Rainfall	0	0	0	4	7	7	6
	Seasonality	1	1	7	4	4	4	2
B5.2[28]	Age	2	1	7	6	0	1	0
	Sex	0	0	0	0	0	0	0
	Natality	0	0	0	2	0	2	0
	Population density	4	3	4	6	3	3	2
	Migration	5	3	8	6	3	3	0
	Spatial spread	5	5	8	9	5	5	3
	Socio-economic	0	0	1	4	4	4	4

[26] Environmental, linked to disease propagation

[27] Environmental, modelled

[28] Demographics, linked to disease propagation

REF	CAT	Transmission modes						
		Direct contact	Sexual contact	Respira-tory	Body fluid	Food-borne	Water contact	Vector-borne
B5.2[29]	Age	10	3	30	22	8	9	2
	Sex	1	0	1	1	1	1	0
	Natality	1	0	2	1	0	0	0
	Population density	9	5	10	9	4	3	1
	Migration	13	7	21	14	8	8	1
	Spatial spread	20	7	37	25	18	17	5
	Socio-economic	1	1	4	6	6	7	1
B6	S	33	5	27	28	2	50	17
	I	33	5	29	28	2	50	17
	R	33	5	24	27	2	36	11
	E	21	2	17	19	1	2	8
	D	14	1	3	10	1	1	0
	F	6	0	0	3	0	0	0
	V	4	0	9	8	0	7	0
	Q	8	0	6	7	0	1	0
	J	0	0	2	0	0	0	0
	C	0	0	1	0	0	0	0
	CT	0	0	0	0	0	0	0
	M	1	0	2	1	0	1	0
	A	1	0	5	0	0	1	1
	T	0	0	2	0	0	1	1
	Y	1	1	0	0	0	0	0
	W	1	0	0	0	0	1	0
	T	0	0	1	0	0	0	0

[29] Demographics, modelled

REF	CAT	Transmission modes						
		Direct contact	Sexual contact	Respira-tory	Body fluid	Food-borne	Water contact	Vector-borne
B6	SS	0	0	1	0	0	0	0
	B	2	1	0	2	2	41	0
	W	2	0	0	0	0	7	0
	M,S	0	0	0	1	0	0	15
	M,I	0	0	0	1	0	0	17
	M,E	0	0	0	0	0	0	6

D.3 Data prior to normalisation, subset 2

Table D.10: Data extracted from dataset prior to normalisation, subset 2.

REF	CAT	Transmission modes						
		Direct contact	Sexual contact	Respira-tory	Body fluid	Food-borne	Water contact	Vector-borne
B2.1	General	17	2	12	10	2	37	10
	Global	1	0	2	0	0	0	0
	Intercountry	1	0	2	2	0	1	0
	Country	15	3	10	15	0	14	3
	Provincial	0	0	8	0	0	4	6
	Small region	3	0	12	3	1	6	17
B2.2	Contextual factors investigated	3	0	11	1	1	14	16
	Contextual factors modelled	12	0	18	10	1	28	11
B2.3	Alternative mixing patterns	4	0	9	3	0	3	1
B3.1	Mathematical	31	5	31	28	2	60	33
	Network	4	0	8	2	0	1	2
	Simulation	4	0	7	2	1	2	3
B3.2	DE	26	3	19	25	2	39	13
	Linear DE	0	0	2	0	0	1	0
	Coupled DE	0	0	0	0	0	3	0
	PDE	0	0	0	1	0	5	0
	FODE	2	2	0	2	0	1	1
	Markov	0	0	0	0	0	1	0
	GLM	0	0	1	0	0	2	1
	GAM	0	0	1	0	0	1	2
	Matrix	1	0	0	0	0	0	0
	Linear model	1	0	1	0	0	0	0
	GEE	0	0	0	0	0	0	1
	GIS	0	0	1	0	0	0	2
	Bayesian	0	0	1	0	0	1	2
	SARIMA	0	0	0	0	0	2	2

REF	CAT	Transmission modes						
		Direct contact	Sexual contact	Respira-tory	Body fluid	Food-borne	Water contact	Vector-borne
B3.2	Regression	0	0	4	0	0	4	8
	Clustering	0	0	1	0	0	0	1
	Other	1	0	1	0	0	1	2
B3.3	Network models	0	0	2	0	0	0	0
	Heterogeneous graph model	0	0	0	0	0	0	0
	Gravity model	0	0	0	0	0	0	0
	Configuration model random graph	1	0	0	0	0	0	0
	Small world network model	2	0	1	0	0	0	0
	Hierarchical model	0	0	1	0	0	0	0
	IBM	0	0	0	0	0	0	1
	Hybrid network model	0	0	1	0	0	0	0
	Complex network models	0	0	1	0	0	0	0
	Metapopulation network model	1	0	2	0	0	1	1
	modular network	0	0	0	0	0	0	0
	Graph transformation	0	0	0	1	0	0	0
	Euclidian	0	0	0	1	0	0	0
B3.4	ABS	4	0	4	2	1	2	2
	General simulation	0	0	0	0	0	0	0
	Microsimulation	0	0	0	0	0	0	0
	Molecular kinematics	0	0	1	0	0	0	0
	Monte Carlo	0	0	1	0	0	0	1
	CASMIM	0	0	1	0	0	0	0
	Continuous time	0	0	0	0	0	0	0

REF	CAT	Transmission modes						
		Direct contact	Sexual contact	Respira-tory	Body fluid	Food-borne	Water contact	Vector-borne
B4	Treatment	16	1	11	12	0	12	1
	Vaccination	8	1	14	14	0	16	0
B4.1	Contact tracing	1	0	1	1	0	0	0
	Quarantine / Isolation	8	1	8	6	0	1	0
	Hospitalisation	6	0	1	6	0	0	0
	Drug / Pharmaceutical	0	0	0	0	0	1	1
	Safe burial	5	0	0	5	0	0	0
	Reduce contact	2	0	0	1	0	2	0
	Reduce contact	0	0	0	0	0	0	0
	Disinfection / sanitation	0	0	0	1	0	11	0
	General	2	0	2	0	0	4	0
	Treatment kits	0	0	0	1	0	0	0
	School closure	0	0	1	0	0	0	0
	Education	2	0	0	2	0	2	0
B4.2	Ring	1	0	1	1	0	0	0
	Target	0	0	1	0	0	0	0
	Mass	1	0	1	0	0	0	0
	Prophylactic	0	0	3	1	0	0	0
	Post exposure	0	0	0	0	0	0	0
	Booster	0	0	2	0	0	0	0
	Pulse	0	0	0	0	0	0	0
	Age	0	0	0	0	0	0	0
	Maternal immunisation	0	0	1	0	0	0	0
	Proportion of susceptibles	6	1	8	10	0	16	0
	Vaccination rate	1	0	0	3	0	0	0
	Starting dates	1	0	0	1	0	0	0
	Coverage levels	1	0	1	0	0	0	0
	Cost and age	0	0	0	0	0	0	0

REF	CAT	Transmission modes						
		Direct contact	**Sexual contact**	**Respira-tory**	**Body fluid**	**Food-borne**	**Water contact**	**Vector-borne**
B5.1	Investigated	3	0	11	1	1	14	16
	Modelled	12	0	18	10	1	28	11
B5.2[30]	Climate	0	0	3	0	1	6	9
	Temperature	0	0	3	0	0	5	15
	Rainfall	0	0	1	0	1	12	15
	Seasonality	0	0	6	0	0	2	1
B5.2[31]	Climate	0	0	0	0	1	3	2
	Temperature	0	0	0	0	0	2	5
	Rainfall	0	0	0	0	1	7	6
	Seasonality	1	0	3	1	0	4	2
B5.2[32]	Age	0	0	5	1	0	0	0
	Sex	0	0	0	0	0	0	0
	Natality	0	0	0	1	0	0	0
	Population density	1	0	0	0	0	2	1
	Migration	1	0	3	0	0	2	0
	Spatial spread	2	0	1	0	1	3	2
	Socio-economic	0	0	1	0	1	3	3

[30] Environmental, linked to disease propagation

[31] Environmental, modelled

[32] Demographics, linked to disease propagation

REF	CAT	Transmission modes						
		Direct contact	**Sexual contact**	**Respira-tory**	**Body fluid**	**Food-borne**	**Water contact**	**Vector-borne**
B5.2[33]	Age	4	0	5	4	0	5	2
	Sex	0	0	0	0	0	1	0
	Natality	1	0	0	0	0	0	0
	Population density	1	0	4	2	0	3	0
	Migration	3	0	3	2	0	8	1
	Spatial spread	5	0	10	2	1	16	4
	Socio-economic	1	0	1	1	1	5	0
B6	S	78	46	126	108	57	60	17
	I	81	46	130	111	57	60	17
	R	74	44	115	98	41	44	11
	E	56	36	85	68	6	8	8
	D	25	21	26	25	1	1	0
	F	8	8	8	8	0	0	0
	V	10	3	25	20	10	12	0
	Q	26	16	30	27	1	1	0
	J	2	0	2	2	0	0	0
	C	0	0	1	0	0	0	0
	CT	1	0	1	1	0	0	0
	M	3	0	8	6	1	2	0
	A	2	0	6	2	2	1	1
	T	0	0	2	0	1	1	1
	Y	1	1	1	1	0	0	0
	W	0	0	1	1	1	1	0

[33] Demographics, modelled

REF	CAT	Transmission modes						
		Direct contact	Sexual contact	Respira-tory	Body fluid	Food-borne	Water contact	Vector-borne
B6	T	1	0	1	1	0	0	0
	SS	1	0	1	1	0	0	0
	B	2	2	2	3	40	41	0
	W	0	0	0	0	7	7	0
	M,S	1	1	1	12	0	0	15
	M,I	1	1	1	13	0	0	17
	M,E	0	0	0	4	0	0	6

D.4 Data prior to normalisation, subset 3

Table D.11: Data extracted from dataset prior to normalisation, subset 3.

REF	CAT	Modelling approaches		
		Mathematical	Network	Simulation
C2.3	None	27	3	4
	Case data	125	19	16
	Travel data	4	2	0
	Parameters from literature	77	9	6
	Population estimates	8	1	2
	Assumed	21	6	3
C5	Compartmental inclusion	177	20	14
C6.1	Investigate causal relationships	64	3	4
	Model disease transmission dynamics	166	27	23
	Develop a model and analyse behaviour	89	19	10
	Forecast disease instance	21	1	1
	Evaluate interventions	97	12	15
	Investigate super spreading events	2	2	3
C6.2	General	90	7	4
	Global	4	4	1
	Intercountry	7	4	1
	Country	72	10	7
	Provincial scope	23	3	1
	Small region	38	5	13
C6.3	Treatment	53	7	10
	Vaccination	61	6	9

REF	CAT	Modelling approaches		
		Mathematical	Network	Simulation
C7.1	General	90	7	4
	Global	4	4	1
	Intercountry	7	4	1
	Country	72	10	7
	Provincial	23	3	1
	Small region	38	5	13
C7.2 Treatment	Contact tracing	4	2	2
	Quarantine / Isolation	21	3	6
	Hospitalisation	15	0	1
	Drug / Pharmaceutical	4	1	2
	Safe burial	7	0	1
	Reduce contact	3	1	1
	Reduce contact	1	0	1
	Disinfection / sanitation	12	0	0
	General	8	0	1
	Treatment kits	1	0	0
	School closure	1	1	1
	Education	4	0	0
C7.2 Vaccination	Ring	4	1	2
	Target	0	1	1
	Mass	2	2	1
	Prophylactic	6	1	4
	Post exposure	0	0	1
	Booster	4	0	0
	Pulse	1	0	0
	Age	1	0	0
	Maternal immunisation	2	0	0
	Proportion of susceptibles	38	2	1
	Vaccination rate	6	0	1
	Starting dates	1	0	0
	Coverage levels	6	1	2
	Cost and age	1	0	0

D.5 Data prior to normalisation, subset 4

Table D.12: Data extracted from dataset prior to normalisation, subset 4.

REF	CAT	Disease classification	
		RI	Non RI
C4.1	DE	27	110
	Linear DE	4	4
	Coupled DE	1	3
	PDE	5	7
	FODE	2	6
	Markov	2	1
	GLM	1	3
	GAM	3	4
	Matrix	1	2
	Linear model	1	2
	GEE	1	1
	GIS	0	3
	Bayesian	2	5
	SARIMA	0	4
	Regression	7	17
	Clustering	0	2
	Other	1	7
C4.2	General	17	82
	Global	4	4
	Intercountry	2	8
	Country	24	61
	Provincial scope	10	16
	Small region	9	46
C4.3	Mentioned	47	122
	Investigated	13	44
	Modelled	36	84
	Environmental factors	13	44
	Human activities	0	6
	Demographics	39	88

REF	CAT	Disease classification	
		RI	Non RI
C4.4	Mentioned	29	161
	Direct contact	3	34
	Sexual contact	0	5
	Respiratory	20	26
	Body fluid	7	23
	Food-borne	0	3
	Water contact	1	61
	Vector-borne	0	37
C4.5	Investigate causal relationships	19	51
	Model disease transmission dynamics	46	159
	Develop a model and analyse behaviour	23	92
	Forecast disease instance	4	18
	Test interventions	39	81
	Investigate super spreading events	1	6
	Vaccination / vaccination strategies	37	40
C4.6	None	5	29
	Case data	41	110
	Travel data	1	4
	Parameters from literature	18	71
	Population estimates	5	6
	Assumed	7	23

D.6 Data prior to normalisation, subset 5

Table D.13: Data extracted from dataset prior to normalisation, subset 5.

REF	CAT	Modelling rationales					
		Investigate causal relationships	Model disease transmission dynamics	Develop a model and analyse behaviour	Forecast disease instance	Test interventions	Investigate super spreading events
C1.3	Considered	8	35	16	4	27	2
C7.2	General	6	84	59	0	47	1
	Global	0	5	3	0	4	0
	Intercountry	5	4	3	0	3	0
	Country	21	63	25	12	43	1
	Provincial	16	12	6	3	6	2
	Small region	22	37	19	7	17	3

D.7 Data prior to normalisation, subset 6

Table D.14: Data extracted from dataset prior to normalisation, subset 6.

REF	CAT	Data sources					
		None	Case data	Travel data	Parameters from literature	Population estimates	Assumed
C7.1	General	29	4	0	45	1	23
	Global	0	6	3	1	3	1
	Intercountry	0	8	1	0	2	1
	Country	1	66	1	27	3	3
	Provincial	0	25	0	4	1	0
	Small region	3	43	0	12	1	2

D.8 Data prior to normalisation, subset 7

Table D.15: Data extracted from dataset prior to normalisation, subset 7.

REF	CAT	Modelling scopes					
		General	Global	Intercountry	Country	Provincial	Small region
C7.3	Incorporated alternative mixing patterns	12	1	1	12	2	13

D.9 Data prior to normalisation, subset 8

Table D.16: Data extracted from dataset prior to normalisation, subset 8.

REF	CAT	Intervention strategies	
		Treatment	Vaccination
C2.2	None	4	7
	Case data	31	27
	Travel data	2	0
	Parameters from literature	31	35
	Population estimates	3	4
	Assumed	12	13
C7.4	General	12	31
	Global	2	1
	Intercountry	0	2
	Country	18	19
	Provincial	1	3
	Small region	7	4

D.10 Data prior to normalisation, subset 9

Table D.17: Data extracted from dataset prior to normalisation, subset 9.

REF	CAT	Contextual factors	
		Linked to disease propagation	Modelled
C2.4[34]	None	0	2
	Case data	40	17
	Travel data	0	0
	Parameters from literature	1	5
	Population estimates	0	0
	Assumed	0	4
C2.4[35]	None	0	15
	Case data	28	46
	Travel data	1	4
	Parameters from literature	3	31
	Population estimates	3	7
	Assumed	1	14
C7.5[36]	General	1	5
	Global	0	0
	Intercountry	1	0
	Country	14	9
	Provincial	9	2
	Small region	16	9

[34] Environmental factors

[35] Population demographic factors

[36] Environmental factors

REF	CAT	Contextual factors	
		Linked to disease propagation	**Modelled**
C7.5[37]	General	2	31
	Global	1	6
	Intercountry	6	5
	Country	10	30
	Provincial	5	8
	Small region	6	20

[37] Population demographic factors

D.11 Overview of detailed analysis sections

An analysis on the relationship between transmission modes and the modelling approach is completed in §D.12, followed by analysis on the modelling scope and the transmission mode in §D.13. An analysis on the transmission mode and incorporation of alternative mixing patterns is completed in §D.14. An analysis of the transmission mode in relation to various treatment and vaccination strategies are analysed in §D.15, followed by the inclusion of contextual factors in relation to different transmission modes in §D.16. Some of the modelling considerations which relate to the selection of alternative mixing patterns are discussed in §D.17, followed by an analysis of the occurrence of the data source in the context of modelling considerations in §D.18. The use of the modelling scope in the context of modelling considerations is analysed in §D.19. The occurrence of compartmental classification in the context of modelling considerations is discussed in §D.20, followed by an analysis on the relationship between the modelling approach and the modelling rationale, modelling scope and presence of intervention strategies in §D.21. Various modelling considerations are analysed in the context of disease categorisation between RI and non-RI in §D.22.

D.12 Modelling approaches in relation to the transmission modes

As mentioned in the previous section, the transmission mode is one of the primary disease characteristics and potentially one of the main drivers of disease dynamics. Within this section, the occurrence of modelling approaches in relation to the transmission mode is analysed. A comparison between the proportion of mentioned transmission modes in relation to the total theoretical transmission modes is discussed in the §D.12.1. A general overview of the modelling occurrences for each of the disease transmission modes is completed in §D.12.2. This is followed by a more in-depth analysis of the mathematical (§D.12.3), network (§D.12.4) and simulation (§D.12.5) modelling approaches applied in relation to each transmission mode in the dataset.

D.12.1 Theoretical transmission modes and mentioned transmission modes

The total number of potential transmission modes in the dataset is captured in S1. As discussed in §4.1.1, however, not all of the transmission modes that theoretically exist for a disease are necessarily considered within the modelling process. To compensate for this uncertainty regarding whether a potential transmission mode has been taken into consideration when formulating the modelling approach, only those transmission modes which are explicitly mentioned within the contextualisation of the disease are noted in S2. The proportion of the theoretical transmission modes which are explicitly mentioned in the dataset are illustrated in Figure D.1. The diseases with the highest instance of explicitly mentioned transmission modes were vector-borne (95%) and water

contact diseases (80%), followed by direct contact (37%), respiratory (27%) and body fluid (19%). The transmission modes described the least were sexual contact (9%) and food-borne (4%).

From this observation it appears that the vector-borne and water contact transmission modes are considered to be particularly salient in modelling disease dynamics, while direct contact, respiratory and body fluid transmission modes appear to be moderately relevant. These observations are captured to Table 4.6 in REF B1.

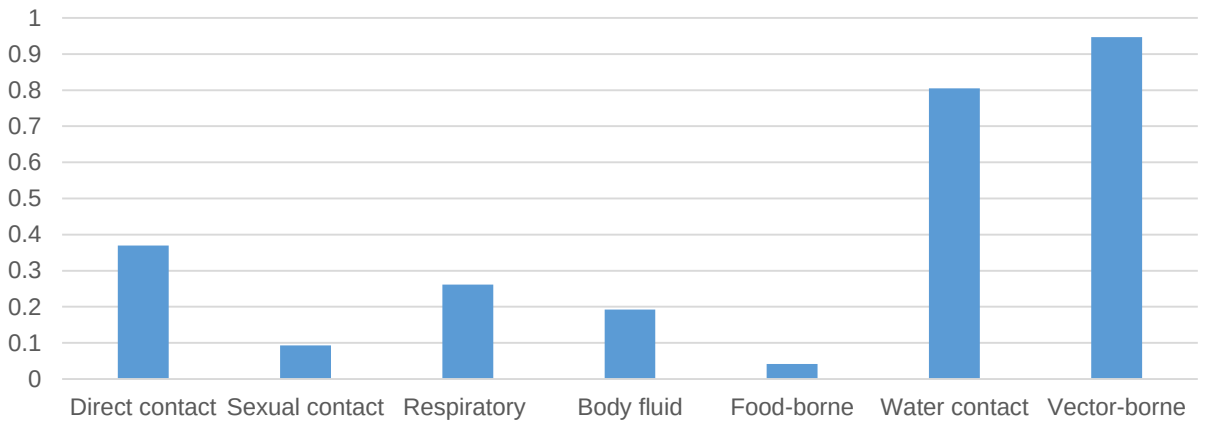

Figure D.1: Proportion of literature pieces in the dataset which explicitly mentions the transmission mode of the disease, normalised according to S1N.

D.12.2 Modelling approaches in the dataset

Within the dataset no system dynamics modelling (mentioned in §2.3.4) applications are observed. The proportion of literature pieces in the dataset which include mathematical, network and simulation modelling approaches in relation to each transmission mode are illustrated in Figure D.2 (S1) and Figure D.3 (S2), namely for all theoretical transmission modes and for explicitly mentioned transmission modes, respectively. Consequently, it would be preferable to infer conclusions regarding the relationship between the transmission mode and the modelling approach from S2 rather than from S1. Caution must be exercised when doing so, however, as the amount of data in certain transmission mode categories in S2 is quite small. Most notably, in S2 the sexual transmission category contains only 5 literature pieces and the food-borne vector category contains only 3 literature pieces.

In both S1 and S2 mathematical modelling is the most frequently used approach across all transmission modes. Mathematical approaches are less prominently used for modelling respiratory transmission where, in S2, network and simulation approaches represent 18% and 12% of the dataset instances respectively. To a lesser extent, mathematical modelling approaches are also less prevalent for direct contact transmission where, in S2, network and simulation approaches represent 11% of the dataset instances each. A final observation based on S2, is that mathematical

approaches are used in more than 90% of modelling instances for the body fluid, water contact, and vector-borne transmission modes. These observations are captured to Table 4.6 in REF B3.1.

Though in S2, sexual contact is exclusively modelled with mathematical approaches and simulation appears to be used more frequently for food-borne transmission than for any other transmission mode, these observations are not taken into consideration when constructing the framework in Chapter 5, due to the small number of literature instances on which these are based.

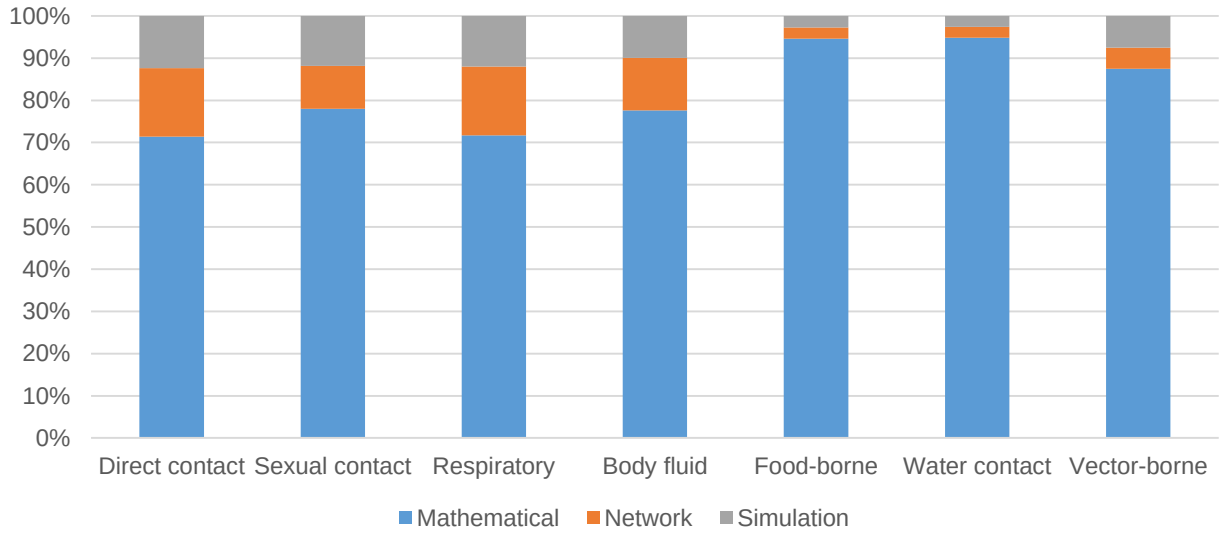

Figure D.2: Proportion of all theoretical transmission modes in the dataset which include mathematical, network and simulation modelling approaches, normalised according to S1N.

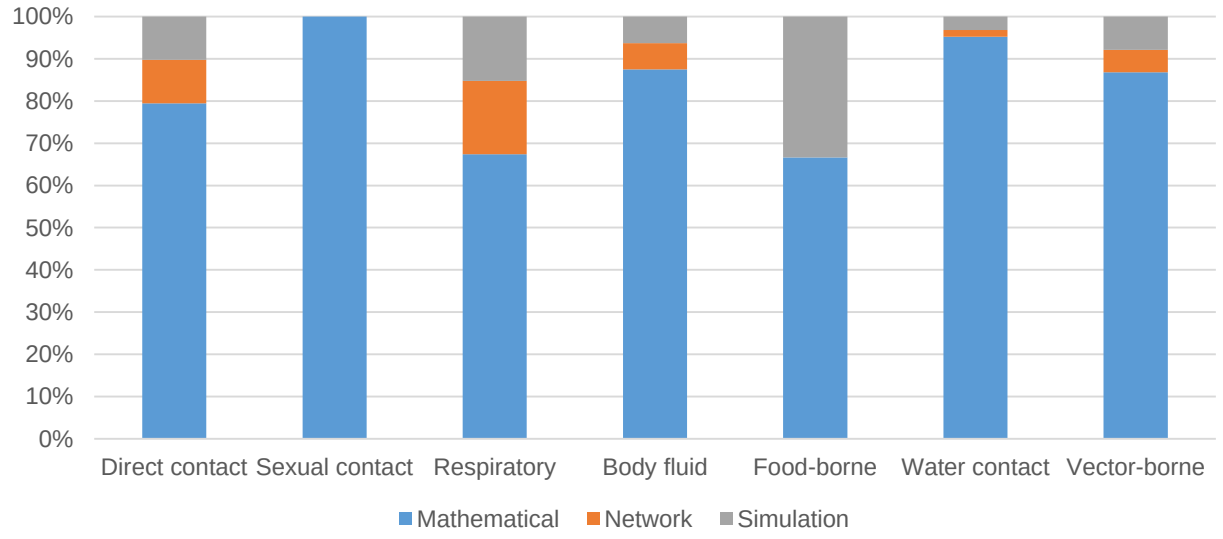

Figure D.3: Proportion of all mentioned transmission modes in the dataset which include mathematical, network and simulation modelling approaches, normalised according to S2N.

D.12.3 Mathematical modelling approaches

The different mathematical modelling approaches used (as a proportion of the total number of modelling instances for each transmission mode) are illustrated in Figure D.4 (S1) and Figure D.5 (S2). In line with reasoning provided previously, conclusions that can be inferred from S2 are preferential to those that can be inferred from S1.

From both S2 and S1, it is clear that DEs are the most frequently used mathematical modelling approach. Additionally, based on S2, the transmission modes with the most diverse range of mathematical modelling approaches used are respiratory, water contact and vector-borne.

In order to enable more detailed visualisation of the use of mathematical approaches other than DE, the figures are reproduced with the exclusion of the DE category in Figure D.6 (S1*) and Figure D.7 (S2*).[38] From S2* it is evident that regression is also a prominent mathematical modelling approach, being used most notably in 22% of vector-borne modelling instances as well as in 9% of respiratory and 6% of water contact modelling instances. Other notable forms of mathematical modelling that can be observed from the visualisation of S2* include: PDE (a variant of DE), used in 8% of the instances where water contact transmission is modelled; FODE, used in 7% of the instances where body fluid and 5% of the instances where direct contact transmission are modelled; coupled DE used in 5% of the instances where water contact transmission is modelled; and GAM, GIS, SARIMA and Bayesian, each used in 5% of the vector-borne transmission instances.

Though in S2* food-borne had no modelling applications and sexual contact only had FODE (a variant of DE) approaches, these observations are not taken into consideration when constructing the framework in Chapter 5, due to the small number of literature instances on which these are based.

Apart from these high-level observations, it is not possible to directly quantify the modelling approach selection solely from the transmission mode, but it is still useful to note some of the relationships to the transmission modes. A selection of these observations are captured to Table 4.6 in REF B3.2.

[38] S1* is constructed as a subset of S1, which only omits DE approaches from S1. S2* is constructed similarly from S2.

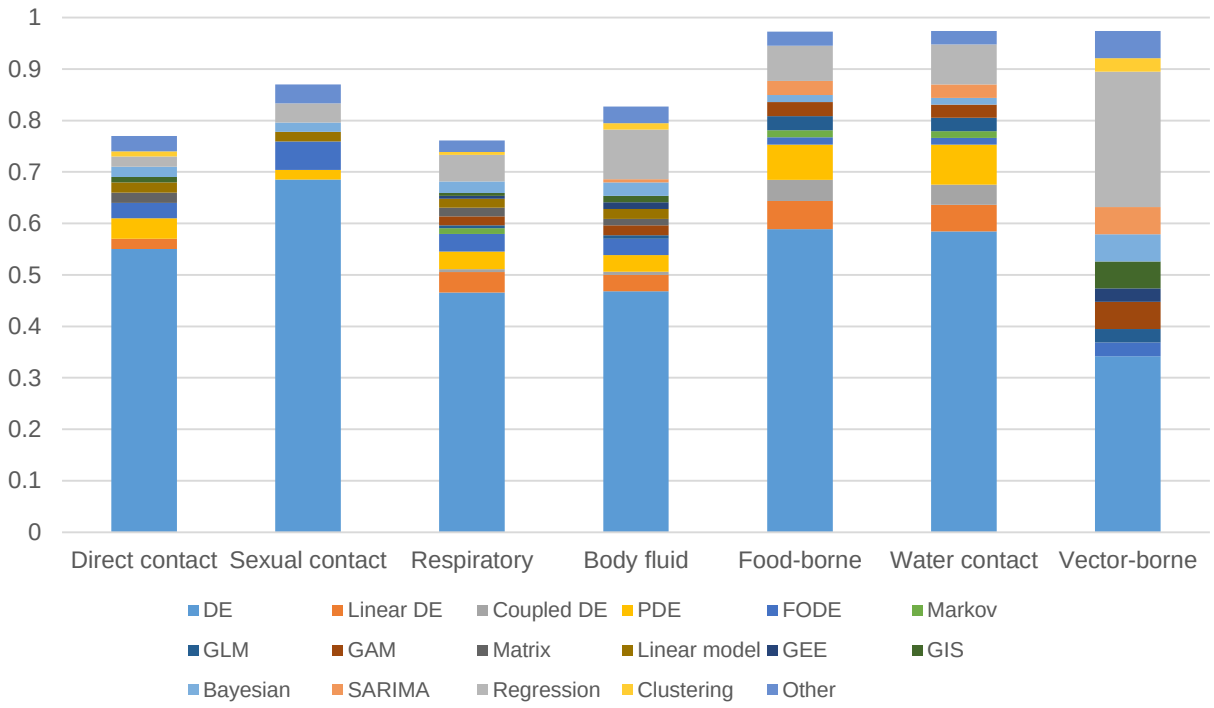

Figure D.4: Proportion of all theoretical transmission modes in the dataset which include mathematical modelling approaches, normalised according to S1N.

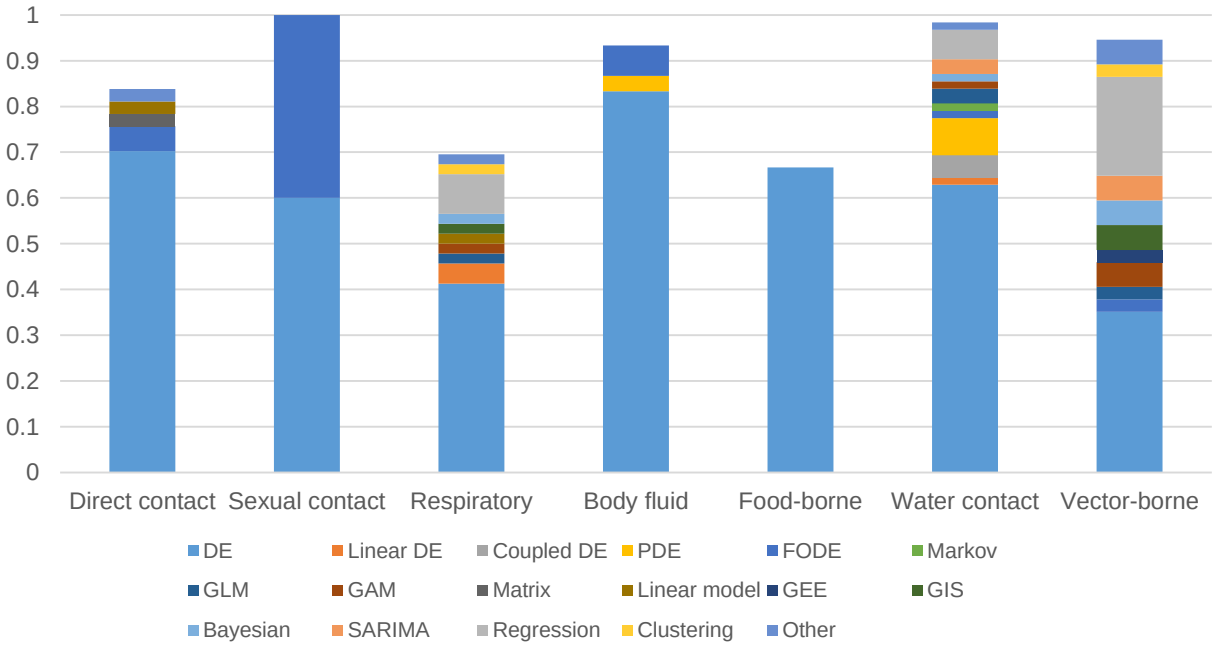

Figure D.5: Proportion of all mentioned transmission modes in the dataset which include mathematical modelling approaches, normalised according to S2N.

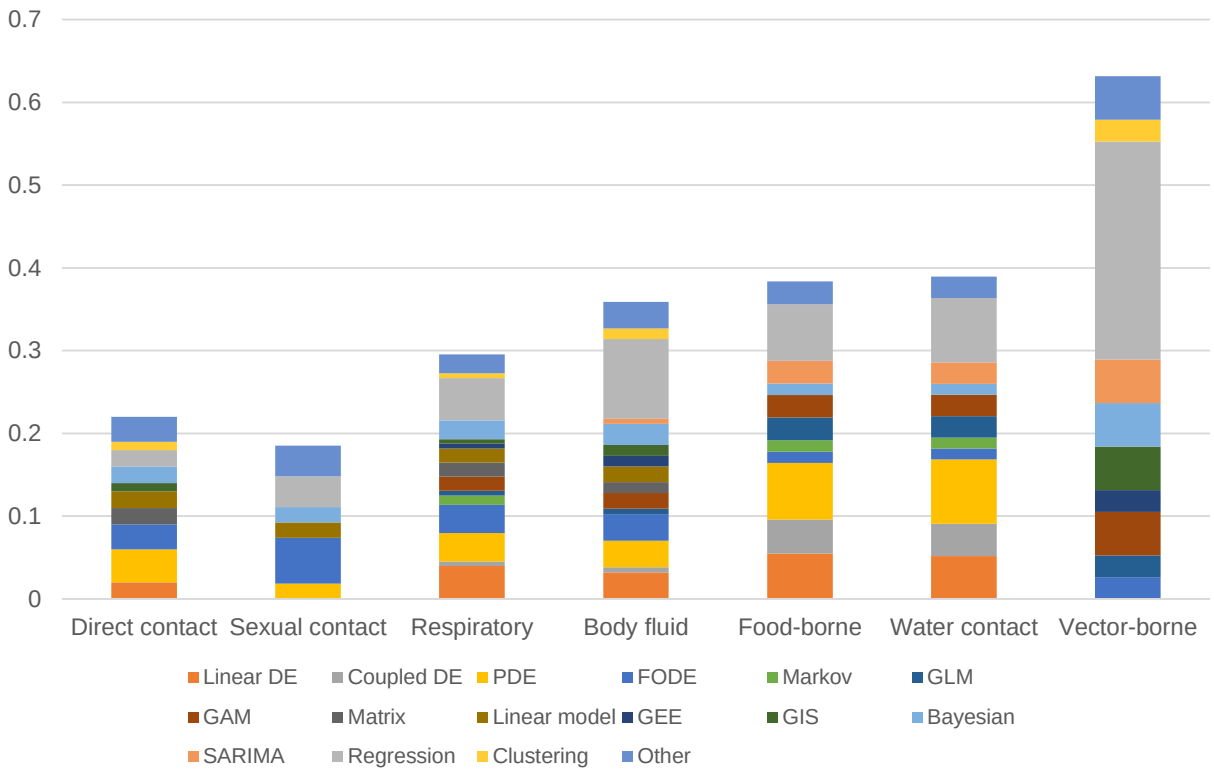

Figure D.6: Proportion of all theoretical transmission modes in the dataset which include mathematical modelling approaches (excluding instances of DE), normalised according to S1N.

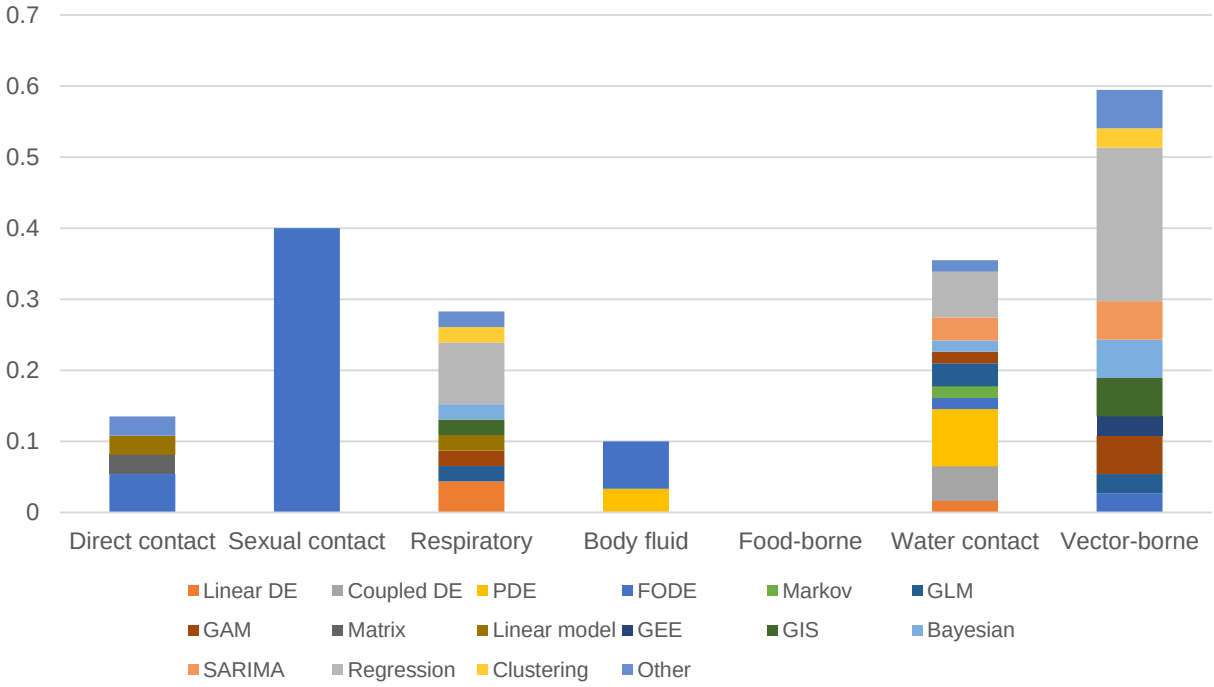

Figure D.7: Proportion of all mentioned transmission modes in the dataset which include mathematical modelling approaches (excluding instances of DE), normalised according to S2N.

D.12.4 Network modelling approaches

The different network modelling approaches used (as a proportion of the total number of modelling instances for each transmission mode) are illustrated in Figure D.8 (S1) and Figure D.9 (S2). In line with reasoning provided previously, conclusions that can be inferred from S2 are preferred to those that can be inferred from S1. S2, however, contains only 33 instances of network modelling. In an attempt to mitigate the risk of drawing inaccurate inferences from such a small dataset, observations based on S1 and other logical reasoning are also included in the discussion below.

It is interesting to note in S1 that the four transmission modes which are modelled the most by means of network models are direct and sexual contact, respiratory and body fluid, which are all transmission modes dependant on human host interactions. The same observations hold for S2, however, without network approaches observed for sexual contact. In S1 it is clear that the metapopulation network models are used for all transmission modes and small world network models are used mainly for direct and sexual contact, respiratory and body fluid. Similar to the observation for mathematical approaches, the transmission modes with the most diverse categories of network approaches were respiratory, followed by body fluid. In S2, no network applications are observed for sexual contact and food-borne transmission modes.

Apart from these high-level observations, it is not possible to directly quantify the modelling approach selection solely from the transmission mode, but it is still useful to note some of the relationships to the transmission modes. A selection of these observations are captured to Table 4.6 in REF B3.3.

D.12.5 Simulation modelling approaches

The different simulation modelling approaches used (as a proportion of the total number of modelling instances for each transmission mode) are illustrated in Figure D.10 (S1) and Figure D.11 (S2). As was the case for the discussion of network modelling approaches in §D.12.4, the S2 dataset contains only a small number of literature pieces in total (namely 27 instances) and a similar approach to that taken in the previous section is employed in an attempt to ensure that inaccurate conclusions are not drawn.

In both S1 and S2 it is clear that ABS is the most frequently applied simulation technique. As observed in §D.12.4 regarding the use of network modelling approaches, it is noted in S1 that the four transmission modes which are dependent on human host interactions (apart from sexual contact) are modelled with a similar proportion of diverse simulation modelling techniques.

Apart from these high-level observations, it is not possible to directly quantify the modelling approach selection solely from the transmission mode, but it is still useful to note some of the relationships to the transmission modes. A selection of these observations are captured to Table 4.6 in REF B3.4.

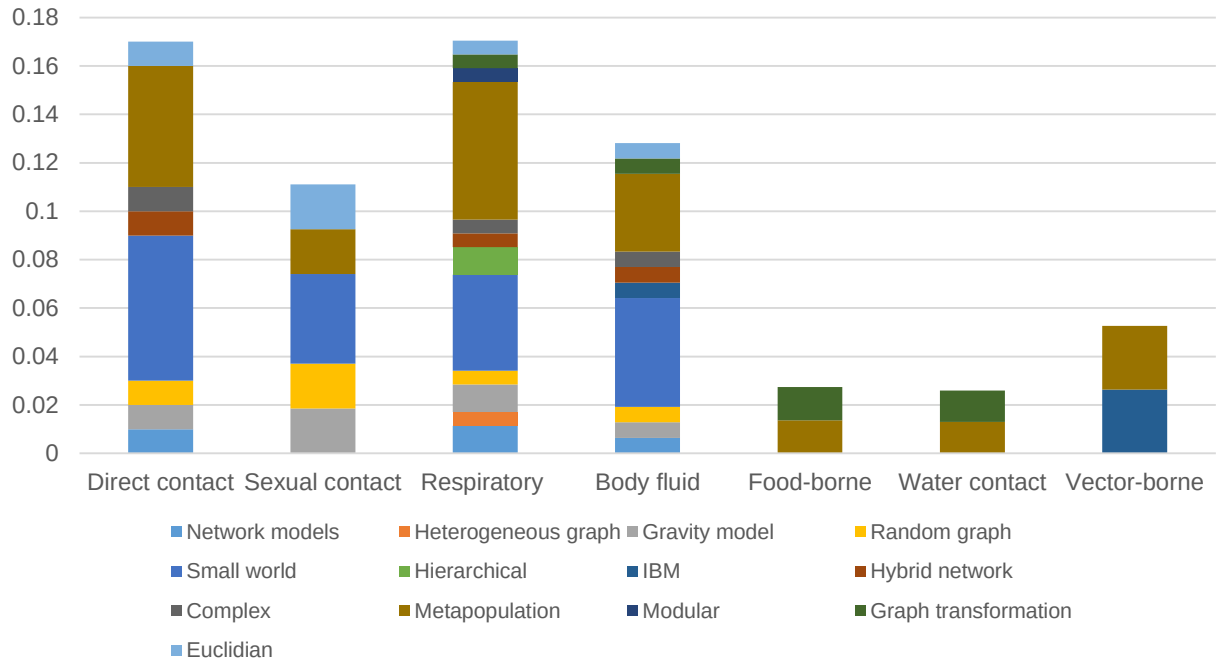

Figure D.8: Proportion of all theoretical transmission modes in the dataset which include network modelling approaches, normalised according to S1N.

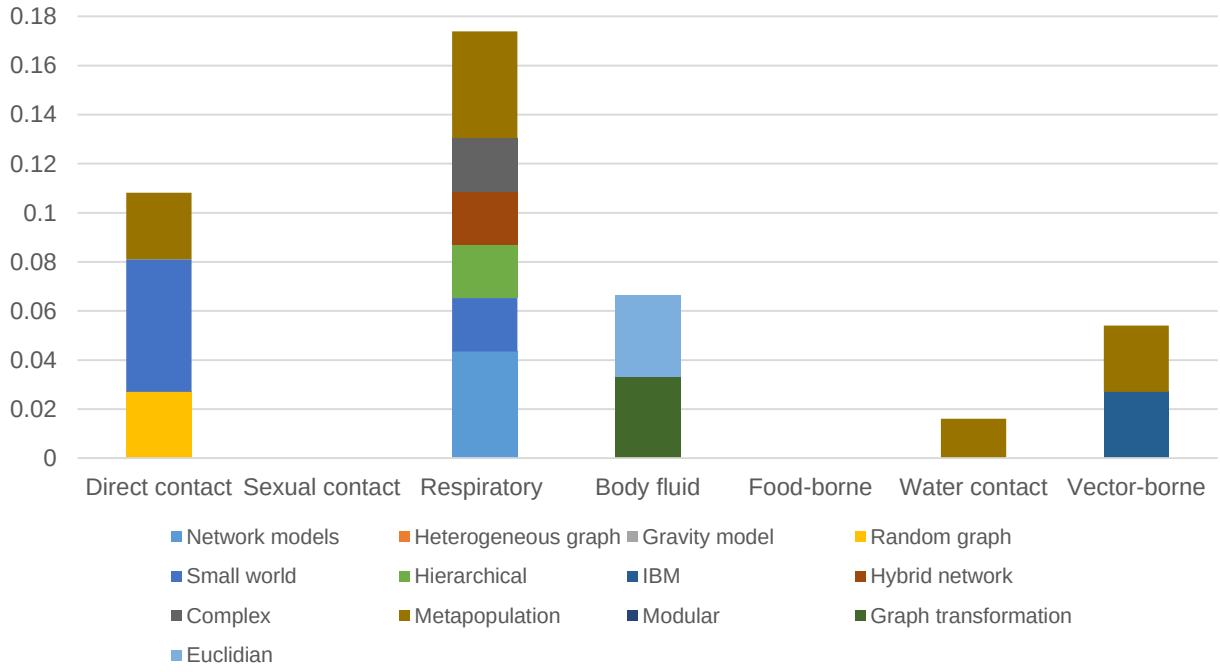

Figure D.9: Proportion of all mentioned transmission modes in the dataset which include network modelling approaches, normalised according to S2N.

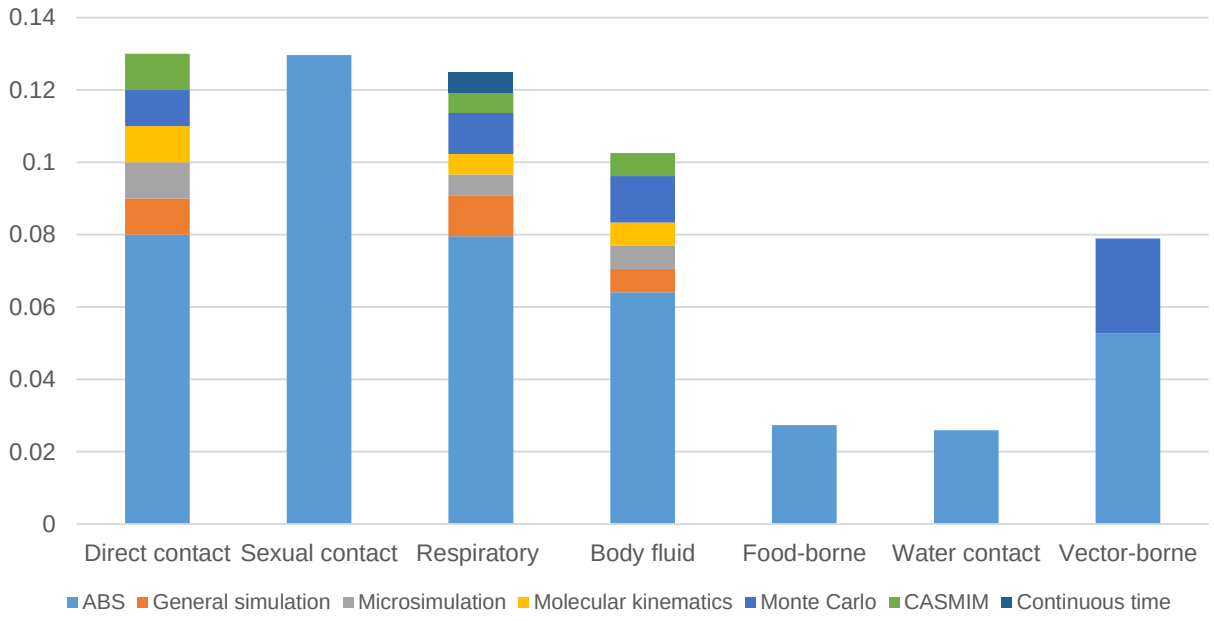

Figure D.10: Proportion of all theoretical transmission modes in the dataset which include simulation modelling approaches, normalised according to S1N.

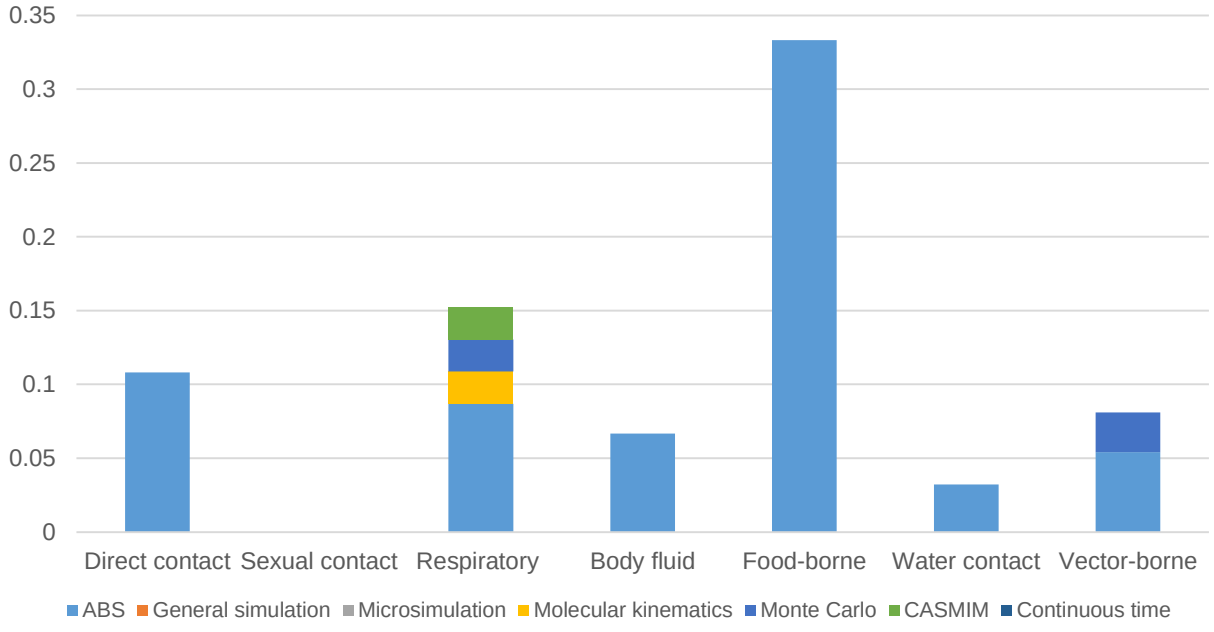

Figure D.11: Proportion of all mentioned transmission modes in the dataset which include simulation modelling approaches, normalised according to S2N.

D.13 Modelling scopes in relation to the transmission modes

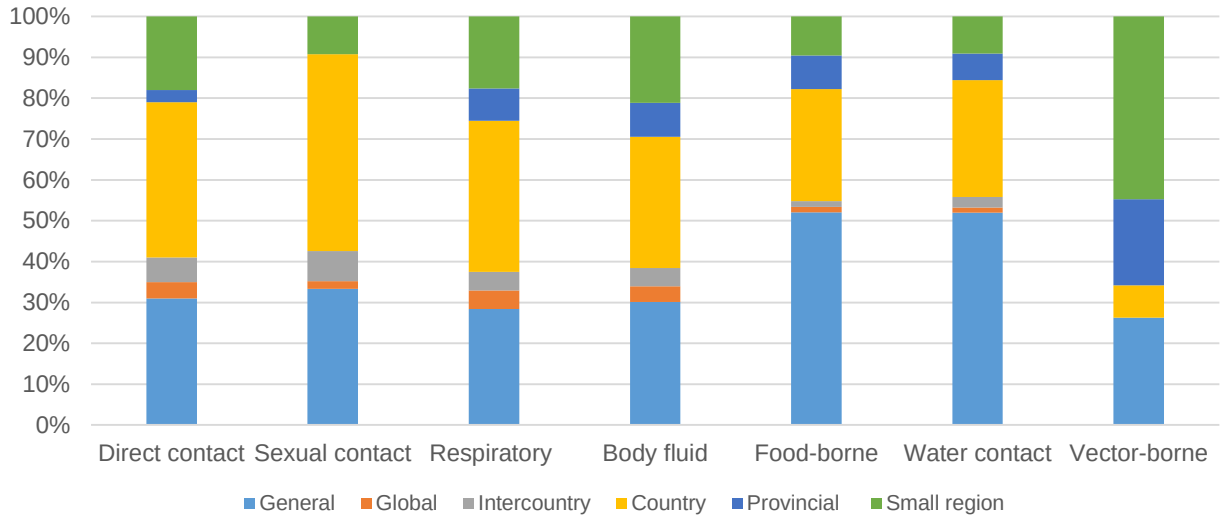

Figure D.12: Proportion of models to which various modelling scopes have been applied, for each theoretical transmission mode, normalised according to S1N.

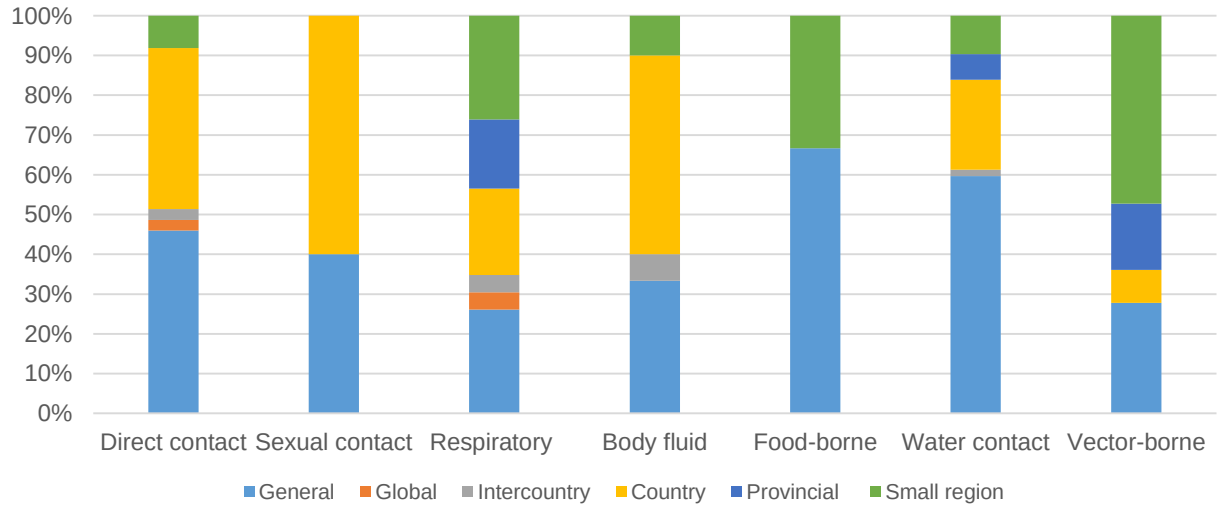

Figure D.13: Proportion of models to which various modelling scopes have been applied, for each mentioned transmission mode, normalised according to S2N.

The proportion of literature pieces in the dataset with a particular modelling scope in relation to the transmission modes are illustrated in Figure D.12 (S1) and Figure D.13 (S2), namely for all theoretical transmission modes and for explicitly mentioned transmission modes, respectively.

A general modelling scope is frequently used across all transmission modes both in S2 and S1. Two notable cases where a country scope is employed are body fluid transmission, where it is the most common modelling scope, and direct contact transmission where it is used in 41% of the modelling instances in S2.

It is also interesting to note that, in S2, vector-borne diseases have the smallest proportion of country scope modelling applications, but the highest proportion of small region scope of all the transmission modes. This makes sense, as vector-borne diseases depend on vectors which typically operate in a small region. According to S2 the only transmission modes which are modelled using a global scope are respiratory and direct contact. It is clear that the most diverse modelling scope is applied to respiratory transmission modes, followed by direct contact and water contact transmission modes. Furthermore, the provincial scope is also used in relation to the respiratory, vector-borne, and water contact transmission modes.

Apart from these high-level observations, it is not possible to directly quantify the modelling scope selection solely from the transmission mode, but it is still useful to note some of the relationships to the transmission modes. A selection of these observations are captured to Table 4.6 in REF B2.1.

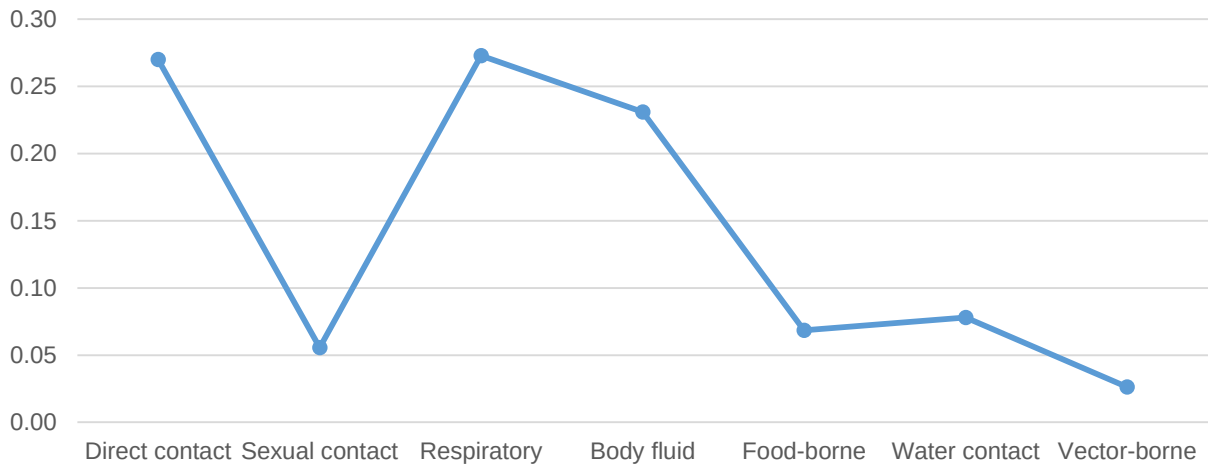

Figure D.14: Proportion of all theoretical transmission modes in the dataset which include alternative mixing patterns in the modelling approach, normalised according to S1N.

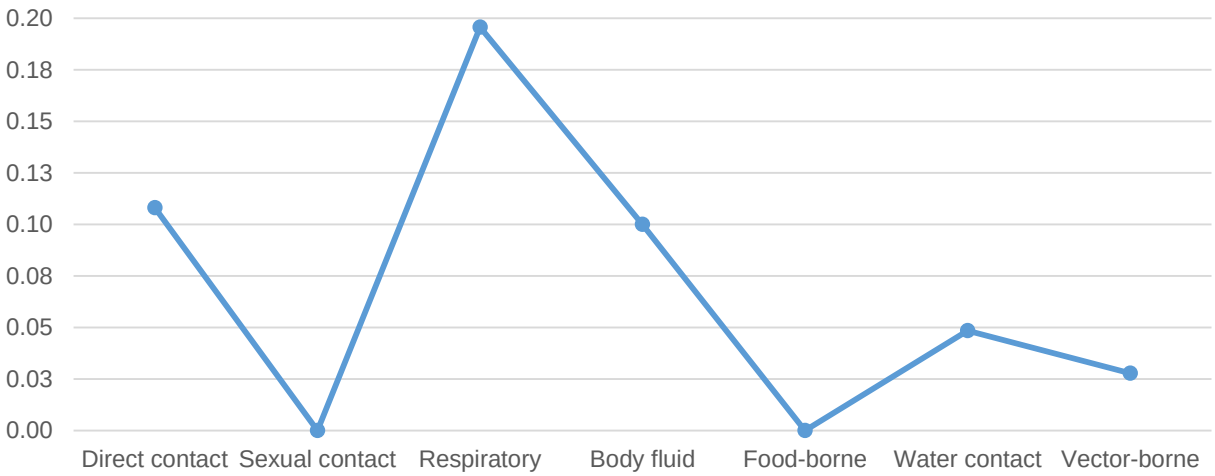

Figure D.15: Proportion of all mentioned transmission modes in the dataset which include alternative mixing patterns in the modelling approach, normalised according to S2N.

D.14 Alternative mixing patterns in relation to the transmission modes

The proportion of literature pieces in the dataset which include alternative mixing patterns relative to the transmission modes are illustrated in Figure D.14 (S1) and Figure D.15 (S2). As before, inferences that are drawn from S2 are preferred to those that are drawn from S1.

From both S2 and S1 it is observed that alternative mixing patterns are the most frequently applied relative to diseases which are transmissible by respiratory contact, direct contact and body fluid. Logically one would expect that alternative mixing patterns would be an important consideration for the sexual contact transmission mode, however, together with the food-borne transmission mode it is seldom modelled using alternative mixing patterns. This is potentially explained by the limited occurrence of explicit modelling of these two transmission modes in the dataset.

Apart from these high-level observations, it is not possible to directly determine the alternative mixing pattern selection solely from the transmission mode, but it is still useful to note some of the relationships to the transmission modes. A selection of these observations is captured to Table 4.6 in REF B2.2. A more detailed analysis on factors relating to alternative mixing pattern selection is completed in §D.17.

D.15 Intervention strategies relative to the transmission modes

The proportion of literature pieces in the dataset which include the modelling of intervention strategies for each of the transmission modes are illustrated in Figure D.16 (S1) and Figure D.17 (S2).

As a general observation, it is clear that treatment strategies are most frequently applied in the context of the first four transmission modes, in addition to the water contact transmission mode. This is particularly interesting, as these transmission modes are dependent on direct contact between humans, apart from body fluid and water contact which requires indirect contact.

In S2, vaccination strategies are the most frequently observed relative to body fluid and respiratory transmission modes, in addition to direct, sexual and water contact transmission modes. Additionally in S2, no vaccination strategies are observed for food-borne and vector-borne transmission modes. The existence of vaccination strategies for the food-borne category in S1 is an unexpected finding, as there are currently no vaccines for food-borne diseases. This can, however, be explained when one considers that food-borne is one of the theoretical transmission modes of cholera. In line with expectations, there are no mentioned food-borne literature occurrences which incorporate vaccination strategies in S2. This is a more realistic representation of vaccination strategy usage in the context of food-borne diseases. Furthermore, no vaccination strategies are observed for vector-borne disease, as vaccines are not currently available for vector-borne disease in general.

Apart from these high-level observations, it is not possible to directly quantify the intervention strategy selection solely from the transmission mode, but it is still useful to note some of the relationships to the transmission modes. A selection of these observations are captured to Table 4.6 in REF B4. The treatment strategies and vaccination strategies are analysed in more detail in §D.15.1 and §D.15.2, respectively.

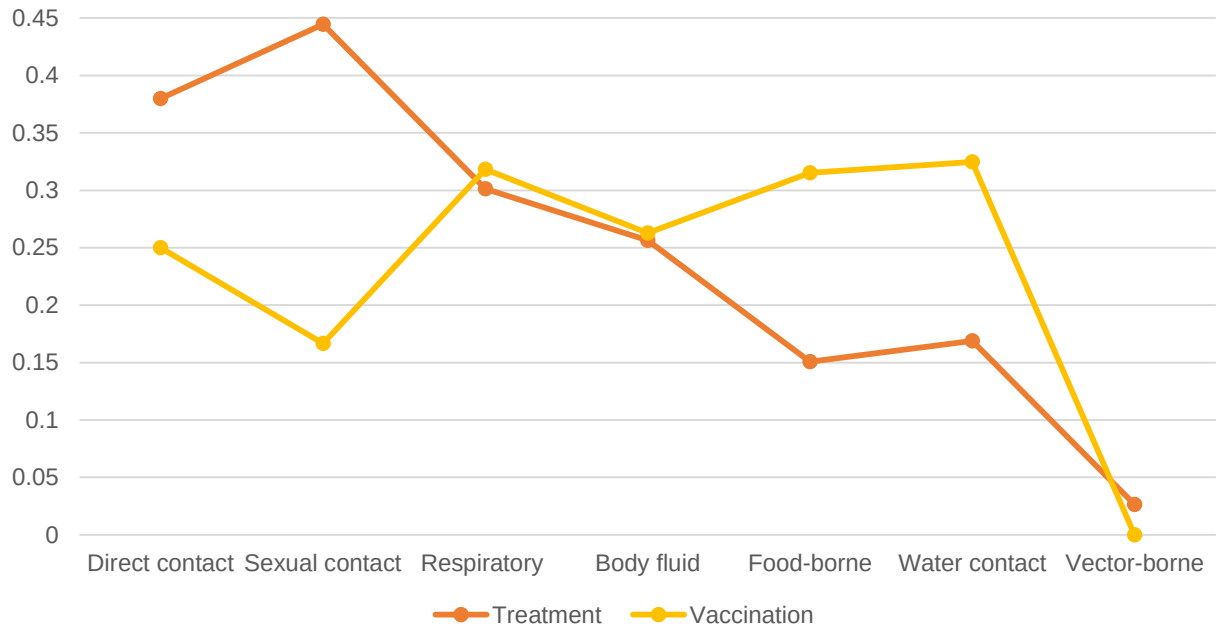

Figure D.16: Proportion of all theoretical transmission modes in the dataset which include two intervention strategies, normalised according to S1N.

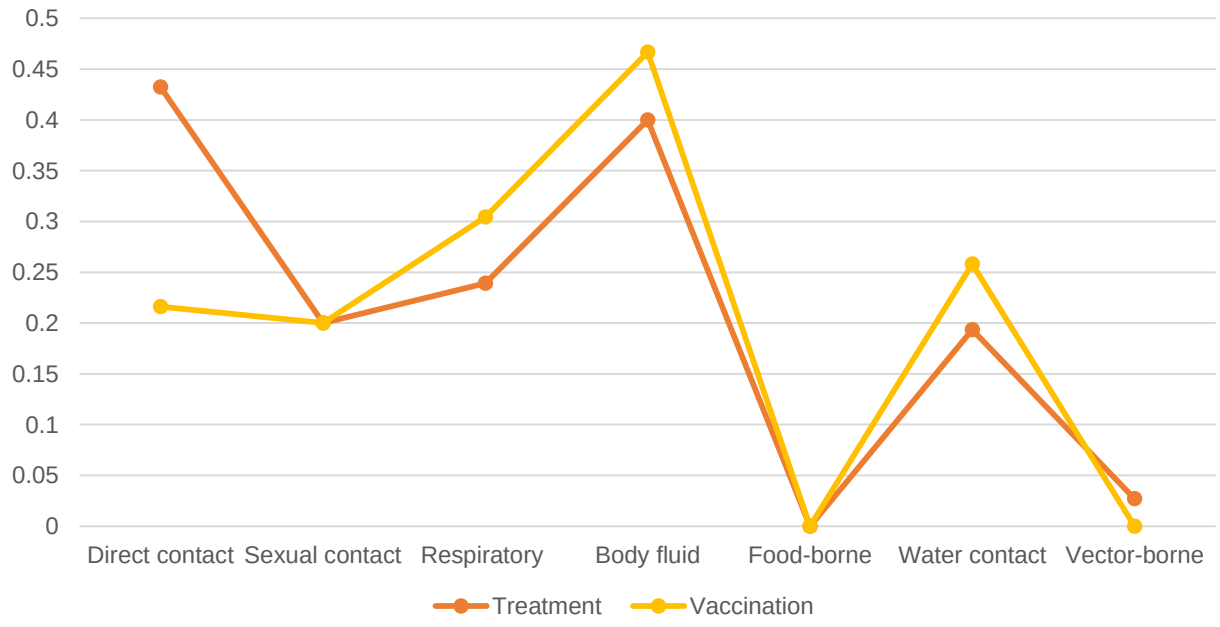

Figure D.17: Proportion of all mentioned transmission modes in the dataset which include two intervention strategies, normalised according to S2N.

D.15.1 Treatment strategies

The proportion of literature pieces in the dataset which include treatment strategies relative to the transmission modes are illustrated in Figure D.18 (S1) and Figure D.19 (S2).

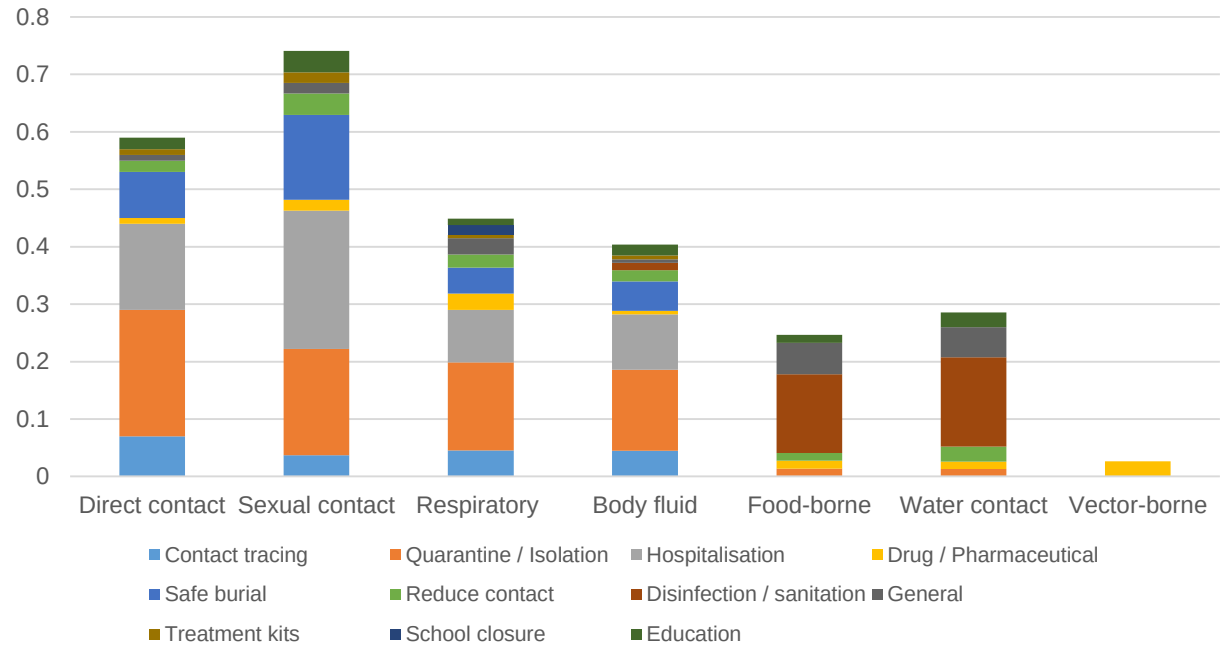

Figure D.18: Proportion of all theoretical transmission modes in the dataset which include different treatment strategies, normalised according to S1N.

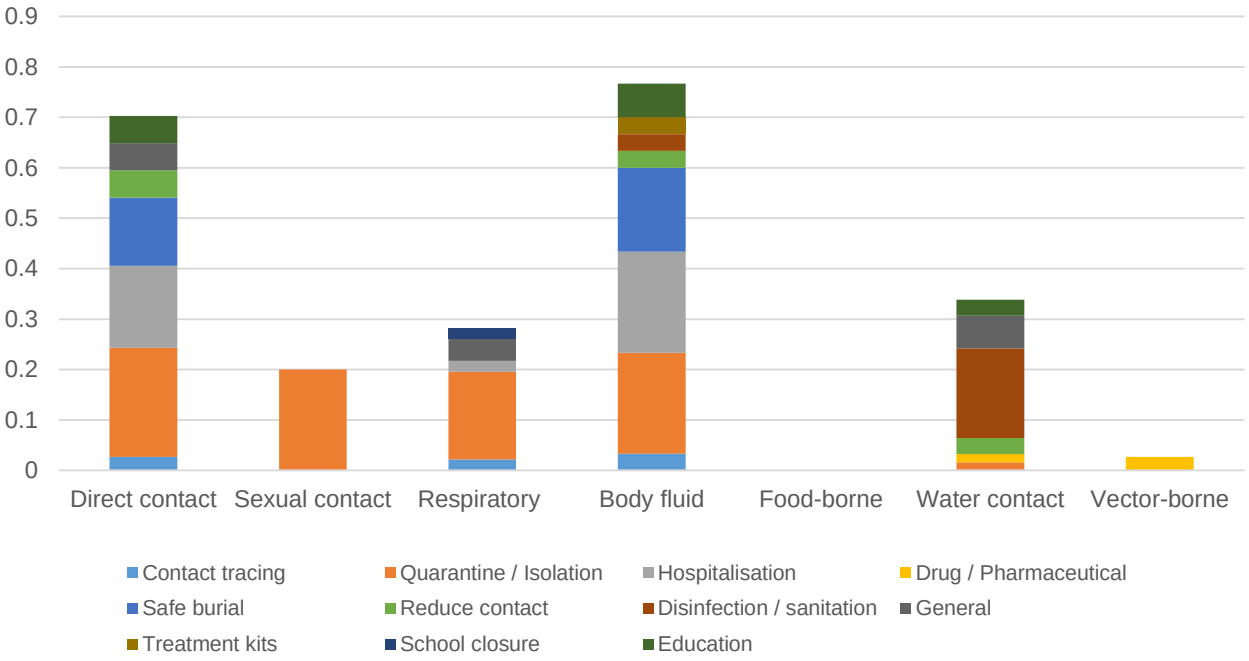

Figure D.19: Proportion of all mentioned transmission modes in the dataset which include different treatment strategies, normalised according to S2N.

In both S2 and S1, quarantine is observed only for the transmission modes which rely on contact between humans. Furthermore, in S2 it is observed that very similar treatment strategies are applied in relation to the direct contact and body fluid transmission modes. With reference to S2, reduced contact is observed especially in relation to the direct contact, body fluid and water contact transmission mode. Furthermore, with reference to S1 it is observed that reduced contact is also a strategy that is applied for all transmission modes, except for a vector-borne transmission mode.

The least amount of treatment strategies are applied in relation to the vector-borne transmission mode, with drug usage as the only observed treatment strategy. In S1 disinfection is observed only for the food-borne and water contact transmission modes.

In S2 it is observed that the most diverse amount of treatment strategies are applied in relation to the body fluid transmission mode. Additionally, no treatment strategies were observed for the food-borne transmission mode.

Apart from these high-level observations, it is not possible to directly quantify the treatment strategy selection solely from the transmission mode, but it is still useful to note some of the relationships to the transmission modes. A selection of these observations are captured to Table 4.6 in REF B4.1.

D.15.2 Vaccination strategies

The proportion of literature pieces in the dataset which include vaccination strategies for each of the transmission modes are illustrated in Figure D.20 (S1) and Figure D.21 (S2).

In both S1 and S2 it is clear that the vaccination strategy that is applied the most frequently is the vaccination of a proportion of the susceptible population. Additionally, the most diverse number of vaccination strategies are applied in relation to the respiratory transmission mode. Of the commonly applied vaccination strategies mentioned in Table 2.2, it is interesting to note that the more reactive strategies, such as ring and targeted vaccination do not occur as frequently as the proactive vaccination strategies, such as vaccination of a proportion of the susceptible population, general vaccination rate and prophylactic vaccination strategies. The latter three vaccination strategies may be regarded as a form of mass vaccination, which is a very general strategy which does not necessarily take into account the underlying disease dynamics or context of the outbreak in order to inform which individuals should receive vaccination. Furthermore, it is interesting that ring vaccination is only applied in relation to the first four transmission modes, which rely on direct or indirect contact between humans in order to successfully transmit the disease (whereas the remaining 3 transmission modes rely on environmental interactions to facilitate disease transmission).

Apart from these high-level observations, it is not possible to directly quantify the vaccination strategy selection solely from the transmission mode, but it is still useful to note some of the relationships to the transmission modes. A selection of these observations are captured to Table 4.6 in REF B4.2.

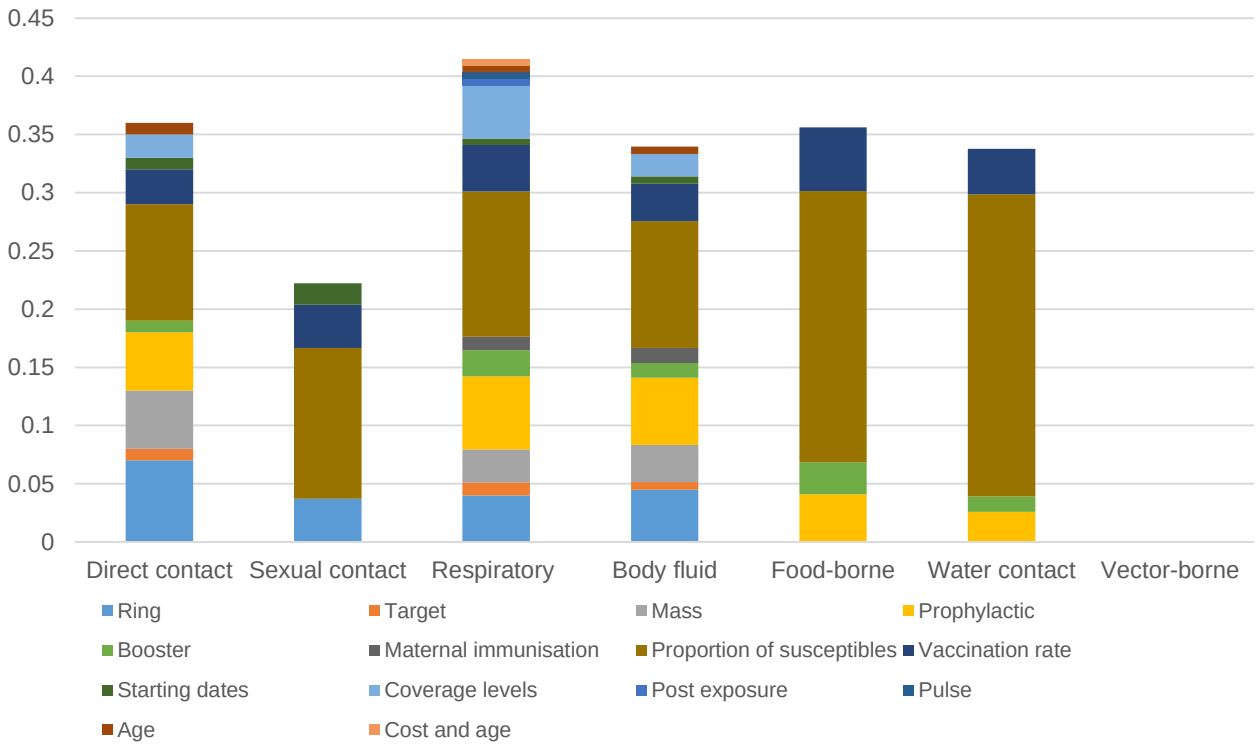

Figure D.20: Proportion of all theoretical transmission modes in the dataset which include different vaccination strategies, normalised according to S1N.

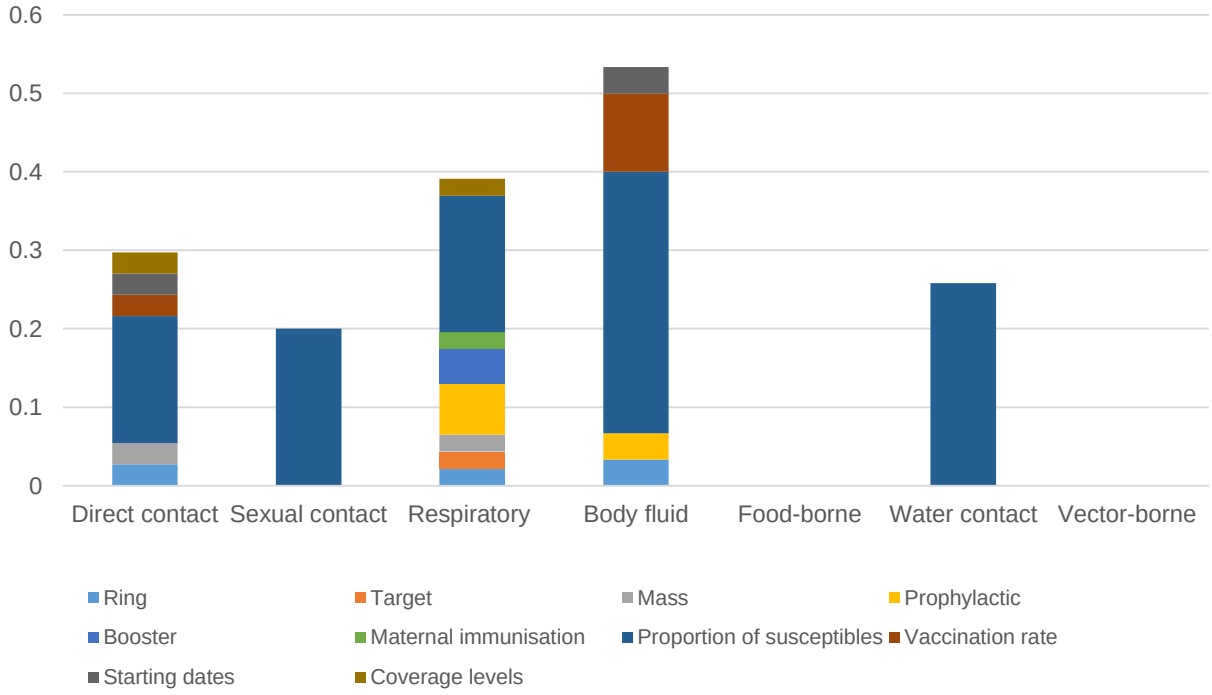

Figure D.21: Proportion of all mentioned transmission modes in the dataset which include different vaccination strategies, normalised according to S2N.

D.16 Contextual factors relative to the transmission modes

The proportion of literature pieces in the dataset which include analysis on contextual factors that are linked to disease propagation and contextual factors included in the modelling approach (but not necessarily linked to the propagation of the disease) relative to the transmission modes are illustrated in Figure D.22 (S1) and Figure D.23 (S2).

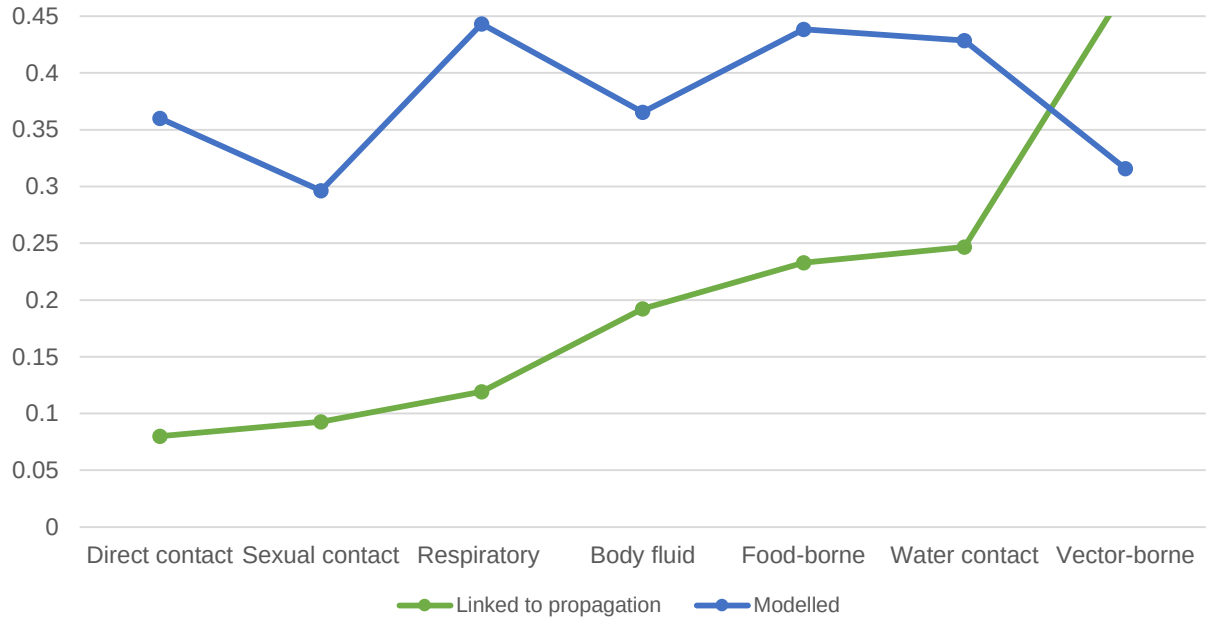

Figure D.22: Proportion of all theoretical transmission modes in the dataset which include contextual factors linked to disease propagation and modelled contextual factors, normalised according to S1N.

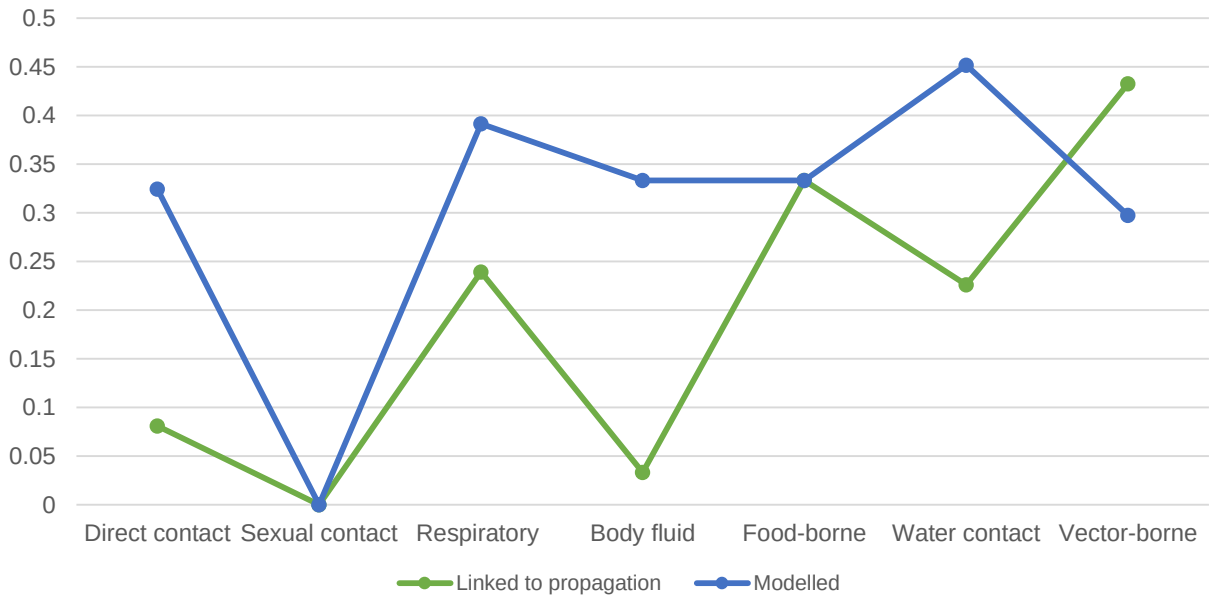

Figure D.23: Proportion of all mentioned transmission modes in the dataset which include contextual factors linked to disease propagation and modelled contextual factors, normalised according to S2N.

As observed in S2, the transmission modes for which disease propagation are most frequently linked to contextual factors are respiratory, water contact and especially vector-borne.[39] Similarly, in S1 the transmission modes for which the contextual factors are most often linked to disease propagation are body fluid, food-borne, water contact and especially vector-borne. This observation is interesting, as the transmission modes which are the most frequently linked to contextual factors are all indirect transmission modes, many of which relate to the interaction with the environment (food-borne, water contact and vector-borne) and not between hosts.

With reference to contextual factors included in modelling approaches, it is observed in S1 that similar proportions of all the theoretical transmission modes included contextual factors in the modelling approach, with the lowest proportion of inclusions for the transmission modes sexual contact and vector-borne. When considering S2, a very similar observation is drawn, however, no modelling approaches which explicitly mentioned sexual contact as a transmission mode included contextual factors within the modelling approach. The lack of diseases transmitted exclusively with sexual contact (as discussed in §D.14) in this dataset potentially explains this observation.

Apart from these high-level observations, it is not possible to directly quantify the contextual factor inclusions solely from the transmission mode, but it is still useful to note some of the relationships to the transmission modes. A selection of these observations discussed within this section are captured to Table 4.6 in REF B5.1. The environmental contextual factors and the population demographic contextual factors are analysed in more detail in §D.16.1 and §D.16.2, respectively.

D.16.1 Environmental factors

The environmental contextual factors linked to disease propagation and the modelled environmental contextual factors are analysed in relation to the transmission modes below.

Linked to disease propagation factors

The proportion of literature pieces in the dataset which include environmental contextual factors linked to disease transmission in relation to the transmission modes are illustrated in Figure D.24 (S1) and Figure D.25 (S2). In S1 it is observed that the respiratory, body fluid, food-borne, water contact and vector-borne transmission modes are the only transmission modes which have inclusions of all four environmental contextual factors within the modelling approach linked to disease propagation. It is observed in S2 that rainfall is especially important to the food-borne, water contact and vector-borne transmission modes and, in general, that linking environmental contextual factors to disease transmission is especially important for the vector-borne transmission mode.

[39] From S2, the modelling of diseases that are food-borne also appears to frequently link contextual factors to propagation of the disease but this observation is based on only a single observation.

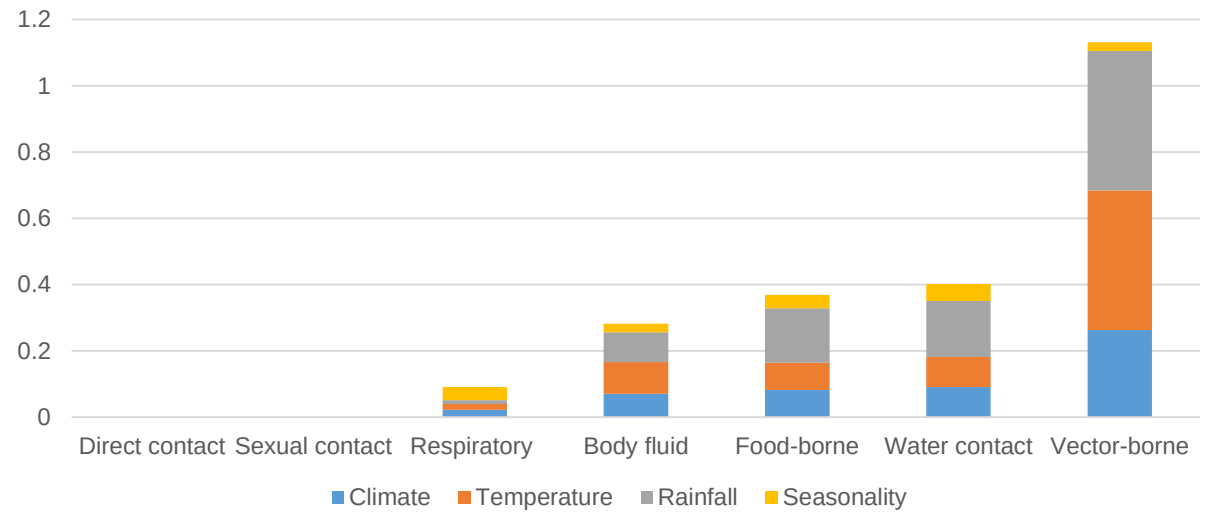

Figure D.24: Proportion of all theoretical transmission modes in the dataset which include environmental contextual factors linked to disease propagation, normalised according to S1N.

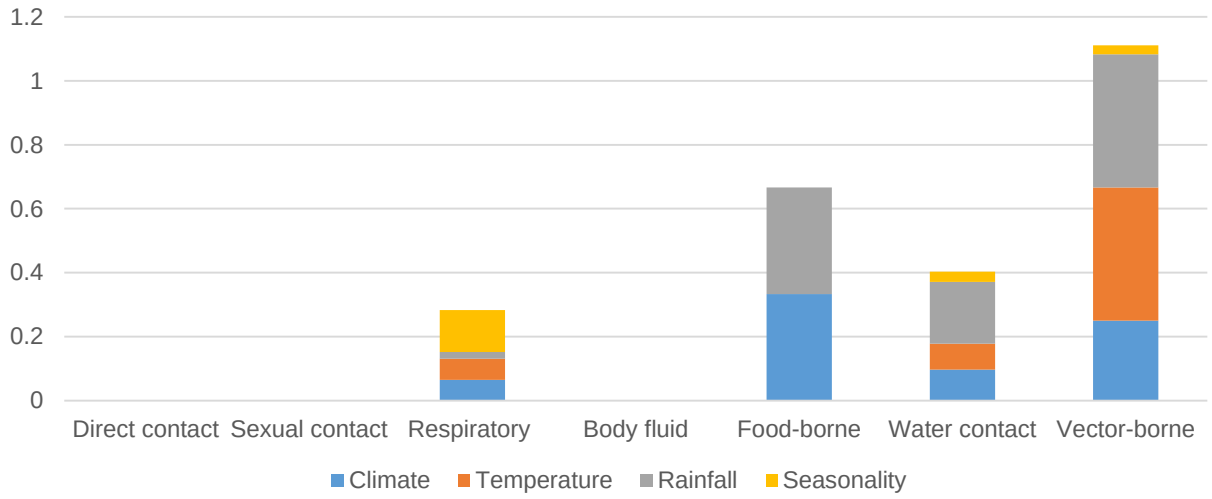

Figure D.25: Proportion of all mentioned transmission modes in the dataset which include environmental contextual factors linked to disease propagation, normalised according to S2N.

Incidentally, in both S1 and S2 the indirect transmission modes which relate to contact with environmental factors (i.e. food-borne, water contact and vector-borne) have the highest proportion of environmental factor inclusions. In contrast, most transmission modes which relate to interactions between humans (i.e. direct contact, sexual contact and body fluid) have little to no inclusions of environmental contextual factors.

Apart from these high-level observations, it is not possible to directly quantify the environmental contextual factor inclusions solely from the transmission mode, but it is still useful to note some of the relationships to the transmission modes. A selection of these observations are captured to Table 4.6 in REF B5.2.

Modelled factors

The proportion of literature pieces in the dataset which include modelled environmental contextual factors in relation to the transmission modes are illustrated in Figure D.26 (S1) and Figure D.27 (S2).

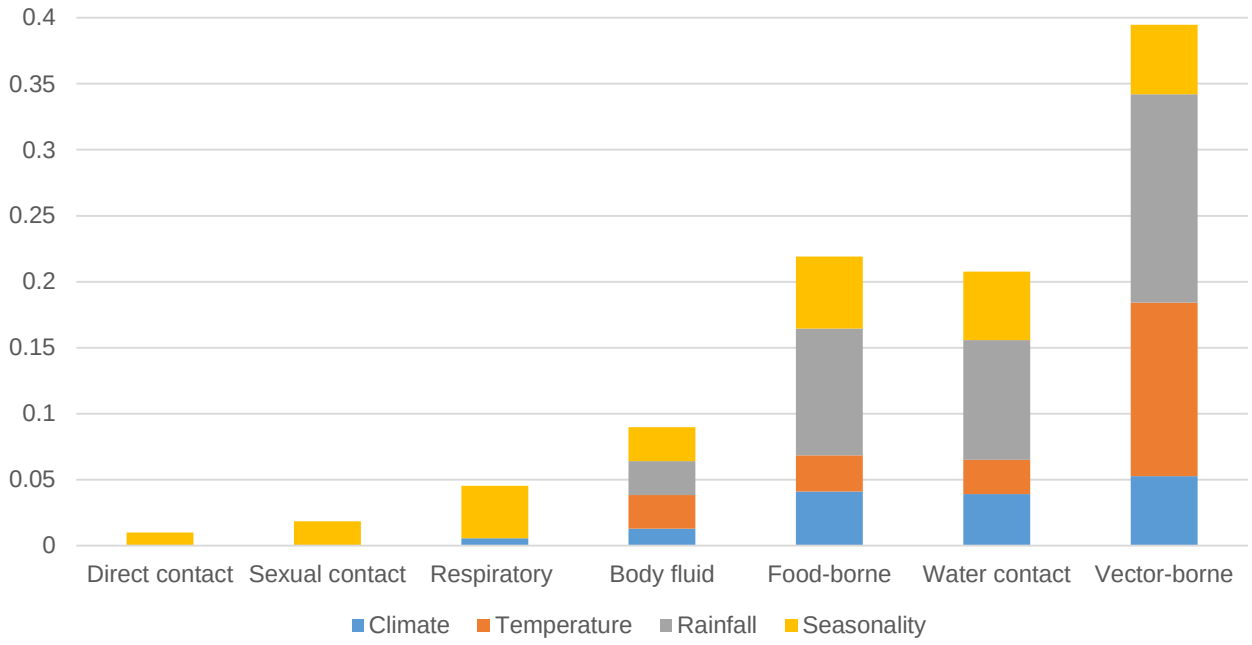

Figure D.26: Proportion of all theoretical transmission modes in the dataset which include modelled environmental contextual factors, normalised according to S1N.

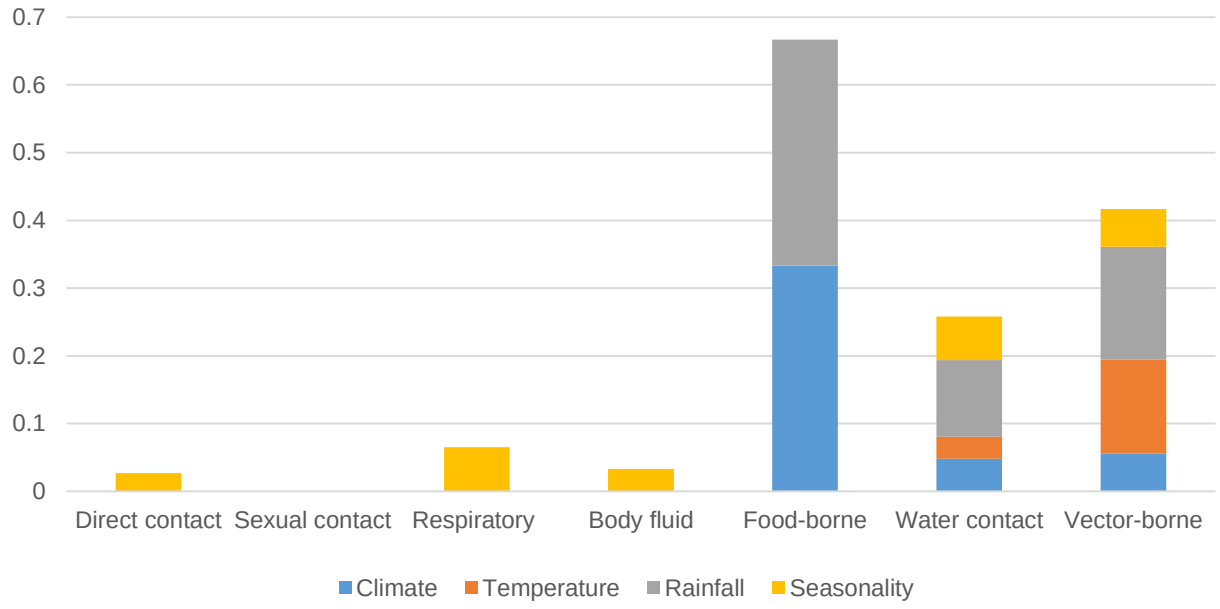

Figure D.27: Proportion of all mentioned transmission modes in the dataset which include modelled environmental contextual factors, normalised according to S2N.

In S1 it is observed that the food-borne, water contact and vector-borne transmission modes have the highest proportion of inclusion of all four environmental contextual factors within the modelling approach. It is observed in S2 that rainfall is especially important to the food-borne, water contact and vector-borne transmission modes and, in general, that modelling environmental contextual factors is especially important for the vector-borne transmission mode.

Similarly to the observation for environmental factors linked to disease propagation discussed previously in this section, in both S1 and S2 the indirect transmission modes which relate to contact with environment factors (i.e. food-borne, water contact and vector-borne) have the highest proportion of environmental factor inclusions. In contrast, for most transmission modes which relate to interactions between humans (i.e. direct contact, sexual contact and body fluid) seasonality is the only contextual factor which is modelled.

When comparing the proportions of contextual factors that are linked to the propagation of diseases (illustrated in Figure D.24 and Figure D.25) to the contextual factors that are modelled, but not necessarily linked to the propagation of the disease (illustrated in Figure D.26 and Figure D.27), it is interesting to note a higher occurrence of environmental contextual factors linked to disease propagation than modelled environmental contextual factors. This suggests the importance of linking disease propagation to environmental contextual factors in relation to the transmission mode.

Apart from these high-level observations, it is not possible to directly quantify the environmental contextual factor inclusions solely from the transmission mode, but it is still useful to note some of the relationships to the transmission modes. A selection of these observations are captured to Table 4.6 in REF B5.2.

D.16.2 Population demographic factors

The population demographic contextual factors linked to disease propagation and the modelled population demographic contextual factors are analysed in relation to the transmission modes below.

Linked to disease propagation factors

The proportion of literature pieces in the dataset which include population demographic factors linked to disease transmission in relation to the transmission modes are illustrated in Figure D.28 (S1) and Figure D.29 (S2).

In both S2 and S1 it is observed that spatial spread is a frequently included contextual factor within the modelling approaches of all transmission modes (apart from sexual contact and body fluid), in addition to population density, migration and age of the population. It is interesting to note the inclusion of socio-economic factors in many of the transmission modes of S2, in relation to vector-borne, water contact and especially food-borne (e.g. cholera) transmission modes.

Apart from these high-level observations, it is not possible to directly quantify the population demographic contextual factor inclusions solely from the transmission mode, but it is still useful to note some of the relations to the transmission modes. A selection of the observations are captured to Table 4.6 in REF B5.2.

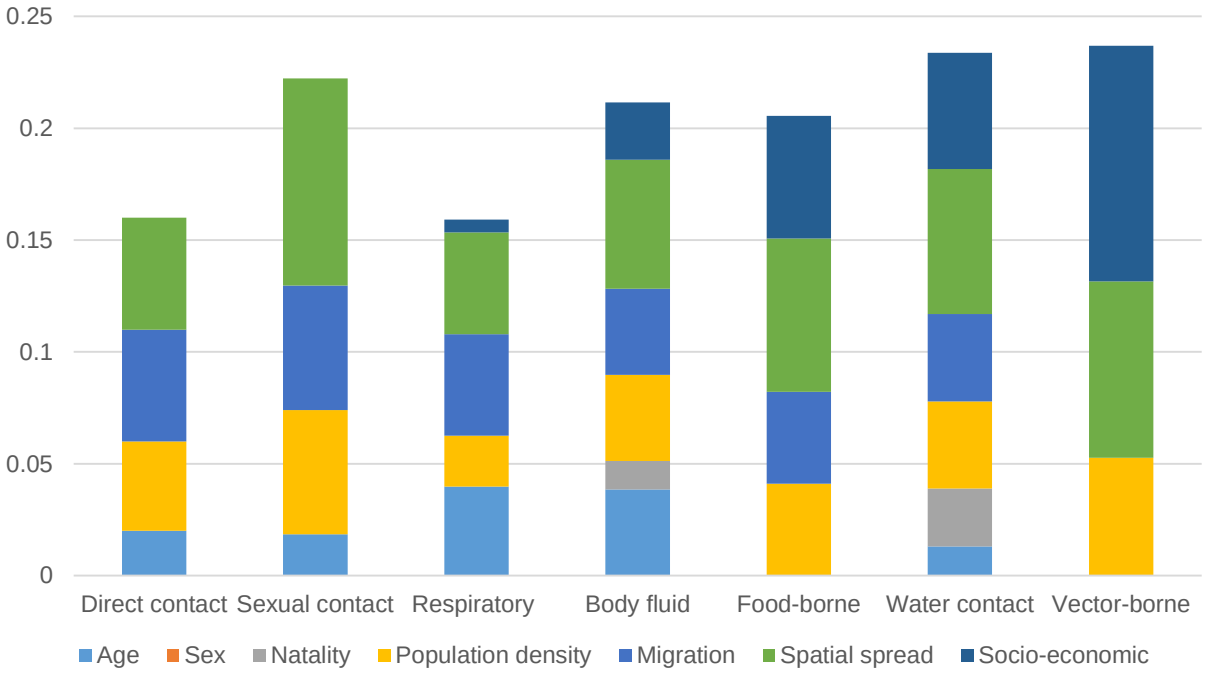

Figure D.28: Proportion of all theoretical transmission modes in the dataset which include population demographic contextual factors linked to disease propagation, normalised according to S1N.

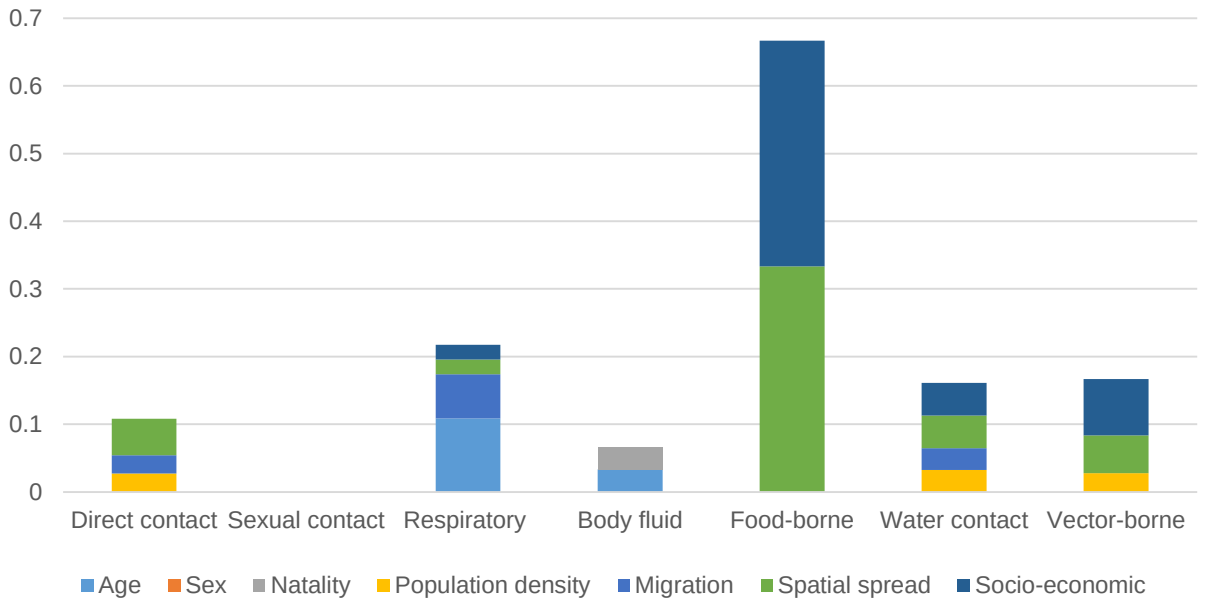

Figure D.29: Proportion of all mentioned transmission modes in the dataset which include population demographic contextual factors linked to disease propagation, normalised according to S2N.

Modelled factors

The proportion of literature pieces in the dataset which include modelled population demographic factors in relation to the transmission modes are illustrated in Figure D.30 (S1) and Figure D.31 (S2).

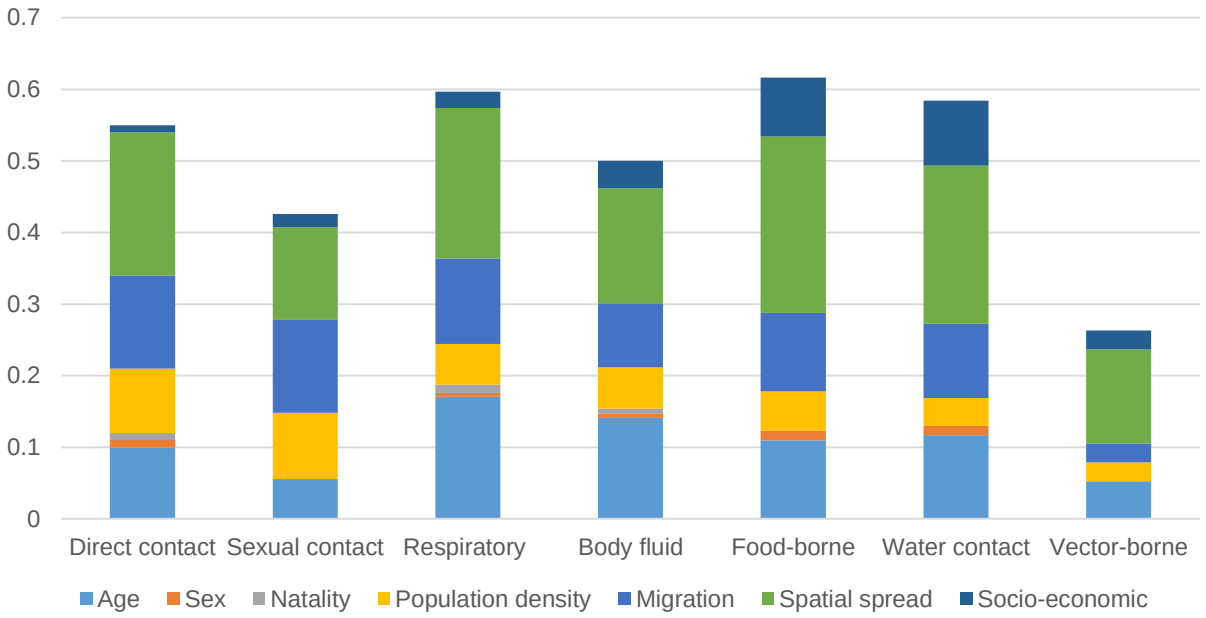

Figure D.30: Proportion of all theoretical transmission modes in the dataset which include modelled population demographic contextual factors, normalised according to S1N.

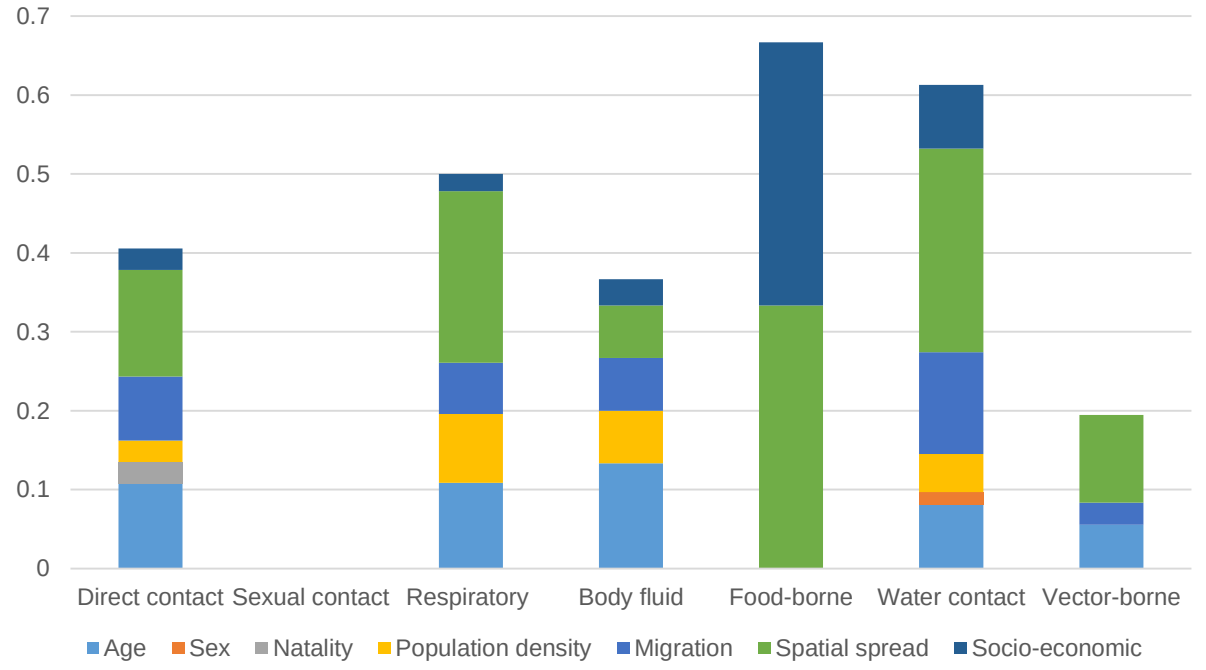

Figure D.31: Proportion of all mentioned transmission modes in the dataset which include modelled population demographic contextual factors, normalised according to S2N.

In both S2 and S1 it is observed that spatial spread is a frequently modelled contextual factor within the modelling approaches of all transmission modes (apart from sexual contact), in addition to population density, migration and age of the population. It is interesting to note the modelling of socio-economic factors in all transmission modes (apart from sexual contact and vector-borne), but a higher inclusion in relation to vector-borne, water contact and especially food-borne (e.g. cholera) transmission modes. Furthermore, when comparing S2 to S1, it is notable that direct contact, respiratory, body fluid and water contact have similarities in the diversity and proportion of modelled population demographic factors.

When comparing the proportions of contextual factors that are linked to disease propagation (illustrated in Figure D.28 and Figure D.29) to the contextual factors that are modelled, but not necessarily linked to the propagation of the disease (illustrated in Figure D.30 and Figure D.31), it is interesting to observe a higher occurrence of modelled population demographic factors than population demographic factors linked to disease propagation. This suggests the importance of modelling population demographic contextual factors in relation to the transmission mode.

Apart from these high-level observations, it is not possible to directly quantify the population demographic contextual factor inclusions solely from the transmission mode, but it is still useful to note some of the relations to the transmission modes. A selection of these observations are captured to Table 4.6 in REF B5.2.

D.17 Alternative mixing patterns in the context of modelling considerations

As analysed in §D.12 - §D.16 the transmission mode is a key characteristic potentially affecting the selection of modelling approaches and considerations. In the context of alternative mixing pattern selection, the transmission mode may also play a role in influencing the selection, as analysed in §D.17.1. It is of further interest to analyse the occurrence of alternative mixing pattern selections in the context of population demographic contextual factors (§D.17.2); modelling approaches (§D.17.3) and modelling rationales (§D.17.4).

D.17.1 Transmission modes

The proportion of literature pieces in the dataset which include alternative mixing patterns in the context of the transmission modes are illustrated in Figure D.32 (S1) and Figure D.33 (S2), namely for all theoretical transmission modes and for explicitly mentioned transmission modes, respectively.

In S2 it is noted that alternative mixing patterns are most often applied in the context of the first four transmission modes (apart from sexual contact). This makes sense, as direct or indirect contact between humans are required to facilitate transmission within these categories, potentially explaining the high occurrence of the incorporation of alternative mixing patterns. Furthermore, in S1 similar mixing patterns are observed for the first four transmission modes.

In S1 it is observed that age stratification of humans was the most prevalent manner in defining alternative mixing patterns in the dataset, followed by social mixing, especially for the first four transmission modes (once again without sexual contact). The theoretical transmission modes of cholera are both water contact and food-borne, which potentially explains the similar mixing pattern observation in S1. The absence of observations for the food-borne transmission mode in S2 is most likely due to this transmission mode often not being explicitly mentioned during modelling of a the disease. A selection of these observations are captured to Table 4.6 in REF B2.3.

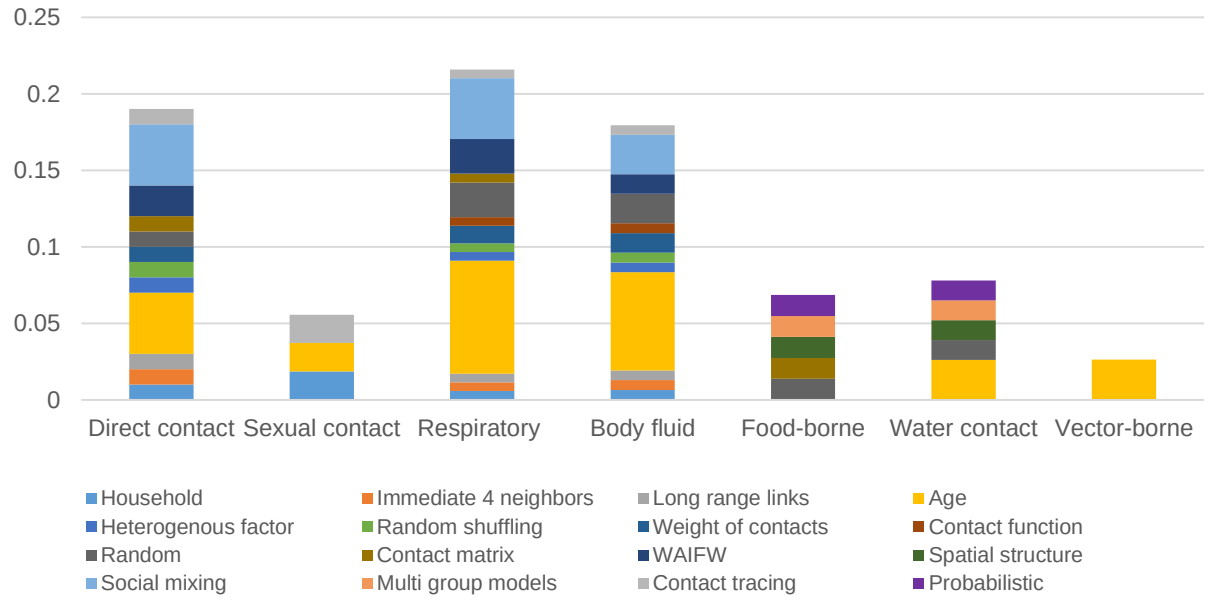

Figure D.32: Proportion of all theoretical transmission modes in the dataset which include alternative mixing patterns normalised according to S1N.

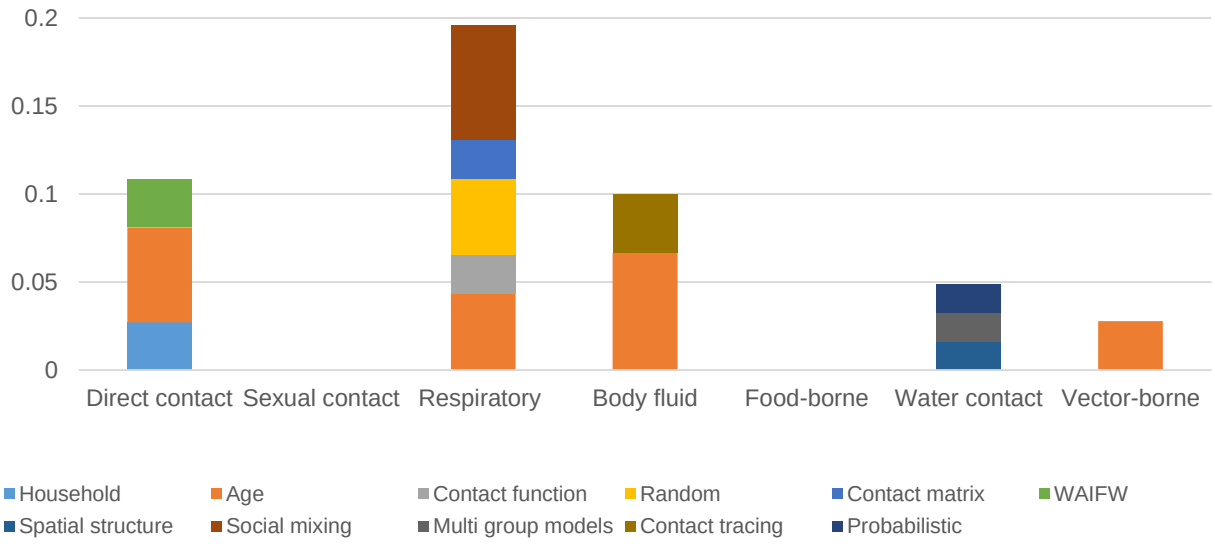

Figure D.33: Proportion of all mentioned transmission modes in the dataset which include alternative mixing patterns normalised according to S2N.

D.17.2 Population demographic factors

Although the disease transmission mode potentially influences the selection of alternative mixing patterns, other factors most likely also play a role in the incorporation and selection of alternative mixing patterns. As the population demographics describe the stratification and structure of a population, it would make sense to investigate a possible relationship between the incorporation of alternative mixing patterns and the incorporation of population demographics in a modelling application, as illustrated in Figure D.34.

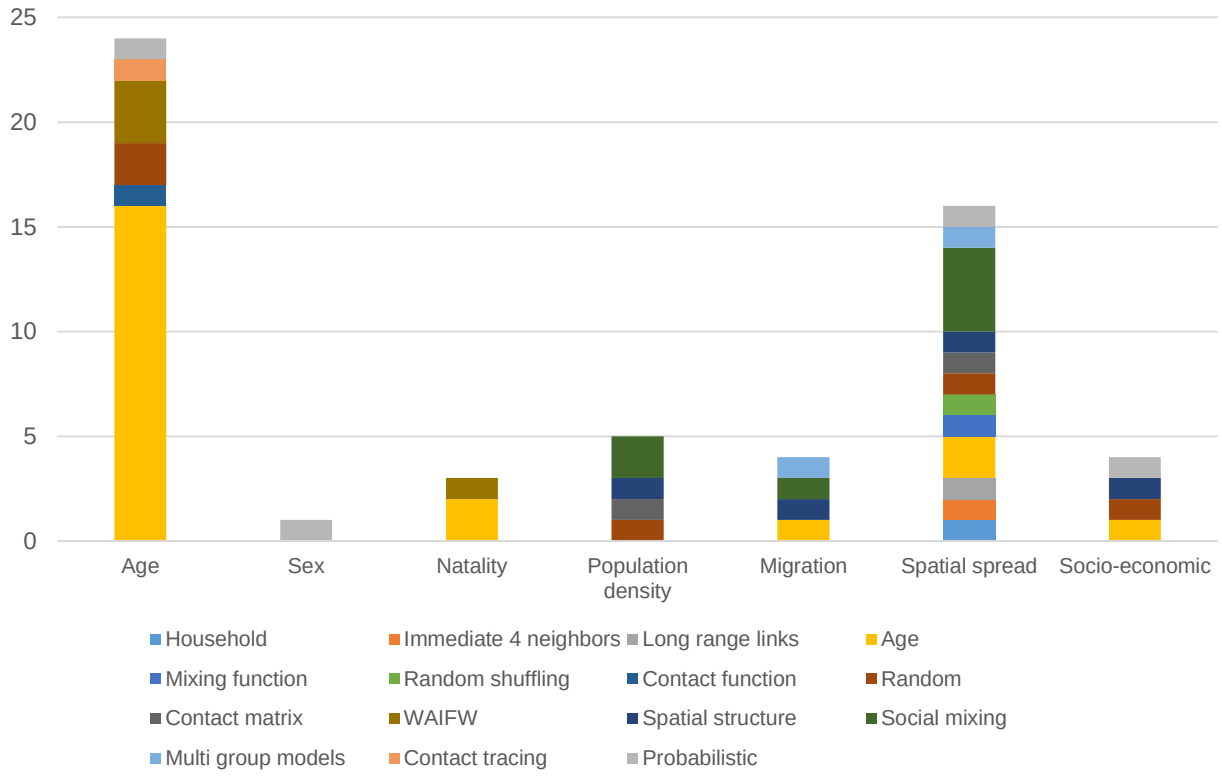

Figure D.34: Number of alternative mixing patterns included in modelling instances when different population demographic contextual factors are also included.

It is observed that the highest occurrence of alternative mixing patterns is present when the age and spatial spread population demographic factors are taken into account during modelling. This observation is as expected. Furthermore, the most diverse number of alternative mixing patterns are applied to instances which included the spatial spread demographic factor in the modelling approach. This is an important observation, as it implies that incorporation of spatial spread in a modelling study requires consideration of non-standard mixing patterns. There is also indication in the diversity of the alternative mixing patterns in the context of population density and migration factors that, even though few of these instances are observed, these contextual factors may play a role in the selection of alternative mixing patterns. This is included in the observations as it is logical to assume that population density and migration sensitively affect the distribution of people within a population and in turn affect the manner in which individuals in the population interact with one another.

The potential relationship between environmental contextual factors and mixing patterns are not analysed in the same rigorous manner as the population demographic contextual factors, as there is no logical argument to support a relationship between mixing patterns and factors such as climate or seasonality (i.e. environmental contextual factors). A selection of these observations are captured to Table 4.9 in REF C1.1.

D.17.3 Modelling approaches

Another consideration is whether there are any modelling approaches which are used more frequently to incorporate alternative mixing patterns, therefore the application of alternative mixing patterns is analysed in the context of three modelling approaches as illustrated in Figure D.35.

Age and social mixing are not only the only alternative mixing patterns that are applied in the context of all three modelling approach categories, but are also the alternative mixing patterns with the highest total occurrence in the dataset. Additionally, WAIFW is considered as a type of age or social mixing depending on the specific context, as it is typically a matrix which determine the probability of transmission between different age or social contacts.

A final observation from Figure D.35 is that there are a number of specific alternative mixing patterns that appear to always be modelled using the same approach, for example, all instances of models that incorporate contract tracing or probabilistic mixing patterns are modelled using simulation approaches. However, this example, and all similar observations, are based on an extremely small number of incidences and are therefore not included in the summarised observations presented in Table 4.8, REF C1.2, used to construct the framework presented in Chapter 5.

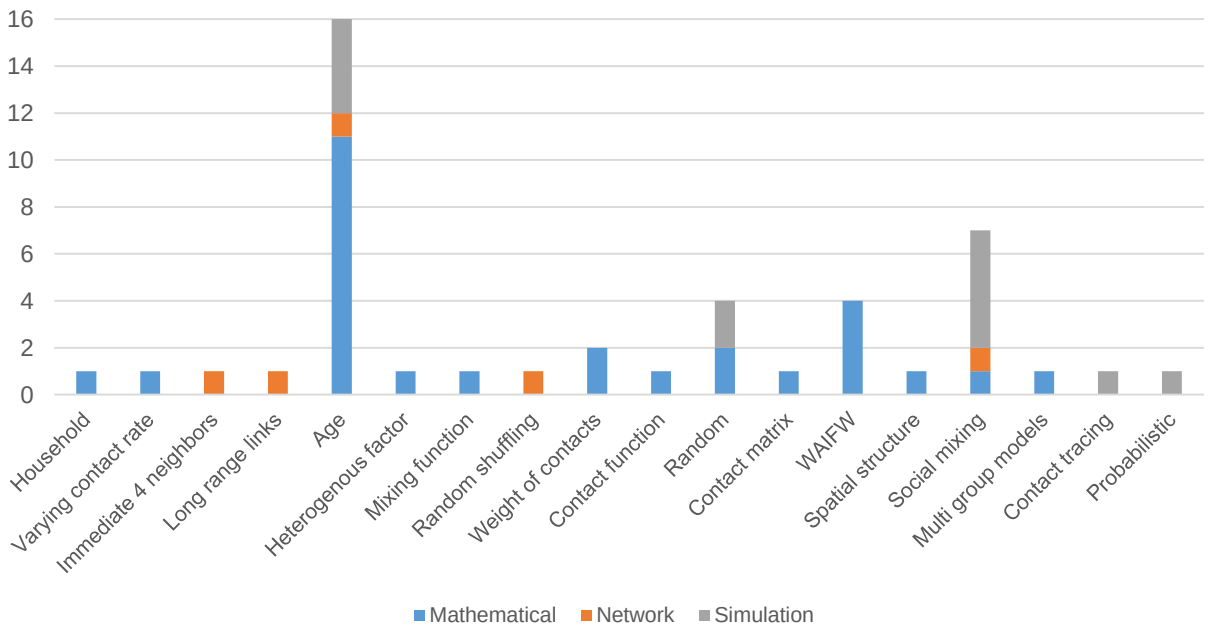

Figure D.35: Number of alternative mixing patterns included in the three modelling approach categories.

D.17.4 Modelling rationales

It is of interest to analyse the proportion of modelling rationales which incorporates alternative mixing patterns, as illustrated in Figure D.36. The three modelling rationales which have the highest inclusion of mixing patterns other than the typical homogenous mixing are the following:

- Modelling disease transmission dynamics;
- Forecast disease instance; and
- Testing interventions.[40]

From Figure D.36, it is clear that there are no modelling rationales which clearly incorporate alternative mixing patterns more than any other modelling rationales. Furthermore, as previously mentioned in §C.3.6, alternative mixing patterns were included only in 41 literature pieces of the dataset. Based on these limited observations, it is not possible to generalise alternative mixing inclusions based solely on the selection of the modelling rationale, however, the highest number of alternative mixing patterns were observed for the 'model disease transmission dynamics' and 'test interventions' rationales. A selection of these observations are captured to Table 4.10 in REF C1.3.

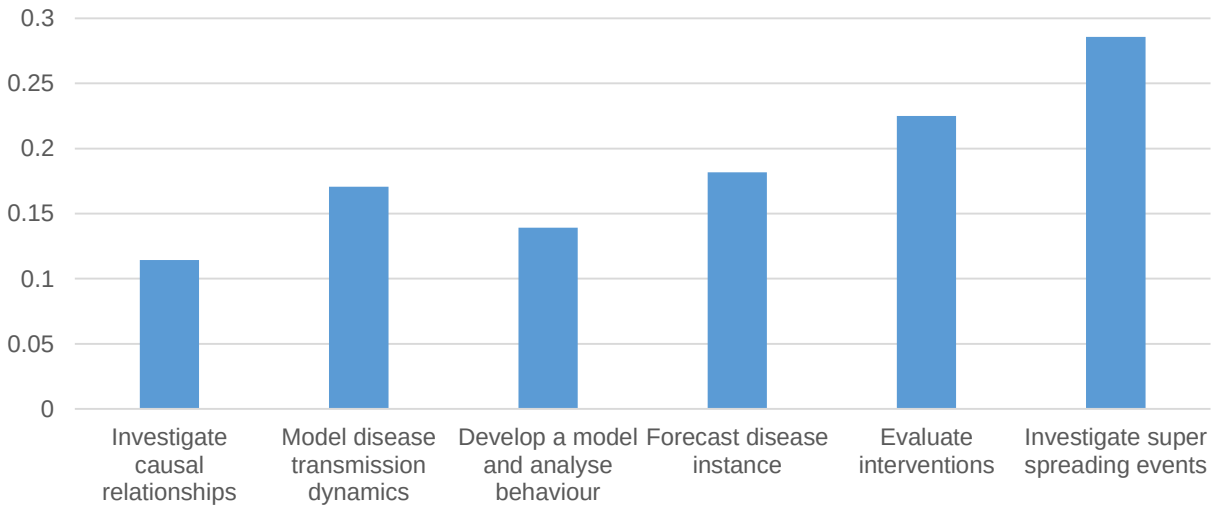

Figure D.36: The proportion of literature pieces for each modelling rationale which incorporates alternative mixing patterns in the modelling approach, normalised according to S5N.

D.18 Modelling considerations in the context of data sources

The data source forms an integral part in a modelling approach, as it determines what data is available to verify and initialise a modelling approach. Within this section, the relationships between the data sources and some of the modelling considerations and approaches are investigated. The

[40] From S5 (a minor subset containing the number of alternative mixing pattern inclusions for each modelling rationale), the investigation of super spreading events also appears to typically include alternative mixing patterns, but this observation is based on only two instances in the dataset.

modelling approach occurrence in the context of different data sources is illustrated and discussed in §D.18.1. Intervention strategies in the context of different data sources is investigated in §D.18.2 which is followed with an investigation of contextual factors in §D.18.3. A discussion on the observed methods used to fit the data source to a model is included in §D.18.4.

D.18.1 Modelling approaches

The proportion of the three modelling approach categories applied in the context of different data sources are illustrated in Figure D.37. In general, a similar pattern of occurrence is observed for all three modelling approach categories, with case data being the most common data source and travel data and population estimates being the least common data sources across all three modelling approach categories. There are, however, some modelling approaches with a marginally higher proportion of observed applications for a selection of the data sources. Of the three modelling approaches, it is observed that mathematical approaches are applied the most frequently in the context of the 'parameters from literature' data source. Network approaches are applied the most frequently when working with assumed data and simulation approaches are applied the most frequently when working with no data source, population estimates and case data. A selection of these observations are captured to Table 4.8 in REF C2.3.

From this analysis it is deduced that all three modelling approach categories are suitable for application in the context of all types of data sources, even though a marginally higher occurrence of some modelling approach categories are observed for certain data sources.

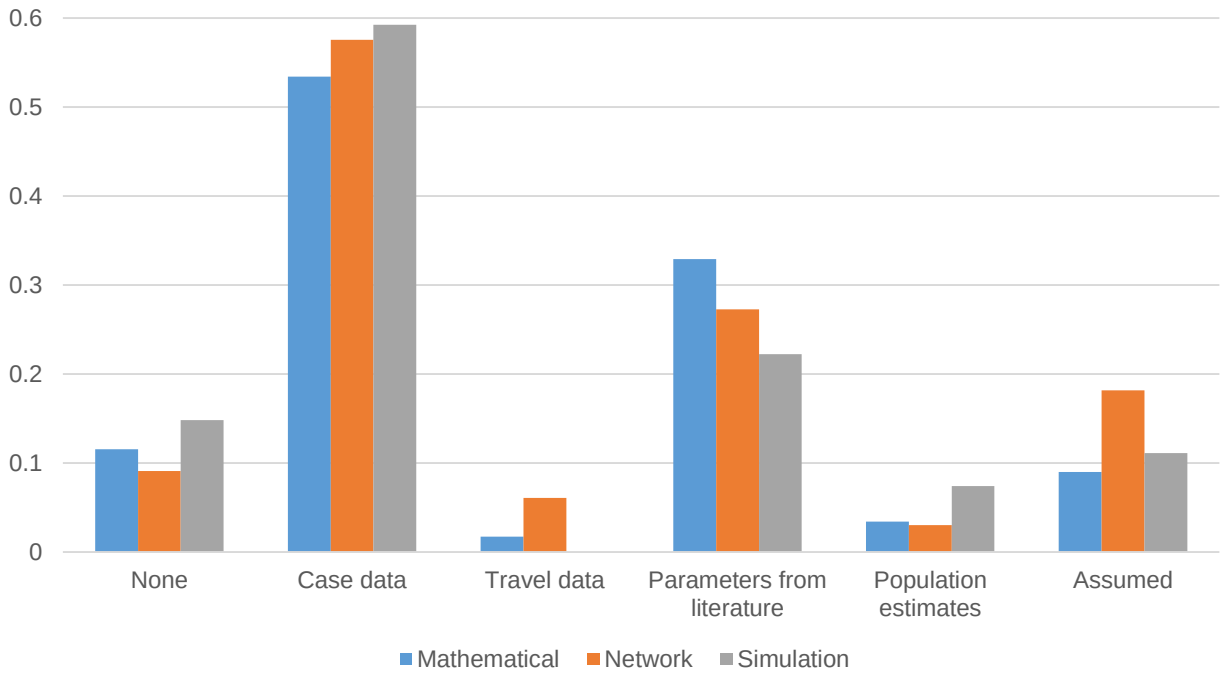

Figure D.37: Proportion of the three modelling approach categories applied in the context of different data sources, normalised according to S3N.

D.18.2 Intervention strategies

The proportion of treatment and vaccination intervention strategies applied in the context of different data sources are illustrated in Figure D.38. The normalisation of the subset (S8) is completed according to the total number of literature pieces where treatment or vaccination intervention strategies are incorporated (S8N). A similar number of proportions for both intervention strategies are observed for the different data source categories. However, a marginally higher number of treatment strategies are observed in the context of the 'case data' and the 'parameters from literature' data source, in contrast to a marginally higher number of vaccination strategies observed in the context of the 'population estimates' data source and no data source. From this observation it is deduced that it is possible to incorporate both categories of intervention strategies in the context of different data sources.

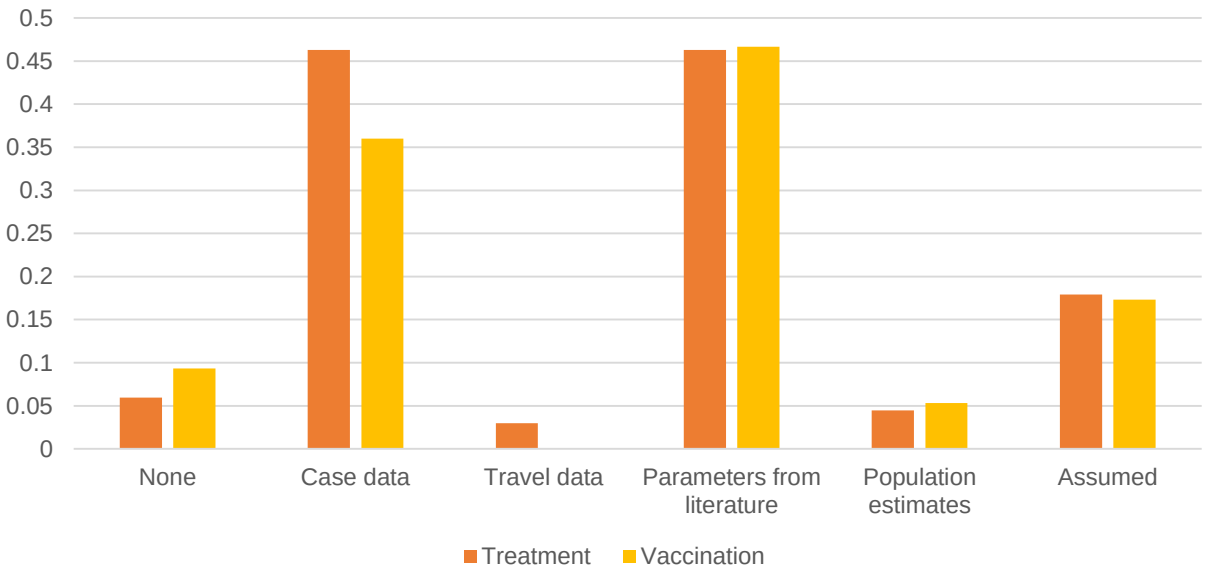

Figure D.38: Number of the two intervention strategies applied in the context of different data sources, normalised according to S8N.

D.18.3 Contextual factors

The proportion of contextual factors included in the context of different data sources are illustrated in Figure D.39. The normalisation of the subset (S9) is completed according to the total number of literature pieces in which contextual factors are either linked to disease propagation or modelled (S9N). The motivation for this alternative normalisation is to highlight the proportions of the contextual factors included in the context of different data sources.

It is clear that case data is used the most frequently to model contextual factors and investigate the effect on disease propagation. Parameters from literature are also used frequently to model population demographics and environmental contextual factors. Although the observation is based on a small number of incidences, it is interesting to note that travel data and population estimates

are used only in the context of population demographic factors. Furthermore, population demographics is also modelled in the context of all the data sources in Figure D.39. A selection of these observations are captured to Table 4.9 in REF C2.4.

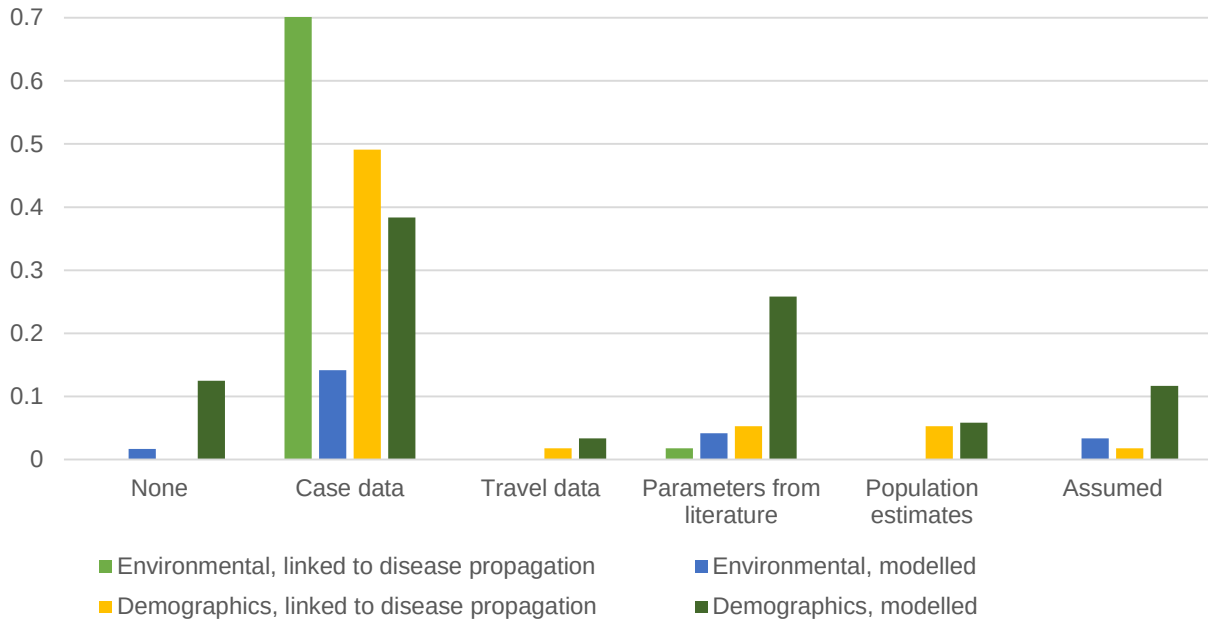

Figure D.39: Proportion of contextual factors included in the context of different data sources, normalised according to S9N.

D.18.4 Method of model fit

The use of fitting methods in the context of different data sources is illustrated in Figure D.40. It is observed that the most diverse set of fitting methods are applied in the context of case data, followed by the 'parameters from the literature' data source. Additionally, it is observed that the visual fit of the data is the most prevalent fitting method utilised within the dataset (the visual fit category includes all articles which state that the data was fit to the model or that the data fits the model well, without specifying the explicit method used to ensure or evaluate this fit).

With reference to the 56 fitting methods illustrated in Figure D.40, 33 methods were applied only within a single modelling instance. It is therefore deduced that the selection of a fitting method is highly dependent on a combination of additional factors apart from the data source, e.g. the modelling approach. The importance of the method utilised to fit a model to the data is not reduced with this assumption, however, it is deemed impractical to attempt to establish a relationship between each individual fitting method and the data source category, in addition to attempting to establish a relationship between each fitting method and a particular modelling approach category. It is therefore assumed that generalisation of fitting methods is not possible with further meta-analysis of the available data in the dataset.

Figure D.40: Number of different fitting methods applied in the context of different data sources.

D.19 Modelling considerations in the context of modelling scopes

It is of interest to determine relationships of various modelling considerations to the modelling scope. To this end, the data source usage in the context of the modelling scopes are investigated in §D.19.1, which is followed by an investigation of the modelling scopes in relation to the modelling rationales in §D.19.2. The incorporation of alternative mixing patterns in relation to the data sources are investigated in §D.19.3.

D.19.1 Data sources

The proportion of modelling scopes applied in the context of different data sources are illustrated in Figure D.41. The normalisation of the subset (S6) is completed according to the total number of instances of each data source category (S6N) to highlight the proportions of the data sources included in the context of different modelling scopes.

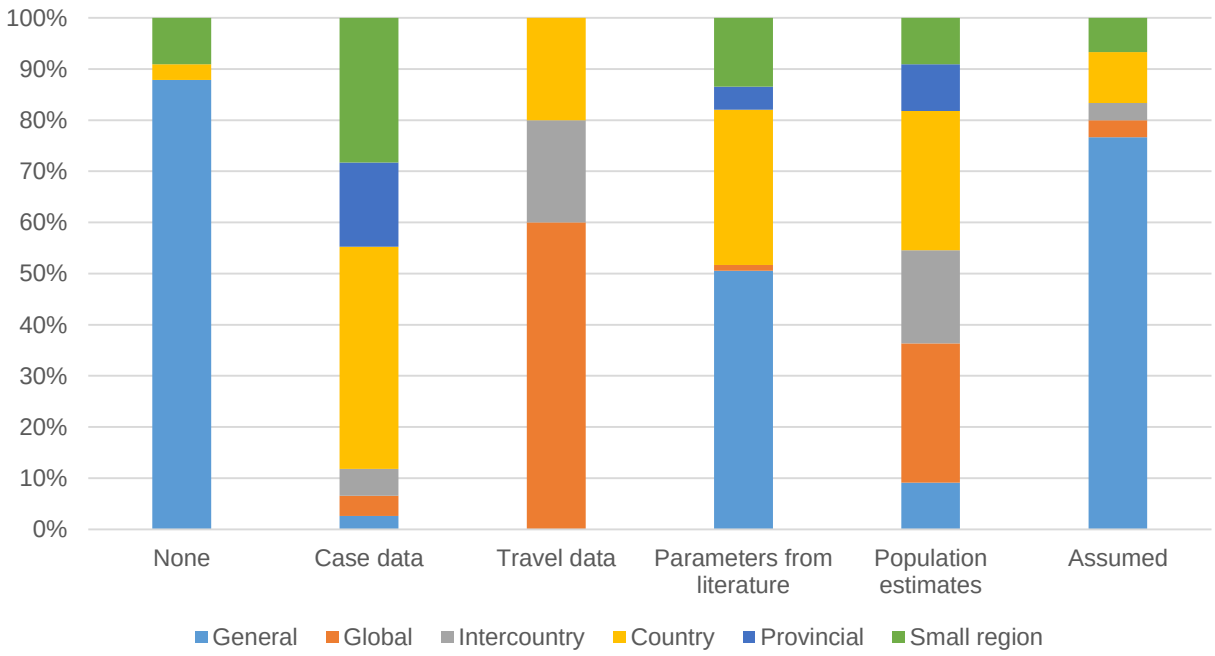

Figure D.41: Proportion of models to which various modelling scopes have been applied, for each data source, normalised according to S6N.

It is observed that when no data source or an assumed data source was used in the modelling application (e.g. for theoretical models without a real-life application) that a general modelling scope was adopted the most frequently (88% and 77%, respectively). Travel data is applied exclusively within the global, intercountry and country modelling scope. Case data (the most frequently occurring data source in the dataset) is used the most frequently in a country, small region and provincial modelling scope. Parameters from literature are used the most frequently in a general modelling

scope, but also in a country and a small region modelling scope. Population estimates are used the most often in a global and country modelling scope, in addition to an intercountry modelling scope.

With respect to the modelling scope, it is observed that the country modelling scope is the only modelling scope applied in the context of all types of data sources. Furthermore, it is observed that case data and population estimates are used in the context of all modelling scopes.

Although it is not possible to directly quantify modelling scope based solely on the data source selection, the observations on some of the observed relationships are captured to Table 4.7 in REF C7.1.

D.19.2 Modelling rationales

The proportion of modelling scopes applied in the context of different modelling rationales are illustrated in Figure D.42. The normalisation of the subset (S5) is completed according to the total number of instances for each modelling rationale category (S5N) to highlight the proportions of the modelling rationales incorporated in the context of different modelling scopes.

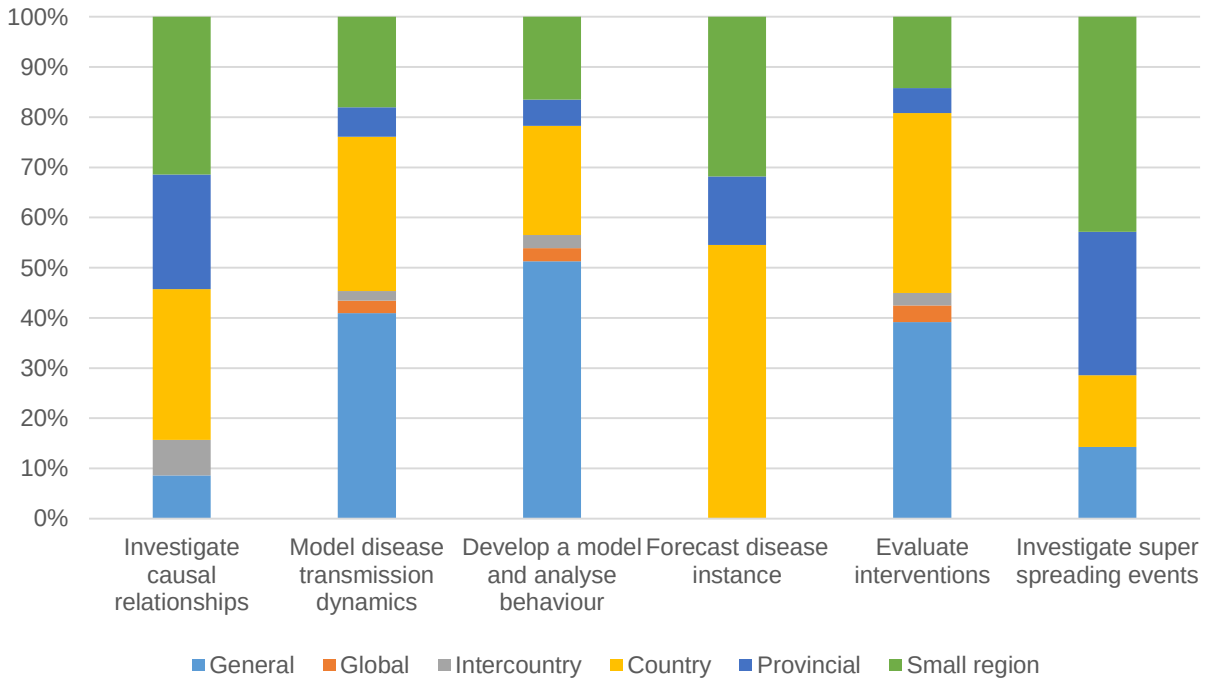

Figure D.42: Proportion of models to which various modelling scopes have been applied, for each modelling rational, normalised according to S5N.

The two most frequently applied scopes used when investigating causal relationships are the small region and country modelling scope. The ‘model disease transmission dynamics’, ‘develop a model and analyse behaviour’ and ‘test interventions’ modelling rationales all had a general modelling scope as the most frequently applied modelling scope, followed by a country scope and a small region modelling scope. The ‘forecast disease instance’ rationale is only used in a country scope,

followed by a small region scope. It is interesting to see that the 'test interventions' rationale is applied the most frequently in a general scope, followed by a country and a small region scope. The 'investigation of super spreading events' rationale is applied the most often in a small region modelling context, followed by a provincial scope modelling context. From this analysis it is observed that some modelling scopes are used more frequently in the context of some modelling rationales. A selection of these observations are captured to Table 4.10 in REF C7.2.

D.19.3 Alternative mixing patterns

The proportion of modelling scope instances in which alternative mixing patterns are used are illustrated in Figure D.43. The normalisation of the subset (S7) is completed according to the total number of instances in each modelling scope category (S7N) to highlight the proportion of the modelling scope instances which include alternative mixing patterns.

It is observed that mixing patterns are used the most frequently in the context of a small region modelling scope (13 observations), followed by a country scope and a general scope (12 observations).[41] From the limited number of observations, it is not possible to directly relate the inclusion of alternative mixing patterns based solely on the modelling scope, however, a selection of these observations are captured to Table 4.7 in REF C7.3.

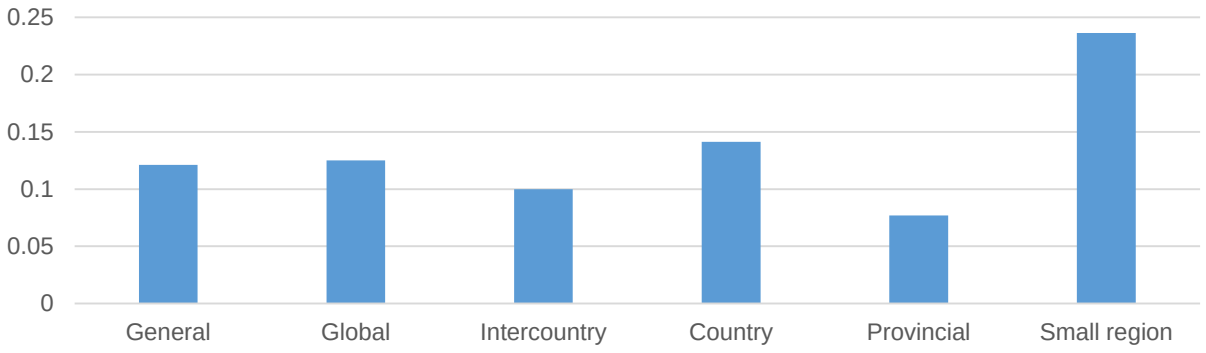

Figure D.43: Proportion of modelling scope instances in which alternative mixing patterns are used, normalised according to S7N.

D.20 Compartmental classification in the context of modelling considerations

Compartmental classification within modelling approaches is a useful manner to capture the dynamics of the chain of infection mathematically. In this section the nature of compartmental classification inclusions and the selection of this approach in relation to modelling considerations are

[41] The global and intercountry scope observations are based on a single instance, furthermore the provincial scope observation is based on two instances.

analysed. The inclusion of compartmental classification in the context of three modelling approaches is discussed in §D.20.1. The detailed selection of compartments in the context of different transmission modes and interventions strategies is discussed in §D.20.2 and §D.20.3, respectively.

D.20.1 Modelling approaches

The proportion of modelling approaches which incorporate compartmental classification are illustrated in Figure D.44. It is observed that the modelling approaches which are most frequently used when compartmental classification is employed are mathematical approaches, followed by network and simulation approaches. This relatively high inclusion of compartmental classification in all three modelling approaches implies that it is possible to incorporate compartmental classification in the context of different modelling approaches, however, the highest occurrence of compartmental classification are observed within the context of mathematical modelling approaches.

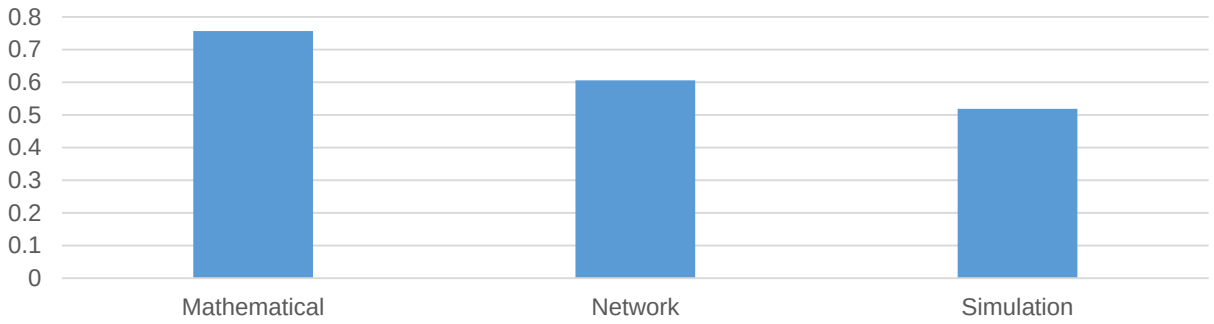

Figure D.44: Proportion of three modelling approach categories which include compartmental classification, normalised according to S3N.

D.20.2 Transmission mode

The proportion of literature pieces in the dataset which include different compartmental classification categories for each of the transmission modes are illustrated in Figure D.45 (S1**) and Figure D.46 (S2**), namely for all theoretical transmission modes and for explicitly mentioned transmission modes, respectively.[42] If a compartmental classification was not used in at least 10% of the modelling instances for at least one transmission mode in S1, such a compartmental classification was not considered for additional analysis. This reduced the number of compartments from 23 (total number of different compartments in the dataset) to 13. Various compartmental categories are defined in the nomenclature (p.xxxiv) and for the sake of brevity, these definitions are not repeated here.

When considering S2**, the following is observed:

[42] S1** is constructed as a subset of S1, which only includes literature pieces from S1 that incorporates compartmental classification. S2** is constructed similarly from S2. S1**N is calculated as the total theoretical transmission modes in S1** and S2**N is calculated as the total mentioned transmission modes within S2**.

- E (exposed): this compartmental classification category is the most frequently used in the context of diseases that are transmitted via direct contact, respiratory and body fluid contact. To a lesser extent, this category is used when modelling diseases that are transmitted via vector-borne methods. The incidence of diseases that are transmitted via sexual contact or that are food-borne in the dataset is insufficient to make any observations on these transmission modes;
- F (burial): this compartmental classification is observed only in the context of direct contact and body fluid transmission modes (most likely due to the Ebola disease outbreaks);
- V (vaccination): as expected, this compartmental classification category is observed for all diseases transmission modes, apart from food-borne and vector-borne disease;
- Q (quarantine): in line with expectations, this compartmental classification category is observed only in the context of direct contact, respiratory and body fluid transmission modes;
- B (bacteria) and W (water): these compartmental classification categories are observed the most frequently in the context of water contact diseases. (The presence of the bacteria category for food-borne diseases is in line with what one would logically expect but this observation is based on only a small number of instances in the dataset.); and
- M (mosquitoes): as expected, this compartmental classification category is observed only in the context of vector-borne diseases and a very small proportion of diseases that are transmitted via body fluid;

With this analysis, it is not possible to generalise the compartmental classification solely from the transmission mode, but it is still useful to note some of the relationships to the transmission modes. A selection of these observations are captured to Table 4.6 in REF B6.

D.20.3 Intervention strategies

The data used in the analysis of compartmental classification in the context of treatment strategies are reproduced in Table D.18. An expected relationship between the quarantine and isolation intervention strategy and the Q (quarantine) compartmental classification is observed. An additional expected relationship between the safe burial strategy and F compartmental classification exists, in addition to the contact tracing strategy and the CT (contact tracing) compartmental classification. Apart from these observations, it is not possible to conclusively confirm any additional relationships between compartmental classification and treatment strategy inclusion.

Similarly, the data used in the analysis of compartmental classification in the context of vaccination strategies are reproduced in Table D.19. An expected relationship is the inclusion of the V (vaccination) compartmental classification in most of the modelling approaches which include compartmental classification. Apart from this observation, it is not possible to conclusively confirm any additional relationships between compartmental classification and vaccination strategy inclusion.

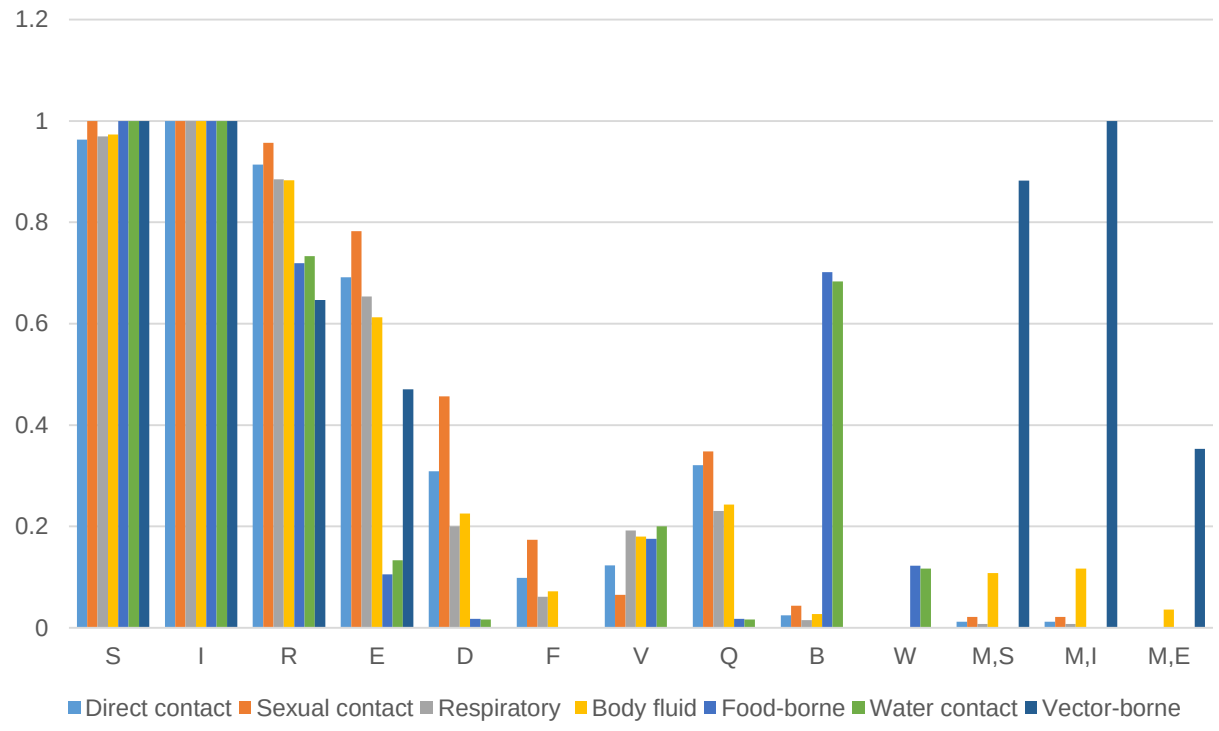

*Figure D.45: Proportion of all theoretical transmission modes in the dataset which incorporate different compartmental categories, normalised according to S1**N.*

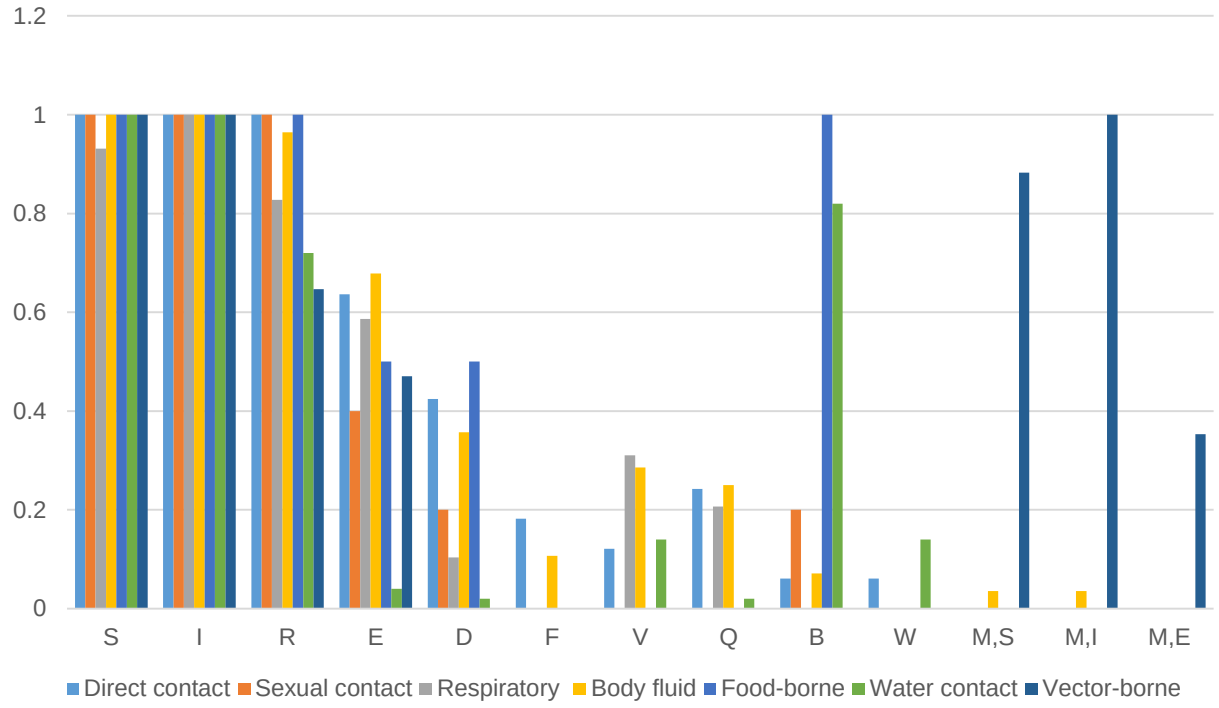

*Figure D.46: Proportion of all mentioned transmission modes in the dataset which incorporate different compartmental categories, normalised according to S2**N.*

Table D.18: Number of compartmental category inclusions for various treatment strategies.

Strategy	**S**	**I**	**R**	**E**	**D**	**F**	**V**	**Q**	**J**	**CT**	**M**	**A**	**T**	**B**	**W**	**M,S**	**M,I**	**M,E**
Contact tracing	3	4	3	4	1	0	2	4	0	1	0	0	0	0	0	0	0	0
Quarantine / Isolation	23	25	23	19	9	0	5	16	2	1	1	0	0	1	0	1	1	0
Hospitalisation	14	14	14	12	7	5	1	10	0	0	0	0	0	0	0	0	0	0
Drug / Pharmaceutical	5	5	5	5	0	0	1	1	0	0	0	2	1	1	0	0	1	0
Safe burial	6	6	6	5	5	3	1	6	0	0	0	0	0	0	0	0	0	0
Reduce contact	4	4	4	2	1	1	1	0	0	0	0	0	0	2	0	0	0	0
Reduce contact	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Disinfection / sanitation	12	12	12	1	0	0	4	0	0	0	0	1	1	10	1	0	0	0
General	8	8	8	4	0	0	2	1	0	0	0	0	3	4	0	0	0	0
Treatment kits	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
School closure	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Education	4	4	4	2	1	0	2	1	0	0	0	0	0	2	0	0	0	0

Table D.19: Number of compartmental category inclusions for various vaccination strategies.

Strategy	**S**	**I**	**R**	**E**	**D**	**V**	**Q**	**CT**	**M**	**A**	**T**	**W**	**B**	**W**	**M,S**	**M,I**
Ring	1	3	1	2	0	1	2	0	0	0	0	0	0	0	0	0
Target	1	1	1	1	0	0	0	0	0	1	0	0	0	0	0	0
Mass	2	3	2	2	0	2	2	1	0	0	0	0	0	0	0	0
Prophylactic	7	7	7	3	0	3	0	0	1	1	0	1	0	0	0	0
Exposure	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Booster	4	4	3	1	0	3	0	0	1	2	0	0	0	0	0	0
Pulse	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Age	1	1	1	1	0	1	0	0	0	1	0	0	0	0	0	0
Maternal	2	2	2	0	0	1	0	0	2	0	0	0	0	0	0	0
Proportion susceptible	40	40	35	17	2	21	5	0	3	3	2	0	14	2	1	1
Vaccination rate	6	6	5	3	0	2	0	0	0	0	0	0	0	0	0	0
Rates	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0
Coverage	6	6	6	4	0	3	1	0	4	0	0	0	0	0	0	0
Cost & age	1	1	0	0	0	1	0	0	1	0	0	0	0	0	0	0

D.21 Modelling approaches in the context of modelling considerations

The relationships between the modelling approaches and the disease transmission modes were previously discussed (in §D.12). Within this section, however, the modelling approach occurrences are analysed in the context of other modelling considerations, namely in the context of different modelling rationales in §D.21.1, modelling scopes in §D.21.2 and the intervention strategy inclusions in §D.21.3.

D.21.1 Modelling rationales

The proportion of the three modelling approach categories applied in the context of different modelling rationales are illustrated in Figure D.47. The proportions of mathematical, network and simulation modelling approaches that are applied in the context of the different modelling rationales are not vastly dissimilar. There are, however, some modelling approaches with a higher proportion of observed applications for a selection of the rationales, which are discussed below.

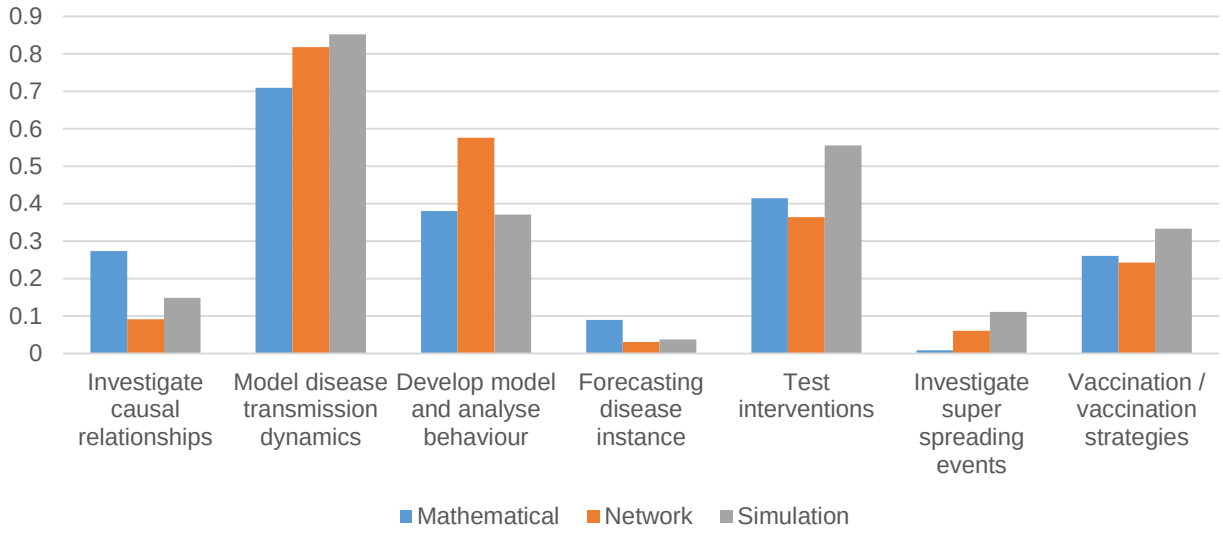

Figure D.47: Proportion of three modelling approach categories within the context of different modelling rationales, normalised according to S3N.

It is observed that a larger proportion of mathematical approaches are used than the other modelling approaches when investigating causal relationships between contextual factors and disease propagation. This is potentially explained by the high occurrence of retrospective analysis on disease prevalence and the contextual factors which influence disease propagation that typically utilise mathematical approaches such as regression analysis.

It is observed that when the rationale is to develop a theoretical model with a view to analyse the model behaviour, a larger proportion of network approaches are utilised than the other modelling

approaches. This suggests that network models may have characteristics which make these a suitable approach to construct a more complex theoretical model of disease transmission.

It is observed that a larger proportion of simulation approaches are utilised than the other modelling approaches when the modelling rationale is to test intervention strategies, investigate super spreading events and incorporate vaccination strategies. This observation suggests the suitability of a well-constructed simulation model to test the effect of interventions and instances of rapid disease transmission.

From this analysis it is deduced that all three modelling categories are suitable for application in the context of all the modelling rationales, however, a higher occurrence of some applications are observed for a selection of the rationales, as discussed. A selection of these observations are captured to Table 4.10 in REF C6.1.

D.21.2 Modelling scopes

The modelling scopes applied within the different modelling approach categories are illustrated in Figure D.48. It is observed that simulation approaches are most frequently utilised when the scope is limited to a small region, nearly 50% of all instances of simulation modelling in the dataset are concerned with a small region. In contrast, it is observed that mathematical approaches are most frequently utilised when the modelling scope is general,[43] which amounts to nearly 40% of all mathematical modelling approaches. It is also observed that mathematical approaches are very rarely used for modelling on a global or intercountry scope and that it is fairly uncommon for simulation approaches to be utilised for modelling on a global, intercountry or provincial scope.

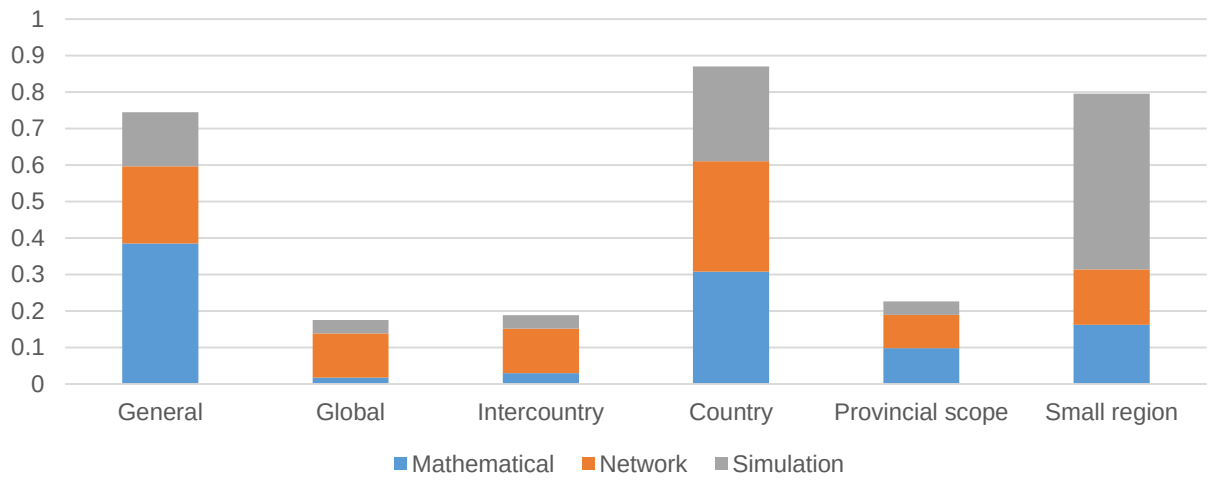

Figure D.48: Proportion of each of the three modelling approaches as applied in the context of various modelling scopes, normalised according to S3N.

[43] As stated in §3.3.4, a general scope is deduced from literature instances when it is not clear from the model description what the scale of the scope is for a given modelling application.

From this analysis it is deduced that, though it is most likely feasible to model any of the defined scopes using any of the three modelling approach categories, a general scope is commonly used in a higher proportion of mathematical approaches, a small region is used in a higher proportion of simulation approaches, and a global or intercountry scope is used in a higher proportion of network approaches. A selection of these observations are captured to Table 4.7 in REF C6.2.

D.21.3 Intervention strategy occurrence

The proportion of studies in each of the three modelling approach categories that incorporate treatment or vaccination strategies are illustrated in Figure D.49.[44] It is observed that treatment and vaccination strategies are incorporated in models that use any of the three modelling approach categories. Very similar proportions of mathematical and network modelling approaches incorporate treatment and vaccination strategies, however, it is observed that, relative to mathematical and network modelling approaches, a larger proportion of the studies that utilised simulation modelling approaches incorporated treatment and vaccination strategies. A selection of these observations are captured to Table 4.8 in REF C6.3.

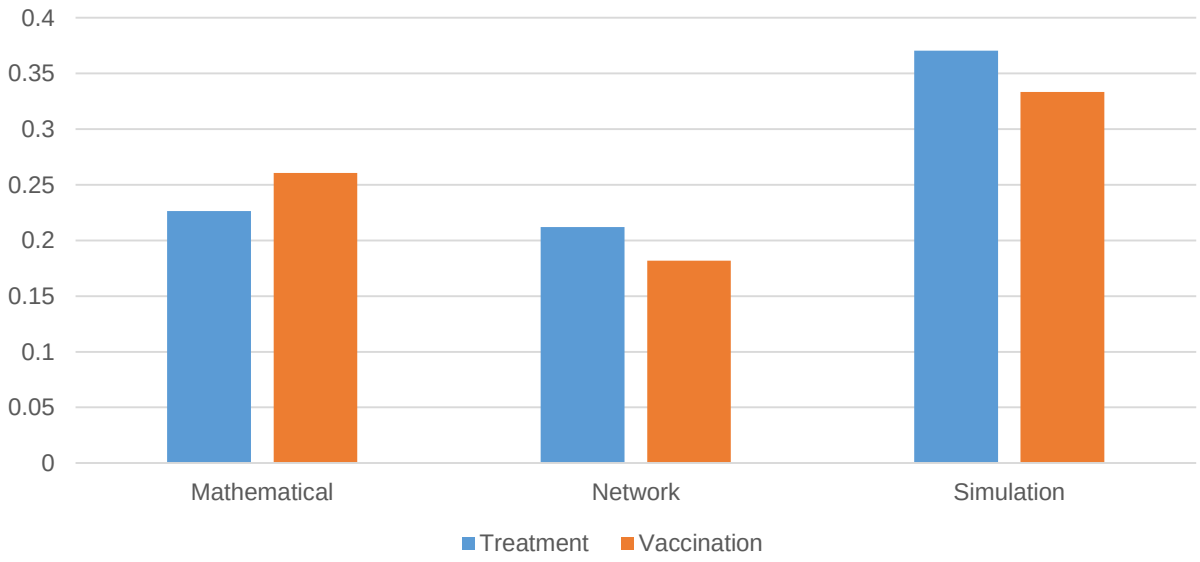

Figure D.49: Proportion of studies in each of the three modelling categories that incorporate treatment or vaccination strategies, normalised according to S3N.

[44] The modelling of intervention strategies relative to the modelling approach utilised is not studied at the same level of detail as the modelling of intervention strategies relative to the transmission mode in §D.15. The differentiated intervention strategies are regarded as being more related to disease characteristics, as opposed to a particular modelling approach.

D.22 Modelling considerations in the context of disease classification

As previously discussed in §3.1.1, the disease outbreak classification as endemic or epidemic has the potential to affect the disease modelling approach selection and contextual factor inclusions. The assumption that RI diseases relate more to endemic disease prevalence and non-RI diseases relate more to epidemic disease outbreaks is used to investigate potential relationships between this form of disease classification and the following modelling considerations:

- Modelling approach in §D.22.1;
- Mathematical approaches in §D.22.2;
- Network approaches in §D.22.3;
- Simulation approaches in §D.22.4;
- Data source in §D.22.5;
- Modelling scope in §D.22.6;
- Contextual factors in §D.22.7;
- Mentioning transmission mode in §D.22.8; and
- Modelling rationale in §D.22.9.

D.22.1 Modelling approaches

The proportion of the three modelling approach categories applied in the context of the two different disease categories is illustrated in Figure D.50. A similar pattern of occurrence is observed in both disease categories, when the change in proportions between modelling categories are considered. However, it is observed that mathematical modelling approaches are used marginally more often for modelling RI diseases than for modelling non-RI diseases, while network and simulation modelling approaches are used marginally more often for modelling non-RI diseases than for modelling RI diseases. As is evident from these high-level observations, it is not possible to recommend a particular modelling approach based solely on the RI or non-RI disease classification.

D.22.2 Mathematical modelling approaches

The proportion of literature pieces in the dataset which include mathematical modelling approaches for each of the two disease categories is illustrated in Figure D.51. Though slight variations can be observed, none of the mathematical approaches appear to be more suited to modelling RI diseases rather than non-RI diseases, or vice versa.

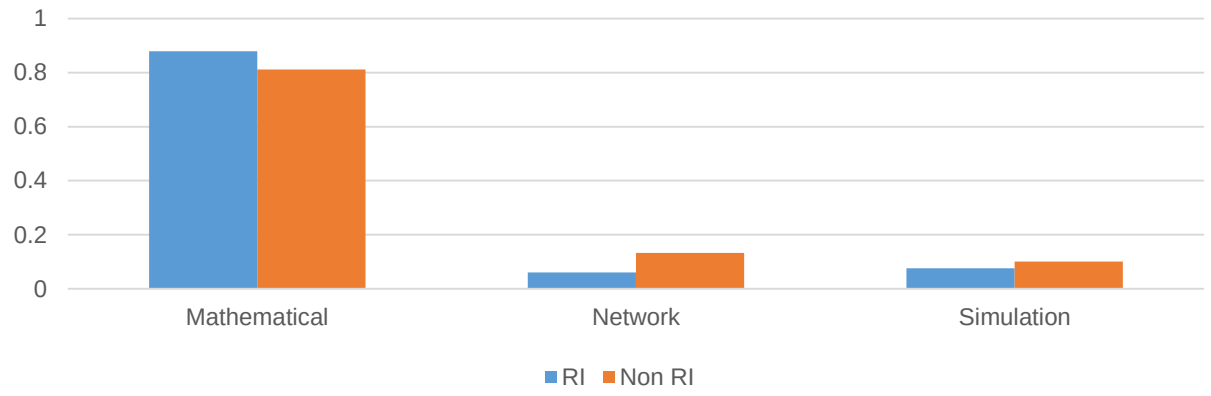

Figure D.50: Proportion of the modelled RI and non-RI disease instances which include mathematical, network and simulation modelling approaches, normalised according to S4N.

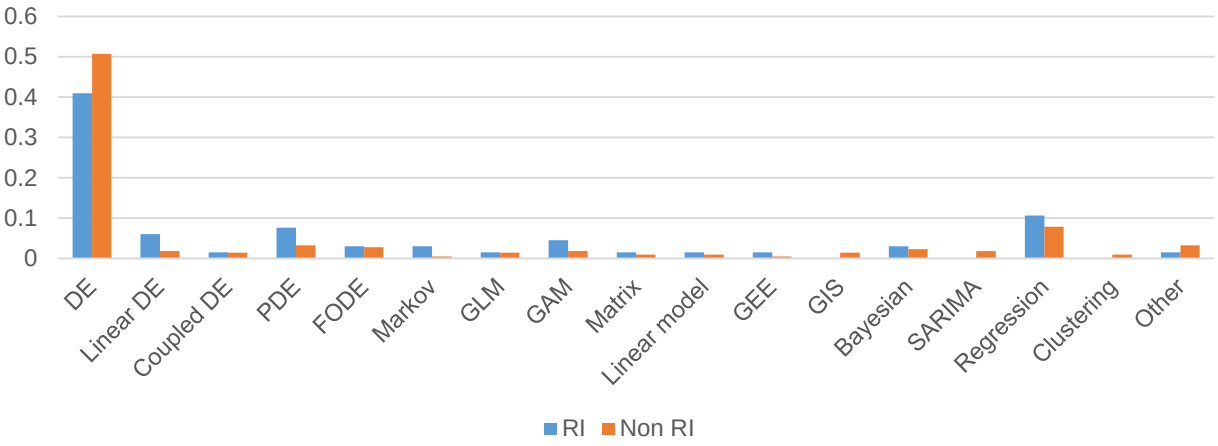

Figure D.51: Proportion of the modelled RI and non-RI disease instances which include mathematical modelling approaches, normalised according to S4N.

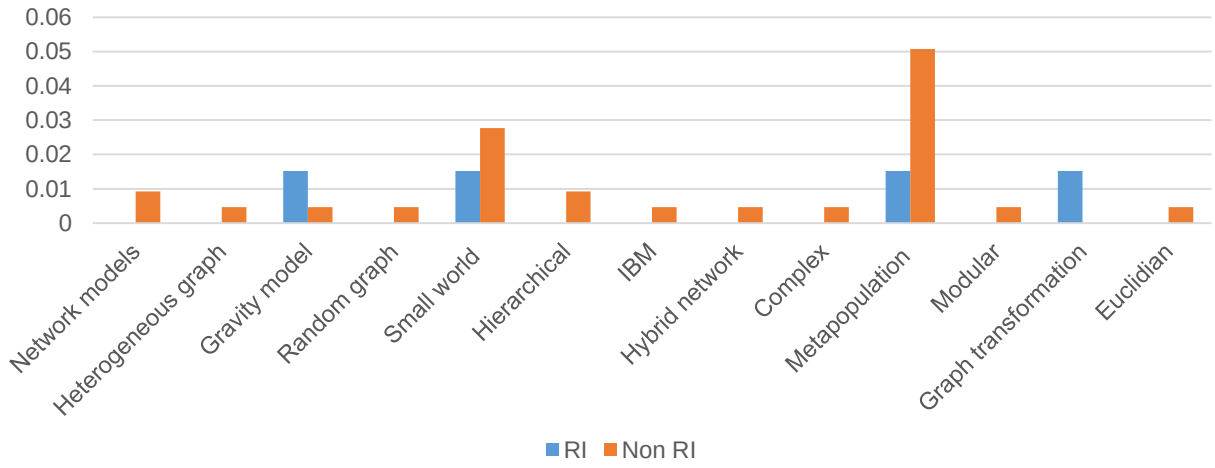

Figure D.52: Proportion of the modelled RI and non-RI disease instances which include network modelling approaches, normalised according to S4N.

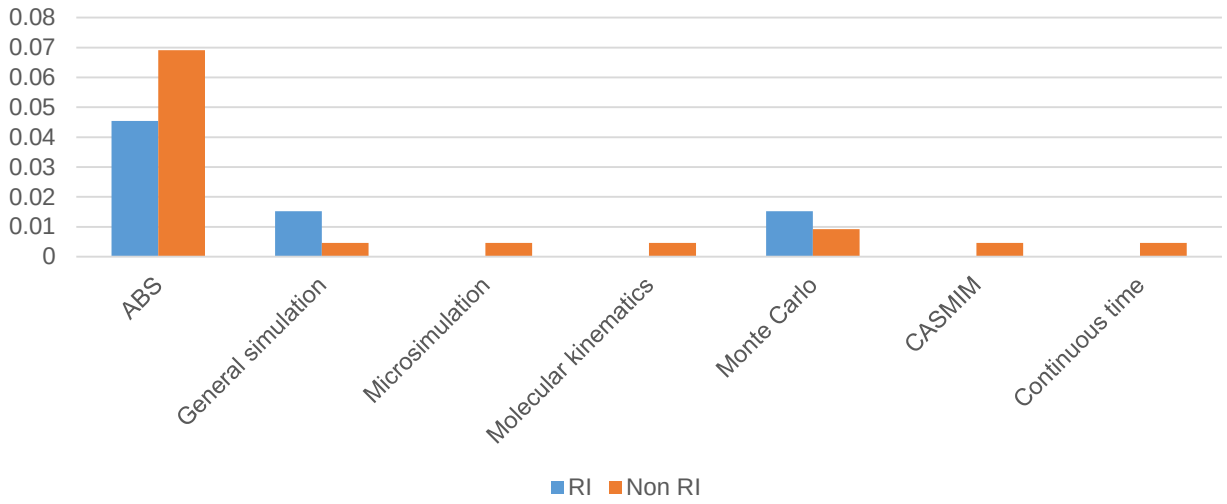

Figure D.53: Proportion of the modelled RI and non-RI disease instances which include simulation modelling approaches, normalised according to S4N.

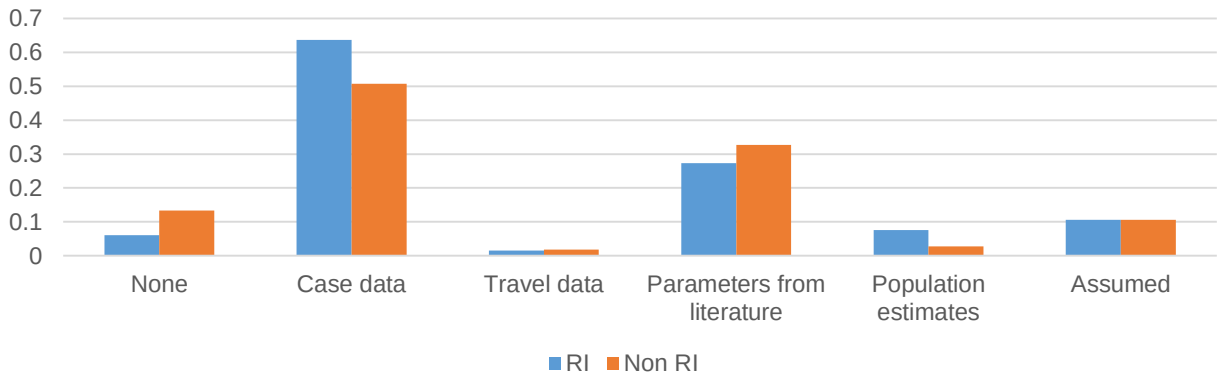

Figure D.54: Proportion of the modelled RI and non-RI disease instances in the context of different data sources, normalised according to S4N.

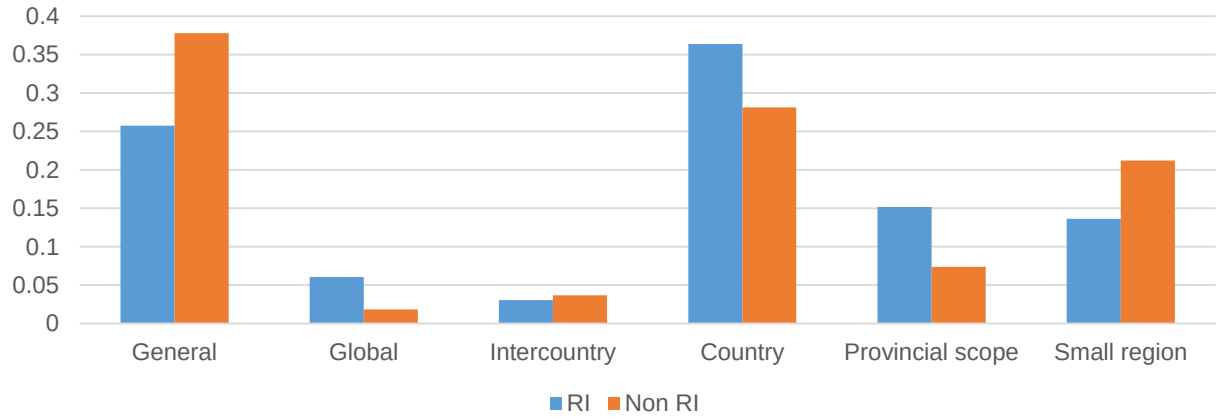

Figure D.55: Proportion of the modelled RI and non-RI disease instances in the context of different modelling scopes, normalised according to S4N.

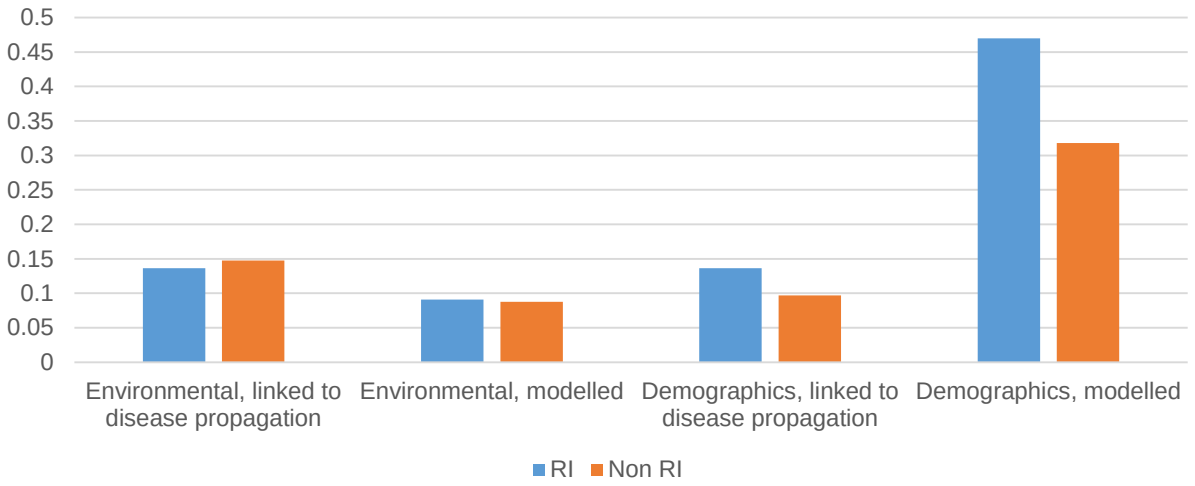

Figure D.56: Proportion of the modelled RI and non-RI disease instances which include different considerations of contextual factors, normalised according to S4N.

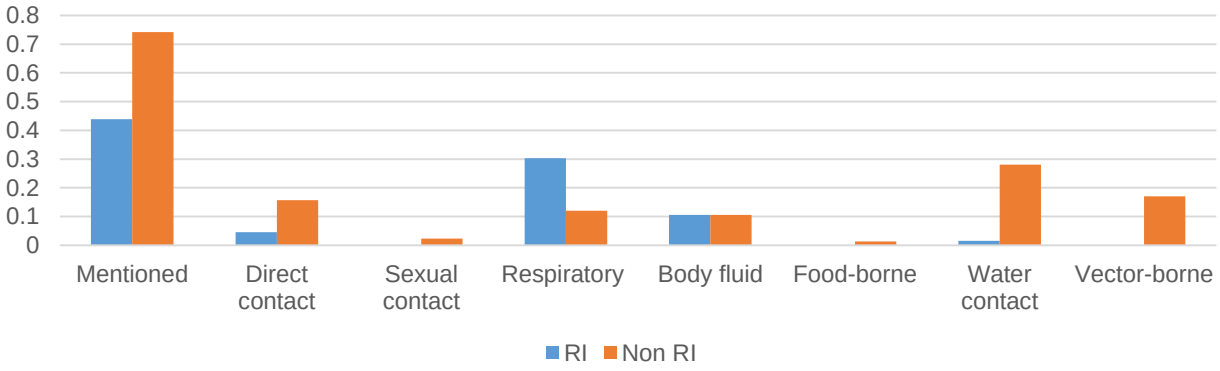

Figure D.57: Proportion of the modelled RI and non-RI disease instances in the context of explicitly contextualised transmission modes, normalised according to S4N.

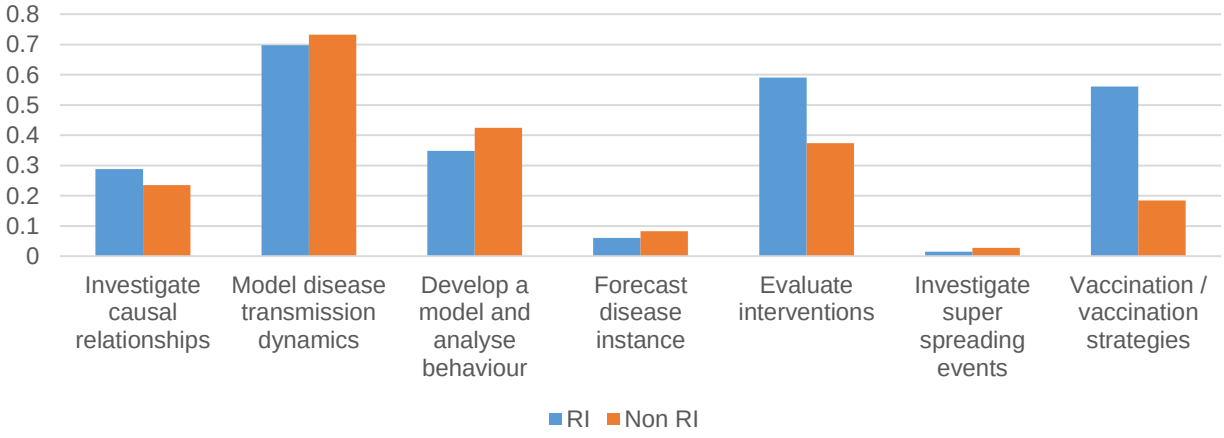

Figure D.58: Proportion of the modelled RI and non-RI disease instances in the context of different modelling rationales, normalised according to S4N.

D.22.3 Network modelling approaches

The proportion of literature pieces in the dataset which include network modelling approaches for each of the two disease categories is illustrated in Figure D.52. It is observed that a larger proportion of non-RI disease modelling instances incorporate network modelling approaches in comparison to RI disease modelling instances. Apart from this high-level observation, it is not possible to recommend a network modelling approach selection based solely on the RI or non-RI disease classification.

D.22.4 Simulation modelling approaches

The proportion of literature pieces in the dataset which include simulation modelling approaches for each of the two disease categories is illustrated in Figure D.53. It is observed that a larger proportion of non-RI disease modelling instances incorporate simulation modelling approaches in comparison to RI disease modelling instances. Apart from this high-level observation, it is not possible to recommend a simulation modelling approach selection based solely on the RI or non-RI disease classification.

D.22.5 Data sources

The proportion of the two disease categories applied in the context of different data sources is illustrated in Figure D.54. Similar proportions are observed for both disease categories in the context of the different data source categories. However, it is observed that a slightly higher proportion of RI disease modelling instances make use of case data and population estimates, in contrast to parameters from literature and no data source for non-RI disease modelling instances. Apart from this high-level observation, it is not possible to recommend the data source selection based solely on the RI or non-RI disease classification.

D.22.6 Modelling scopes

The proportion of the two disease categories applied in the context of different modelling scopes is illustrated in Figure D.55. Similar proportions are observed for both disease categories in the context of different modelling scope categories. However, it is observed that a slightly higher proportion of RI disease modelling instances are modelled with a country and provincial modelling scope, in contrast to a general and small region scope for non-RI disease modelling instances. Apart from this high-level observation, it is not possible to recommend a modelling scope selection based solely on the RI or non-RI disease classification.

D.22.7 Contextual factors

The proportion of the two disease categories which include different contextual factors is illustrated in Figure D.56. Similar proportions are observed for both disease categories in the context of different

contextual considerations. However, it is observed that a higher proportion of RI disease modelling instances included modelled contextual factors when compared to non-RI disease modelling instances, in addition to the inclusion of population demographics. This does not necessarily imply that contextual factors are less important in the context of non-RI diseases, as additional considerations may influence contextual factor inclusion. Apart from this high-level observation, it is not possible to recommend contextual factor inclusion and selection based solely on the RI or non-RI disease classification.

D.22.8 Mentioning transmission modes

The proportion of the theoretical transmission modes which are explicitly mentioned in the context of two disease categories are illustrated in Figure D.57. It is observed that a higher proportion of non-RI disease modelling instances explicitly contextualise the transmission mode. Furthermore, a higher proportion of non-RI disease modelling instances contextualise the direct contact, water contact and vector-borne transmission modes, in contrast to the respiratory transmission mode for RI disease. This does not necessarily imply that certain transmission modes are more important in the context of RI and non-RI disease modelling instances, as additional considerations may influence the contextualisation of the disease transmission mode. Apart from this high-level observation, it is not possible to recommend the importance of the contextualising the transmission mode based solely on the RI or non-RI disease classification.

D.22.9 Modelling rationales

The proportion of the two disease categories applied in the context of different modelling rationales are illustrated in Figure D.58. Similar proportions are observed for both disease categories in the context of different modelling rationale occurrences. However, it is observed that a higher proportion of RI disease modelling instances include intervention strategies and investigate causal relationships, in contrast to a slightly higher proportion of non-RI disease modelling instances which include model development, analysis and forecasting of disease prevalence. This does not necessarily imply that certain modelling rationales are more relevant in the context of modelling RI and non-RI diseases, as additional considerations may influence the selection of a modelling rationale. Apart from this high-level observation, it is not possible to recommend a modelling rationale selection based solely on the RI or non-RI disease classification.

Appendix E (Chapter 5)

A number of tables and figures which supports the construction of the framework (as described in Chapter 5) is presented within this appendix.

E.1 Tables and sections used in construction of the framework

The tables used as part of different framework construction phases are referred to in Table E.1

Table E.1: Reference table for modelling considerations which are used to construct the framework.

Modelling considerations	**Analysis on modelling considerations**	**Capturing outbreak contextualisation**	**Informative modelling suggestions**	**Details pertaining to construction**
	Chapter 4 (§D.12 – §D.22)	Chapter 5 (§5.3)	Chapter 5 (§5.4)	
Transmission modes	Table 4.6	Table 5.6	N/A	N/A
Data source	N/A	Table 5.10	N/A	N/A
Modelling scope	Table 4.7	N/A	Table 5.11	Table E.2
Modelling approaches	Table 4.8	N/A	Table 5.12	Table E.3
Mixing patterns	N/A	N/A	Table 5.14	Table E.4
Intervention strategies	N/A	Table 5.7	Table 5.15	Table E.5
Contextual factors	Table 4.9	Table 5.8 & Table 5.9	Table 5.16	Table E.6
Compartmental classification	N/A	N/A	Table 5.13	Table E.7
Modelling rationales	Table 4.10	Table 5.5	N/A	Table E.8

References to the sections and tables used in construction of the modelling scope guideline are noted in Table E.2.

Table E.2: Sections and tables used in construction of the modelling scope guideline table.

CAT	Section used for analysis	Tables used (if applicable)
Scope most frequently observed	§D.13	Table 4.6
Modelling rationale	§D.19.2	Table 4.10
Transmission mode	§D.13	Table 4.6
Data source	§D.19.1	Table 4.7
Modelling approach	§D.21.2	Table 4.7

References to the sections and tables used in construction of the modelling approach guideline table are noted in Table E.3.

Table E.3: Sections and tables used in construction of the modelling approach guideline table.

CAT	Section used for analysis	Tables used (if applicable)
Methods observed most frequently	§D.12	Table 4.6
Modelling rationale	§D.21.1	Table 4.10
Transmission mode	§D.12	Table 4.6
Data source	§D.18.1	Table 4.8
Modelling scope	§D.21.2	Table 4.7

Reference to the sections and tables used in construction of the alternative mixing pattern guideline table are noted in Table E.4.

Table E.4: Sections and tables used in construction of the alternative mixing pattern guideline table.

CAT	Section used for analysis	Tables used (if applicable)
Mixing methods observed most frequently	§D.17.1	Table 4.6
Transmission mode	§D.14	Table 4.6
Modelling scope	§D.19.3	Table 4.7
Population demographics	§D.17.2	Table 4.9
Modelling approach	§D.17.3	Table 4.8

Reference to the sections and tables used in construction of the intervention strategy guideline table are noted in Table E.5.

Table E.5: Sections and tables used in construction of the intervention strategy guideline table.

CAT	Section used for analysis	Tables used (if applicable)
Transmission mode: Potential relevance of inclusion	§D.15	Table 4.6
Transmission mode, Recommended strategies	§D.15	Table 4.6
Data source	§D.18.2	N/A
Modelling approach	§D.21.3	Table 4.8

References to the sections and tables used in construction of the contextual factor guideline table are noted in Table E.6.

Table E.6: Sections and tables used in construction of the contextual factor guideline table.

CAT	Section used for analysis	Tables used (if applicable)
Transmission mode and environmental factors	§D.16.1	Table 4.6
Transmission mode and population demographics	§D.16.2	Table 4.6
Data source	§D.18.3	Table 4.9

References to the sections and tables used in construction of the compartmental classification guideline table is noted in Table E.7.

Table E.7: Sections and tables used in construction of the compartmental classification guideline table.

CAT	Section used for analysis	Tables used (if applicable)
General observations	§D.20.1.	N/A
Transmission mode	§D.20.2	Table 4.6

References to the sections and underlying reasoning used to determine the relationship between the modelling rationale and different modelling considerations are noted in Table E.8.

Table E.8: Sections used to determine the relationship between modelling rationales and modelling considerations.

Intervention and control	Contextual factors	Mixing patterns
Per definition of the modelling rationale descriptions	Per definition of the modelling rationale descriptions	§D.17.4

E.2 Relationships analysed between modelling contextualisation and modelling selection framework steps

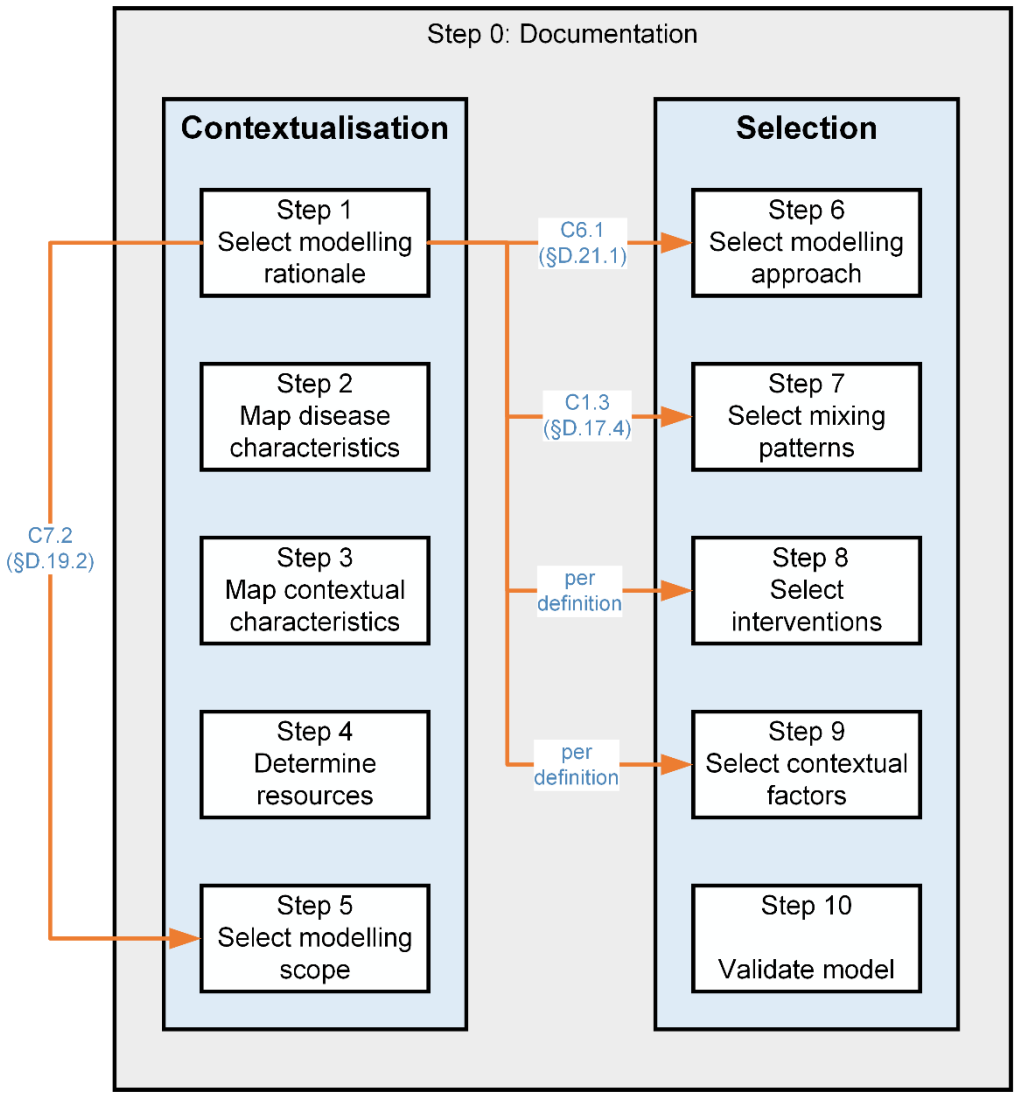

Figure E.1: Relationships analysed between the modelling rationale and a selection of the steps of the framework.

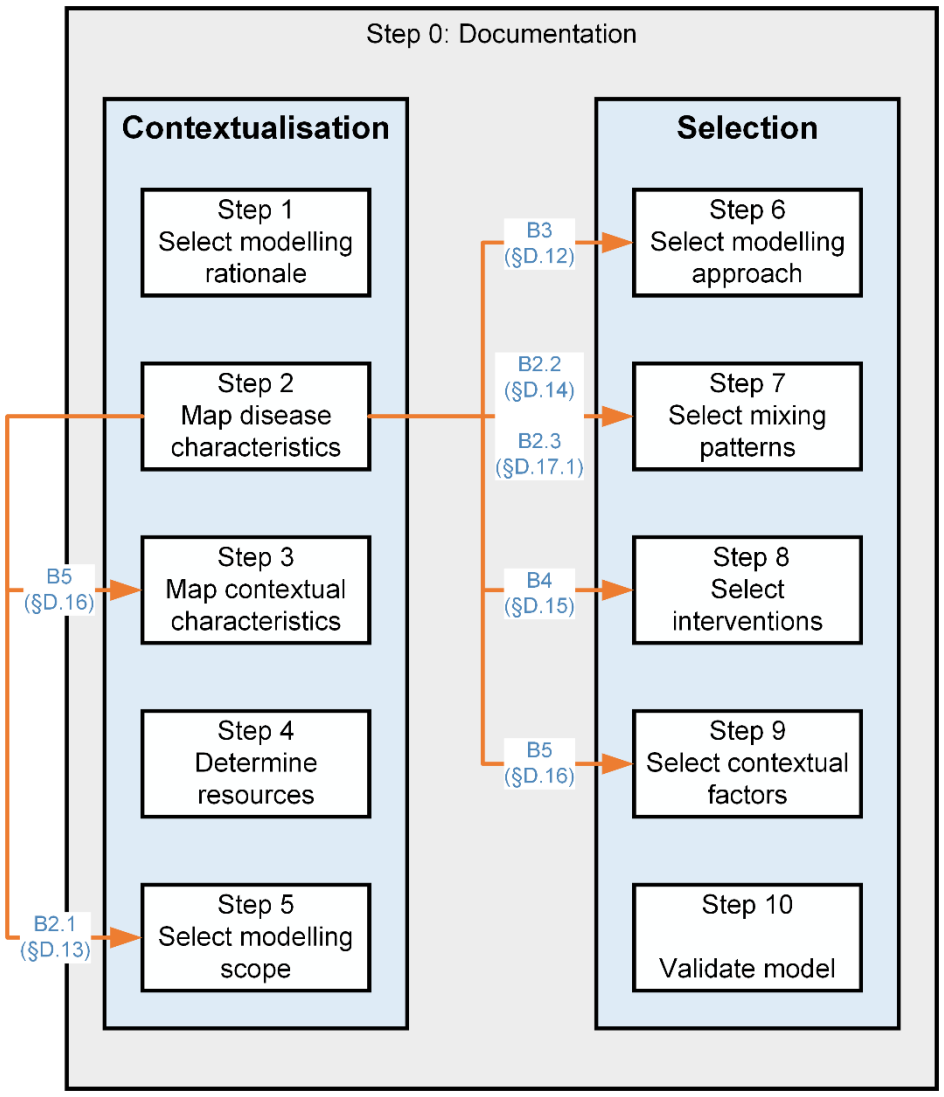

Figure E.2: Relationships analysed between the disease characteristics and a selection of the steps of the framework.

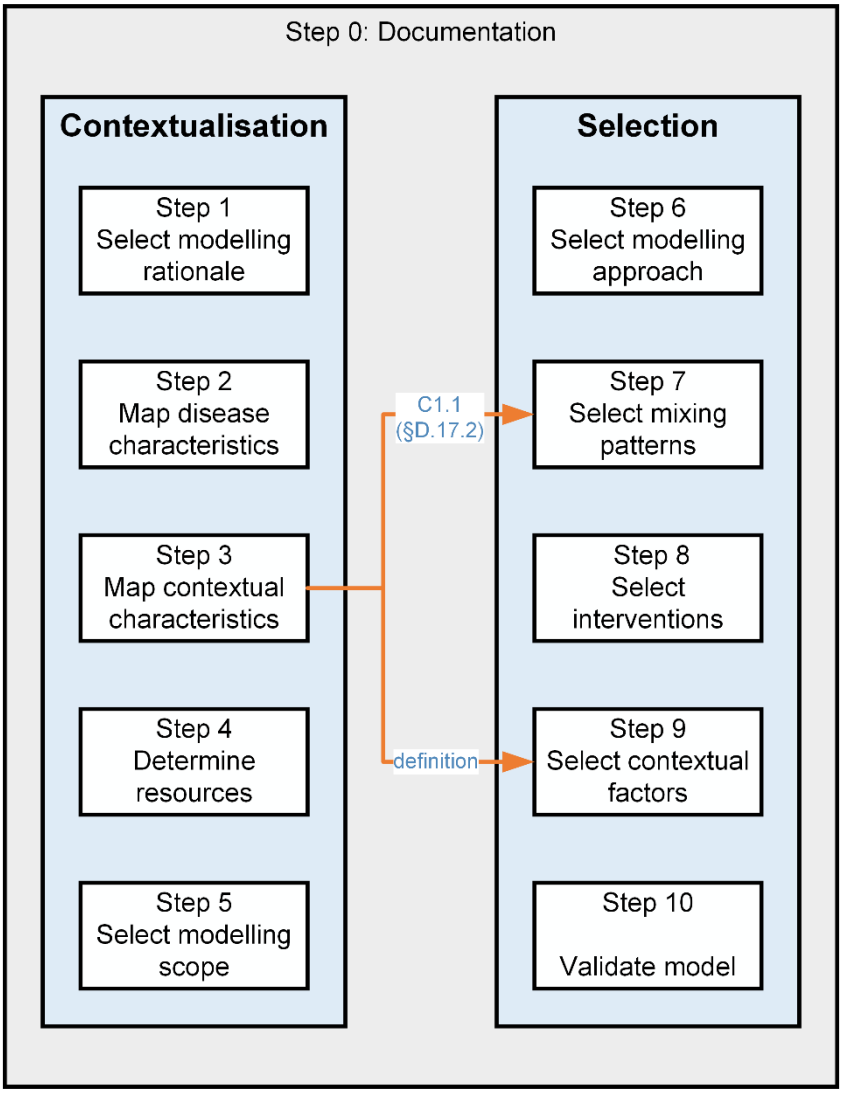

Figure E.3: Relationships analysed between the contextual characteristics and a selection of the steps of the framework.

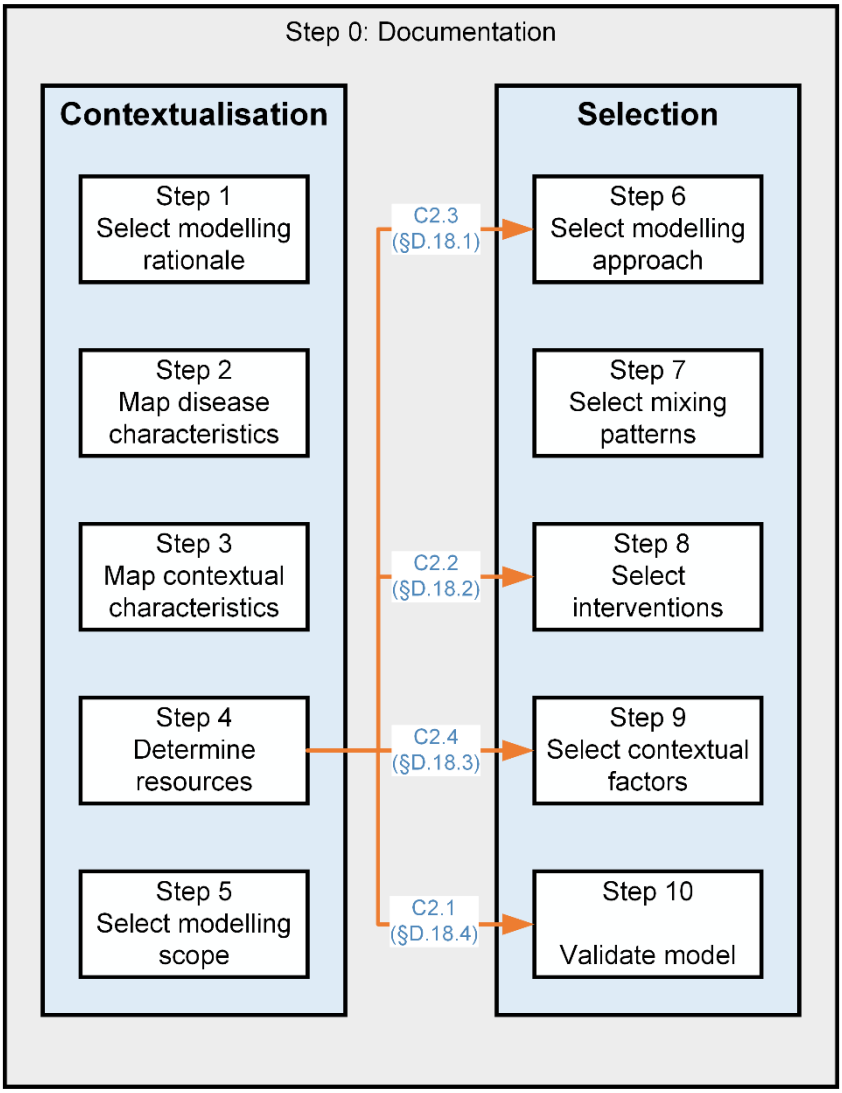

Figure E.4: Relationships analysed between the available resources and a selection of the steps of the framework.

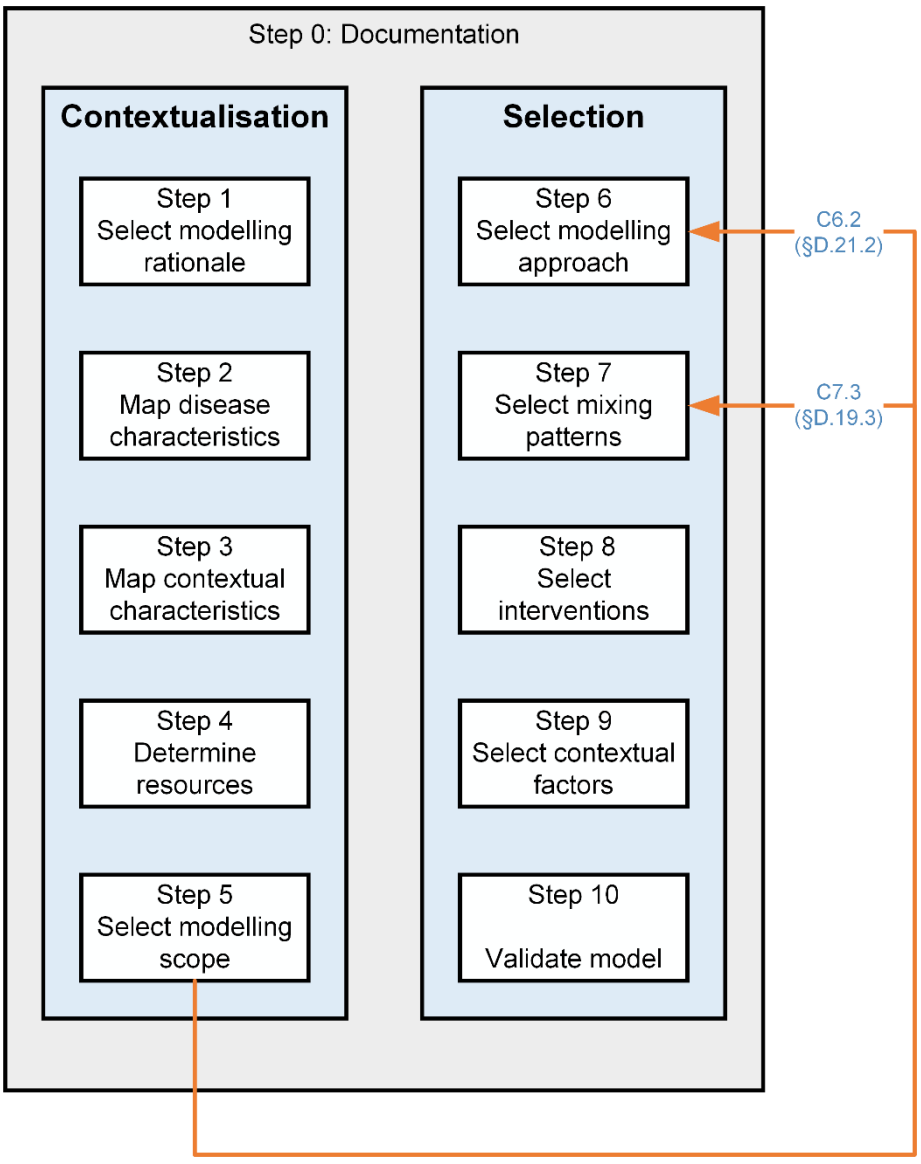

Figure E.5: Relationships analysed between the modelling scope and a selection of the steps of the framework.

Appendix F (Validation document)

The content of the validation document as presented to the SMEs in preparation of the semi-structured interviews is presented verbatim in this appendix. The table of contents of the validation document is, however, not included in this appendix.

Validation document:

A framework for modelling approach and selection support in the context of communicable disease modelling.

The document is structured as follows:

- Section F.1 contains an introduction to the research problem and a high-level overview of the methodology followed towards construction of the framework;
- In Section F.2, the framework is presented;
- In Section F.3, an illustrative case study is used to describe the use of the framework; and
- In Section F.4, the validation questionnaire is presented.

Author: Bernie Cronje, Study leader: Louzanne Bam

F.1 Introduction

F.1.1 Background and origin of the problem

Mathematical modelling of infectious disease is an approach used to describe the prevalence of disease in humans. A flowchart of the relationship between biological problems and mathematical models is illustrated in Figure F.1. The modelling process starts with identifying a biological problem (i.e. a disease outbreak). Underlying assumptions which characterise the disease outbreak are used to describe the biological problem mathematically. Further analysis of the mathematical model is used to create a modelling solution to the biological problem. This subsequently allows the testing of different conditions and scenarios of the model, to create a predicted outcome to the model. Comparing the outcome of the model to the real data is considered an indication of the suitability of the model in describing the biological problem mathematically.

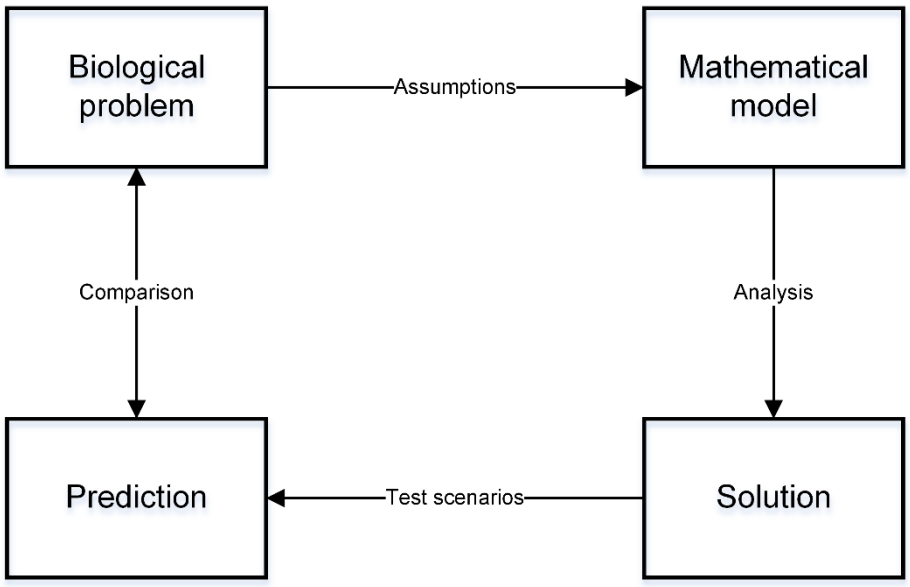

Figure F.1: Flowchart of mathematical modelling of infectious disease.

From this discussion, the capturing of the disease dynamics and contextual factors of the disease outbreak are very important goals from which secondary modelling goals typically follow (e.g. vaccine demand estimation, effect of quarantine strategies, estimated number of infected individuals at a specific point in time).

F.1.2 Problem background

As illustrated in Figure F.2, during the past two decades major outbreaks strained the global health system. Such disease outbreaks often require rapid response and frequently result in global collaboration between various health care professionals and modellers. In the context of constructing

a modelling application, the literature on available modelling approaches is well established, however the factors which affect the selection and the application of one approach above another is not always clear as a result of the densely published field of infectious disease modelling. Health care professionals who frequently model infectious disease are likely to be very well acquainted with the process of modelling approach selection and which modelling considerations to include, but individuals who are not well acquainted with the field might not always know which considerations and incorporations are necessary in modelling applications.

Furthermore, when modelling an infectious disease outbreak, there are no response strategies which are universally viewed as the most efficient and effective strategies. This further highlights the importance of accurately describing the context in which a disease outbreak occurs, in order to construct a realistic mathematical model of the biological problem.

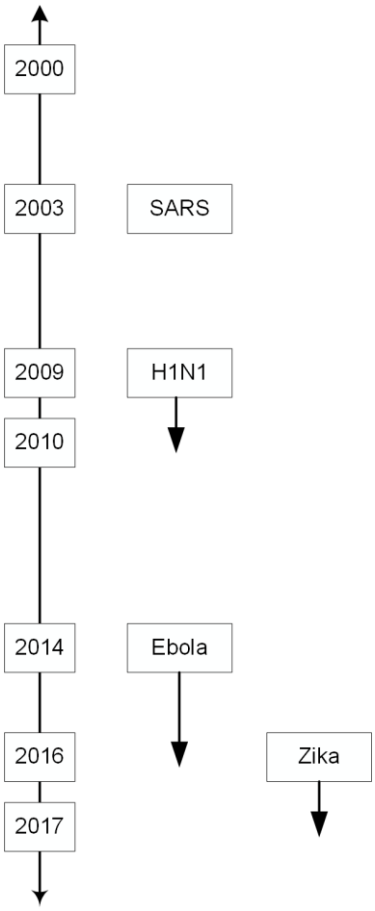

Figure F.2: Timeline of major disease outbreaks.

F.1.3 Problem statement

A visualisation of the problem statement is illustrated in Figure F.3. Given the rapid response required when modelling disease outbreaks and preparing intervention strategies, modellers and decision makers in the health care system would benefit from a holistic framework capable of

assisting the selection of modelling approaches and the incorporation of relevant modelling considerations. The numerous low level drivers of disease dynamics, such as the disease characteristics and the contextual factors of the disease outbreak are expected to play a role in the selection of modelling approaches. Of all the potential approaches available in literature, only a select number of these approaches are typically applied and published within the modelling literature. A structured review of the modelling literature, in the context of disease dynamics and the available modelling approaches, is performed to construct a dataset on existing modelling approaches. This dataset is then analysed, in order to construct the proposed modelling framework. The framework is used to assist the modeller with the selection of the assumptions of mathematical modelling as illustrated in Figure F.1.

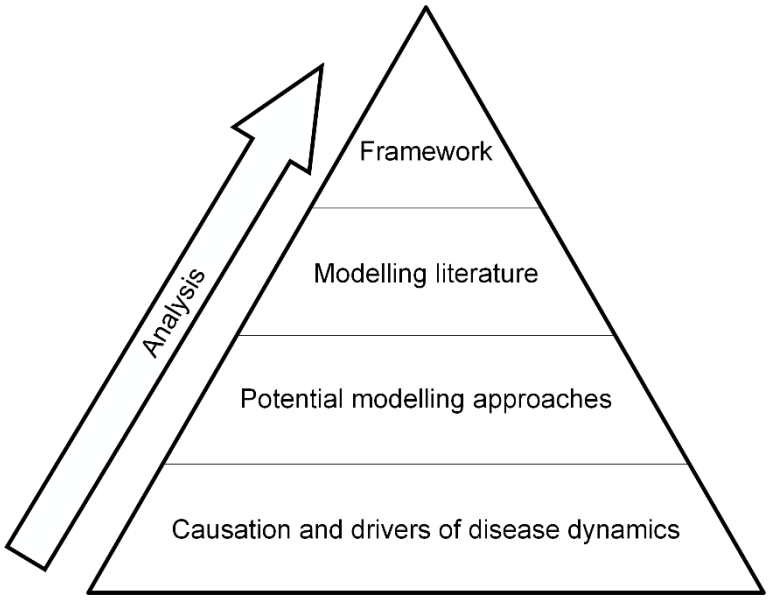

Figure F.3: A visualisation of the problem statement.

F.1.4 Research aim

The aim of the research is to conceptualise a framework support tool consisting of two modules used to formalise decisions and considerations which form part of modelling approach implementation. The first module of the framework is used to contextualise the aims and considerations of the disease outbreak and establish relationships to the second module of the framework, which relates to modelling approach and consideration selection.

F.1.5 Methodology

The objectives of the framework consist of the following:

- Presenting a well-researched modelling approach which formalises all relevant decisions and considerations of the modelling;

- Ensuring that the disease outbreak is properly contextualised; and
- Linking the contextualisation to the modelling decisions and implementations.

A brief overview of the methodology followed towards the framework construction follows. The chain of infection as illustrated in Figure F.4 is used as a departure point to understand the process of disease propagation and transmission.

Figure F.4: A visualisation of the chain of infection.

With a view to analyse and relate drivers of disease dynamics to disease propagation, various disease characteristics are linked to aspects of the chain of infection, in addition to various contextual factors which potentially affect the chain of infection, as illustrated in Figure F.5.

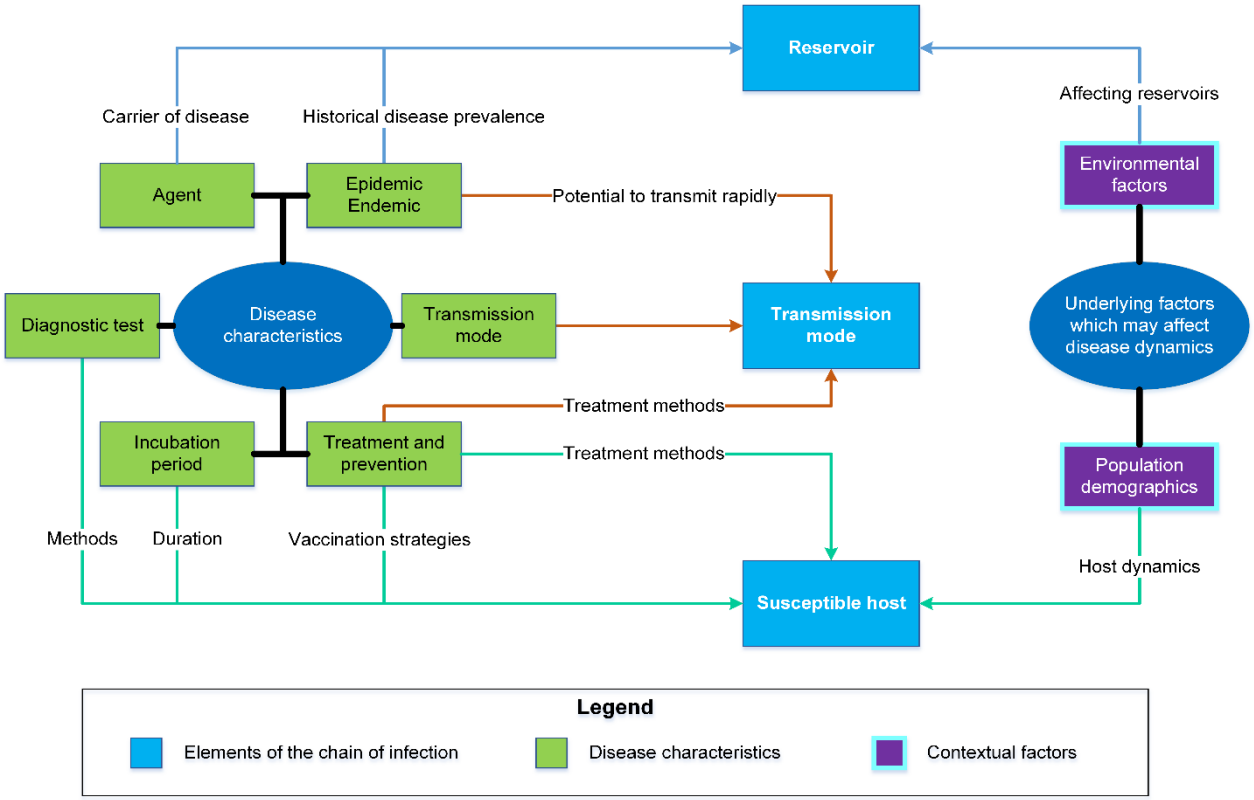

Figure F.5: Linking disease characteristics and contextual factors to the chain of infection.

Additional factors such as computing power requirements, level of mixing and detail in modelling approaches influence the selection of one modelling approach above another, as illustrated in Figure F.6.

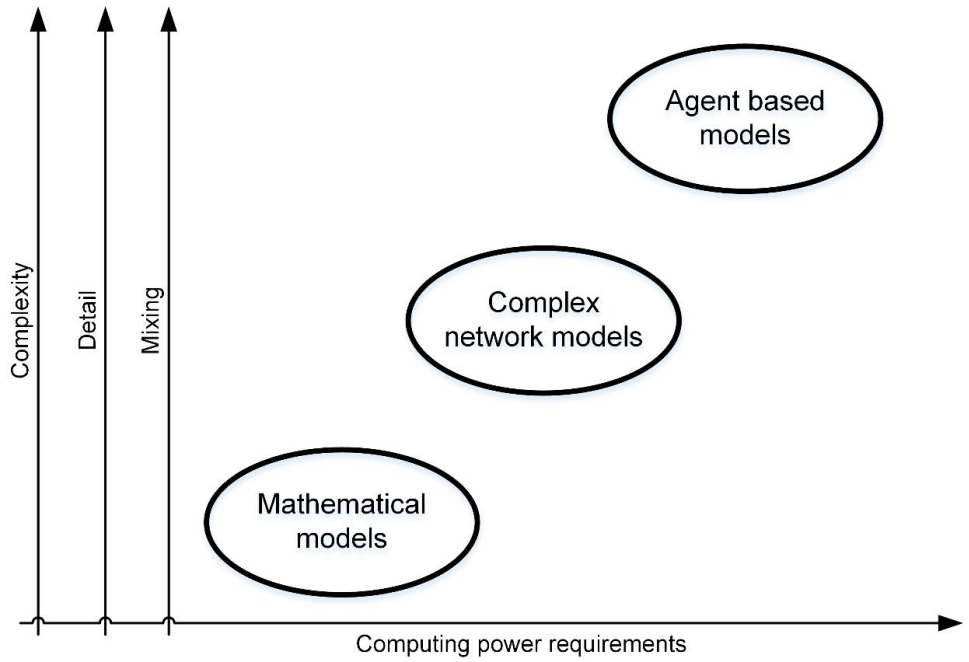

Figure F.6: A comparison between generic model choice and required modelling resources and specifications.

A structured literature review is designed and executed. The literature is selected according to instances which model disease on a population level, or instances which incorporate contextual factors as part of the modelling approach. The potential literature pieces are selected according to an iterative filtering process and the modelling considerations which are captured from the literature instances are as follows:

- Data source;
- Method of model fit;
- Modelling scope;
- Rationale of article;
- Compartmental classification;
- Modelling approaches;
- Transmission mode mentioned;
- Theoretical transmission modes;
- Mixing patterns;
- Disease name;
- Intervention strategies; and
- Contextual factors.

The 283 literature instances uncovered in the structured literature review are analysed to inform the suggestions and preparation considerations as illustrated in Figure F.7. The framework is then constructed with two modules. The first module concerns the contextualisation of the disease

outbreak (i.e. **capturing outbreak preparation**) which is used to inform the **outbreak modelling selection** of modelling approaches and modelling considerations.

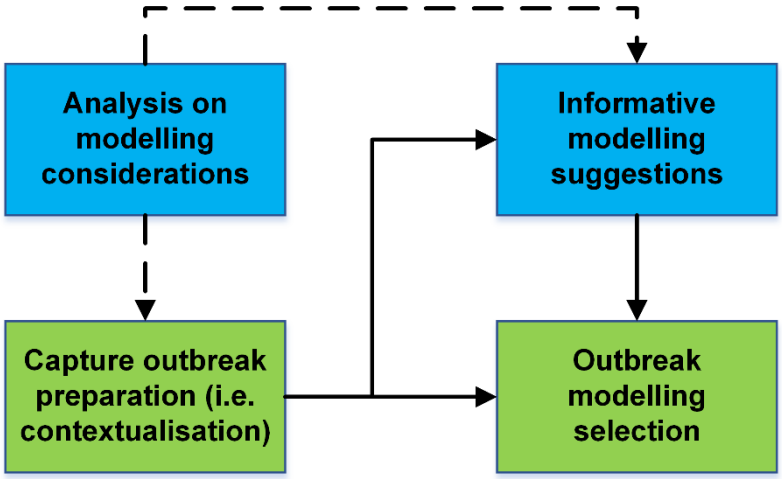

Figure F.7: High-level overview of the framework construction.

Modelling approach selection is a complex endeavour and the decision is not reducible to a single factor or consideration. The goal of the framework is not to establish hard and fast rules which are universal in all instances or to suggest every single potential theoretical modelling approach, mainly because this is infeasible due to the interaction of various factors and considerations which influence the selection of a modelling approach. Instead, the framework prompts the modeller to ensure that all relevant modelling considerations are taken into account and it guides the modelling approach selection by proposing options based on observed relationships in the published literature. Furthermore, the framework steps guide the modeller to systematically document the approach selection process, thus creating a paper trail of factors that were taken into account when selecting the model approach and developing the model.

F.2 Framework presentation

The stepwise overview of the framework is illustrated in Figure F.8. Within the remainder of this section, the framework steps are defined and briefly explained.

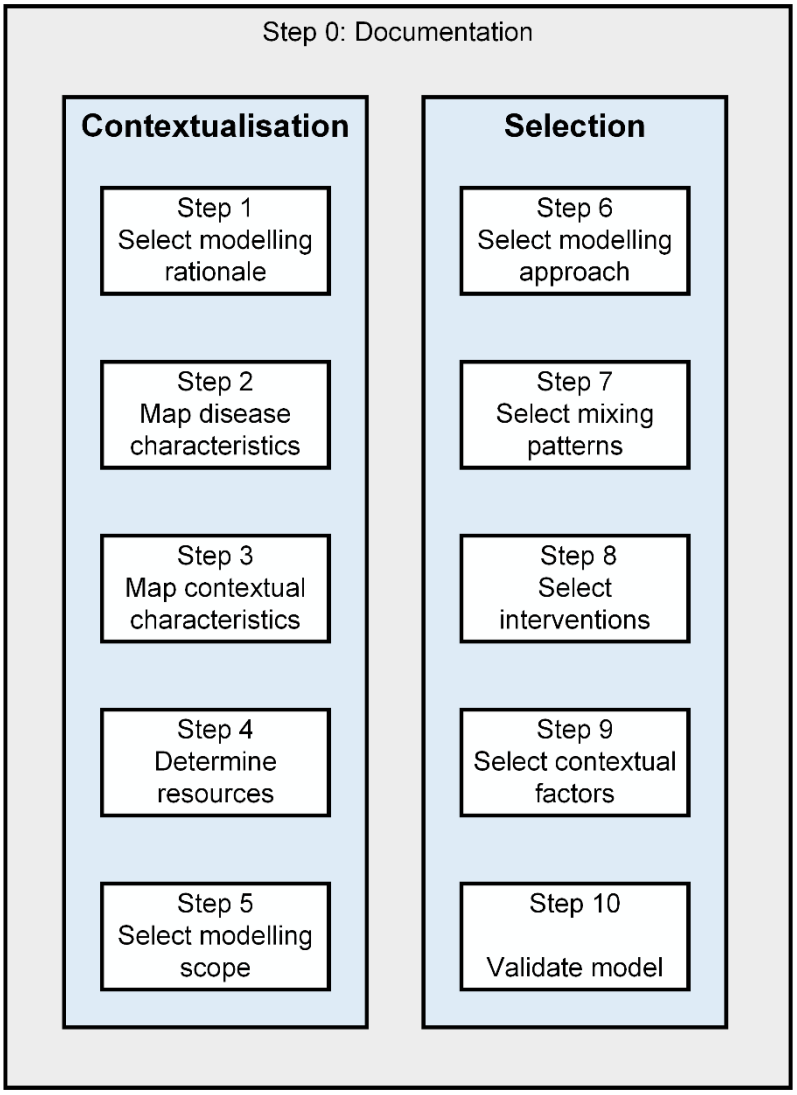

Figure F.8: Stepwise overview of the framework.

Step 0. Documentation

The documentation of the modelling approach is a step that runs concurrently through each of the steps of the framework. This step serves the purpose of documenting both the aspects of the outbreak modelling preparation and the outbreak modelling selection phase, analogous to creating a roadmap of the modelling process. The main reasons for incorporating this step in the framework are as follows:

- Modelling assumptions and selections are captured clearly and concisely.

- Provides assurance to the modeller that all relevant factors were considered in the modelling process, in addition to describing why some considerations were omitted and how the outbreak context relates to the selection of the modelling application.
- The ability to extend or clarify aspects of the modelling application in future work is assisted, in the sense of showing which modelling considerations were incorporated or explicitly omitted from the modelling application.

The considerations of the contextual mapping of the disease outbreak (i.e. Step 1 – 4) is done according to the template of Table F.1, whereas the modelling approach selection (i.e. Step 5 – 10) is done according to the template of Table F.2.

Step 1. Select modelling rationale

Setting the rationale (i.e. modelling goal) of the modelling application as part of the modelling preparation will guide the modelling process. The set of potential modelling rationales that can be selected are reproduced below, namely:

- Model disease transmission dynamics (develop a model to study disease transmission dynamics);
- Investigate causal relationships (develop a model to investigate the effect of factors which affect the chain of infection and correlates to changes in disease propagation or prevalence);
- Investigate super spreading events (develop a model to highlight the specific instance of unusually high secondary infections from a few individuals);
- Forecasting disease instance (develop a model to not only fit data or parameters, but to explicitly forecast future disease prevalence from the model);
- Develop model and analyse behaviour (develop a theoretical model of disease transmission and investigate behaviour of the model in the context of varying parameter values);
- Test interventions (develop a model to evaluate one or more treatment strategies or vaccination strategies).

Following the modelling rationale selection (which is noted in Table F.1), the relationships to a select number of outbreak modelling considerations are produced in Table F.3. This is used to suggest the potential importance of modelling considerations of Step 2 and Step 3 in the context of a selected modelling rationale. The strength of the relationships are characterised according to the following guidelines, namely:

Table F.1: Reference table to capture decisions from outbreak preparation phase.

Modelling rationale	Selected (✓ / ✗)	Treatment included (✓ / ✗)	Vaccination included (✓ / ✗)	Environmental factors included (✓ / ✗)	Demographics included (✓ / ✗)	Alternative mixing patterns included (✓ / ✗)
Model disease dynamics						
Investigate causal relationships						
Investigate super spreading events						
Forecasting disease instance						
Develop model and analyse behaviour						
Test interventions						

Table F.2: Reference table to capture decisions from the outbreak modelling phase.

Category		Selection (✓)	Methods and/or categories selected	Modelling assumptions	Additional comments
Modelling scope	General		N/A		
	Global				
	Intercountry				
	Country				
	Provincial				
	Small region				
Modelling application	Mathematical				
	Network				
	Simulation				
	Compartmental classification				
Mixing patterns	Homogeneous		Homogeneous		
	Alternative				
Intervention and control	None		N/A		
	Treatment				
	Vaccination				
Contextual factors	None		N/A		
	Environmental				
	Demographics				
Validate model	Does the model answer research question?		N/A		
	Is the model comprehensible?				
	Is the model believable?				
	Does the model fit the data?				
	Fitting methods used:				
Future work					
Documentation completed	Outbreak preparation	Table F.1	Table F.4 – Table F.9		
	Outbreak modelling	Table F.2	Table F.10-Table F.16		

- **Strong**, the modelling consideration has a significant relevance in the context of the selected modelling rationale;
- **Potentially**, the modelling consideration is typically included in the context of the selected modelling rationale, however, the inclusion thereof is not a set requirement; and
- **Context**, the context of the modelling application will determine the potential inclusion of the modelling consideration (i.e. the modelling application is not explicitly related to the modelling rationale).

Table F.3: Effect and relevance of the modelling rationale on the outbreak modelling choices.

Selected modelling rationale	Modelling approach	Mixing patterns	Intervention and control	Contextual factors
Model disease dynamics	Strong	Potentially	Potentially	Potentially
Investigate causal relationships	Strong	Context	Context	Strong
Investigate super spreading events	Strong	Strong	Potentially	Strong
Forecasting disease instance	Strong	Potentially	Context	Potentially
Develop model and analyse behaviour	Strong	Context	Potentially	Context
Test interventions	Strong	Potentially	Strong	Potentially

Step 2. Map disease characteristics

The disease characteristics which relate to the incubation period and the transmission mode are captured and described according to Table F.4. The vehicles and vectors (retrieved from clinical knowledge or from the GIDEON disease database) which are responsible for disease transmission are used to determine the disease transmission mode according to Table F.5.

The captured disease transmission modes are used in the sections that follow to inform a selection of the modelling considerations.

In addition to the transmission mode, the availability of different intervention strategies also form part of the disease characteristics description. The following data is captured and described in Table F.6 according to available clinical knowledge of the disease, or retrieved from the GIDEON disease database, namely:

- **Vaccines** which are available; and
- **Treatments** which are typically used.

To inform the potential relevance of the inclusion of intervention strategies when modelling a given disease, the following guidelines are used, namely:

- Potential relevance of intervention strategies in relation to the transmission mode category in Table F.14; and
- Intervention strategies in the context of the modelling rationale as described in Table F.3.

Additional columns for modelling assumptions and additional information are available to capture any information relevant to the consideration and selection of intervention strategies in Table F.6.

Following the considerations of this step of the framework, the inclusion or exclusion of

- treatment; and
- vaccination;

in the proposed modelling approach are noted in Table F.1.

Table F.4: Mapping disease characteristics.

Category		Transmission modes present (✓ / ✗)	Modelling assumptions	Additional information
Incubation period	Lower	N/A		
	Upper			
Disease transmission mode	Direct contact			
	Sexual contact			
	Respiratory			
	Body fluid			
	Food-borne			
	Water contact			
	Vector-borne			

Table F.5: A classification of the GIDEON vehicles and vectors according to 9 disease transmission categories.

Animal contact	Direct contact	Sexual contact	Respiratory / droplet	Blood / body fluid	Food-borne	Soil contact	Water contact	Vector-borne
Amphibian Reptile Animal bite Snail Earthworm Slug	Physical contact	Sexual contact	Droplet Dust Aerosol Respiratory Pharyngeal acquisition	Breastfeeding Fecal-oral Secretion Blood Tissue	Dairy products Eaten insect Fish Food Meat or poultry Shellfish Vegetable Fruit	Soil contact Vegetable matter	Water Fecal-oral	Fly Mosquito

Table F.6: Mapping disease intervention strategies and modelling assumptions.

Category	Accounted for (✓ / ×)	Modelling assumptions	Additional information
Availability of vaccine			
Treatment options			

Step 3. Map contextual characteristics

The contextual factors which are considered in the modelling approach are described in this step. The contextual factors relate to environmental contextual factors and population demographic contextual factors.

Environmental factors

The environmental factors which are considered within the disease modelling approach are described and captured in Table F.7. The suggested factors to consider include the following:

- **Seasonality** of disease dynamics;
- **Climate**, which may include rainfall and temperature; and
- **Additional factors**, which are determined at the discretion of the modeller.

To inform the potential relevance of the inclusion of this contextual factor, the potential relevance of environmental factors in relation to the transmission mode category in Table F.16 is used.

During the process of describing the environmental factors in increased detail, additional columns for modelling assumptions and additional information are available to capture any additional information relevant to the factors in Table F.7.

Table F.7: Mapping environmental contextual factors.

Category	Accounted for (✓ / ×)	Modelling assumptions	Additional information
Seasonality			
Climatic factors			
Additional factors			

Population demographics

The population demographic factors which are considered within the disease modelling approach are described and captured in Table F.8. The suggested factors to consider include the following:

- **Population structure**, which relates to the age structure of the population;
- **Spatial spread**, how the population is dispersed geographically;
- **Mixing and migration** of the population, directly affecting the manner in which individuals move, interact and create potential contacts which may facilitate disease transmission;
- **Socio-economic** profile, which may indirectly affect the susceptibility of individuals; and
- **Additional factors**, which are determined at the discretion of the modeller.

To inform the potential relevance of the inclusion of this contextual factor, the potential relevance of demographic factors in relation to the transmission mode category in Table F.16 is used.

During the process of describing the population demographics factors, in increased detail, additional columns for modelling assumptions and additional information are available to capture any additional information relevant to the factors in Table F.8.

Table F.8: Mapping population demographic contextual factors.

Category	Accounted for (✓ / ✗)	Modelling assumptions	Additional information
Age structure			
Spatial spread			
Mixing			
Migration			
Socio-economic			
Additional factors			

In addition to the population demographics, alternative mixing pattern consideration is also part of the mixing and migration population demographic factor. To inform the potential relevance of the inclusion of alternative mixing patterns in relation to the transmission mode of a given disease, the following guidelines are used, namely:

- Alternative mixing patterns in relation to the transmission mode category in Table F.13; and
- Alternative mixing patterns in the context of the modelling rationale as described in Table F.3.

Following the considerations of this step of the framework, the inclusion or exclusion of:

- environmental factors;
- population demographics; and
- alternative mixing patterns;

in the proposed modelling approach are noted in Table F.1.

Step 4. Determine resources

Following the contextualisation of the disease outbreak, the next preparation step is describing the available data sources in Table F.9. The available data source categories are reproduced below in descending order of resolution, namely:

- **Case data** (data on confirmed cases of disease infection);
- **Parameters from literature** (data on transmission parameters previously formalised in the literature);
- **Population estimates** (data on population age structure or census data);
- **Travel data** (data on movement of individuals);
- **Assumed** (data which assumes important transmission characteristics); and
- **None** (when no data source is used).

Table F.9: Mapping quality and source of data.

Category	Data source used (✓ / ✗)	Modelling assumptions	Additional information
Case data			
Parameters from literature			
Population estimates			
Travel data			
Assumed			
None			

The data source resolution does not necessarily imply or limit modelling considerations such as the modelling scope, modelling approach or incorporation of mixing patterns, but merely the resolution at which the disease outbreak may be described within the population. With this in mind, in order to

better describe and capture the use of the data source, additional columns for modelling assumptions and additional information are available to capture any additional information relevant to the data source in Table F.9.

Another resource apart from data which may prove useful is the availability of previous modelling applications. This may serve as a starting point for the current modelling application or enable the use of a previous modelling application following small extensions and alterations of the model. This would be context-specific for each modelling application and require sufficient research of the modelling literature. This would ideally be used to guide the selection and mapping of disease characteristics within this phase of the framework.

Step 5. Select modelling scope

Although the modelling scope selection is presented as part of the outbreak preparation phase, the selection of the scope is also viewed as a contextual characteristic of the outbreak modelling selection steps. The options for selecting the scope of the modelling application are the following:

- General (a general modelling application with no indication of the scale of the application, typically a theoretical model for a specific disease instance);
- Global (disease transmission between more than two countries);
- Intercountry (disease transmission between two countries);
- Country (disease transmission within a single country);
- Provincial (disease transmission within a province); and
- Small region (disease transmission in a small region, such as a city or small village).

The modelling scope selection relates to the resolution of the area which the modelling application should model. To aid the modeller in the selection of the modelling scope, the following modelling considerations are used in Table F.10:

- Modelling rationale (captured in Table F.1);
- Transmission mode (captured in Table F.4); and
- Data source (captured in Table F.9).

The selections within the aforementioned three categories guide and recommend the selection of the modelling scope in Table F.10. The selection of the scope does not, however, relate solely to these three modelling considerations and the modeller has the freedom to select a different modelling scope regardless of the recommendations, should this be a modelling application requirement. Following the considerations of this step of the framework, the selection of the modelling scope is documented in Table F.2.

Table F.10: Scope consideration and selection guidance within the framework.

Category	Effect on incorporation		Modelling scope					
			General	Global	Intercountry	Country	Provincial	Small region
Modelling rationale	Most modelling scopes are used and suitable in the context of all modelling rationales, however, the three modelling scopes which are most frequently employed for each modelling rationale are:	Investigate causal relationships			✓		✓	✓
		Model disease transmission dynamics	✓			✓		✓
		Develop model and analyse behaviour	✓	✓				✓
		Forecasting disease instance				✓	✓	✓
		Test interventions	✓	✓		✓		
		Investigate super spreading events				✓	✓	✓
Transmission mode	The most diverse modelling scope is applied to respiratory transmission modes, followed by direct contact and water contact transmission modes. Frequently observed modelling scopes in relation to the transmission mode are:	Direct contact	✓	✓	✓	✓		
		Sexual contact	✓			✓		
		Respiratory	✓	✓	✓		✓	✓
		Body fluid	✓		✓	✓		
		Food-borne	✓					✓
		Water contact	✓			✓	✓	
		Vector-borne	✓				✓	✓
Data source	Not all data sources are observed in the context of the modelling scope. The recommended scope for each data source category is:	Case data		✓	✓	✓	✓	✓
		Parameters from literature	✓			✓	✓	✓
		Population estimates		✓	✓	✓		
		Travel data		✓	✓	✓		
		Assumed	✓			✓		
		None	✓					

Step 6. Select modelling approach

In the framework, three broad modelling approach categories are available for selection, namely

- Mathematical;
- Network; and
- Simulation.

To aid in the selection of a modelling approach category, the following modelling considerations are linked to the three modelling approaches in Table F.11:

- Modelling rationale (captured in Table F.1);
- Transmission mode (captured in Table F.4);
- Data source (captured in Table F.9); and
- Modelling scope (selected in Step 5).

Similar to Step 5 in which the modelling scope selection is described, the modeller has the freedom to select any modelling approach regardless of the recommendations, especially if a particular modelling approach is a modelling application requirement. Following the considerations and recommendations of this step of the framework, the selection of the modelling approach is documented in Table F.2.

Compartmental classification

The choice of incorporating compartmental classification of individuals is an additional step of the modelling approach selection. It is not possible to generalise the inclusion of compartmental classification, however, recommendations on the selection of disease states are produced in Table F.12 in the context of the transmission mode of the disease (captured in Table F.4).

Following the considerations of this step of the framework, the inclusion or exclusion of compartmental classification, in addition to the selected categories are documented in Table F.2.

Step 7. Select mixing pattern

Depending on the mapping completed relating to the preparation steps (noted in Table F.1), the inclusion of alternative mixing patterns may form part of the outbreak modelling selection. The default mixing pattern in modelling approaches is homogenous mixing of contacts. Although alternative mixing patterns reflect the interactions between contacts more realistically, it is more difficult to incorporate these mixing patterns in modelling applications.

Table F.11: Modelling approach consideration and selection guidance within the framework.

Category	Effect on decision		Modelling approach categories		
			Mathematical	Network	Simulation
Methods observed most frequently	Numerous modelling approaches exist for the three categories, however, the following approaches are observed the most frequently:		DE Regression	Small world Metapopulation	ABS
Modelling rationale	All three modelling approaches are used and suitable in the context of all modelling rationales, however, the modelling approach which is used the most frequently per modelling approach category is:	Investigate causal relationships	✓		
		Model disease transmission dynamics			✓
		Develop model and analyse behaviour		✓	
		Forecasting disease instance	✓		
		Test interventions			✓
		Investigate super spreading events			✓
Transmission mode	All three modelling approaches are used and suitable in the context of all transmission modes, however, the modelling approach(es) which are used the most frequently per transmission mode category are:	Direct contact		✓	✓
		Sexual contact	✓		
		Respiratory		✓	✓
		Body fluid		✓	✓
		Food-borne	✓		
		Water contact	✓		
		Vector-borne	✓		
Data source	All three modelling approaches are used and suitable in the context of all types of data sources, however, the modelling approaches which are used the most frequently per data source category are:	Case data			✓
		Parameters from literature	✓		
		Population estimates			✓
		Travel data		✓	
		Assumed		✓	
		None			✓

Category	Effect on decision		Modelling approach categories		
			Mathematical		
Modelling scope	All three modelling approaches are used and suitable in the context of all modelling scopes, however, when selecting a modelling approach, the modelling approach which is most frequently used for a given scope is:	General	✓		
		Global		✓	
		Intercountry		✓	
		Country	✓	✓	✓
		Provincial		✓	✓
		Small region			✓

Table F.12: Compartmental classification consideration and selection guidance within the framework.

Category	Effect on decision		Transmission mode						
			Direct contact	Sexual contact	Respira-tory	Body fluid	Food-borne	Water contact	Vector-borne
Compartmental categories in relation to the transmission mode	Modelling delay or exposure to disease	E	✓		✓	✓			✓
	Isolation from population	Q	✓		✓	✓			
	Prevent transmission with safe burial	F	✓			✓			
	Dependant on availability of (theoretical) vaccine	V	✓	✓	✓	✓		✓	
	Water-bodies are studied in relation to human populations	B W						✓	
	Mosquito populations are studied in relation to human populations	M							✓
General observation	It is not possible to recommend incorporation of compartmental classification based solely on the disease characteristics or contextual factors.Furthermore, all three broad modelling approaches are suitable to incorporate compartmental classification.								

Table F.13: Mixing consideration and selection guidance within the framework.

Category	Effect on decision		Mixing incorporated	Occurrence of inclusion
Mixing methods observed most frequently	Of alternative mixing patterns included in modelling approaches, age and social mixing are the most frequently modelled. WAIFW matrices to model probability of disease transmission between different age groups or compartmental groups are also utilised to model alternative mixing patterns.		N/A	
Transmission mode	When considering the inclusion of alternative mixing patterns in relation to the transmission mode, the following recommendations are made:	Direct contact	✓	High
		Sexual contact		N/A
		Respiratory	✓	High
		Body fluid	✓	High
		Food-borne		N/A
		Water contact	✓	Moderate
		Vector-borne	✓	Moderate
Modelling scope	Alternative mixing patterns are applied in the context of all modelling scopes, however, not all modelling scopes have equal proportions of inclusion of alternative mixing patterns. The occurrence of alternative mixing patterns in the context of the modelling scope guide the following recommendations:	General	✓	High
		Global	✓	Moderate
		Intercountry	✓	Moderate
		Country	✓	High
		Provincial	✓	Moderate
		Small region	✓	Very high
Population demographics	The following population demographic contextual factors are typically present in modelling approaches when alternative mixing patterns are included in the modelling approach:	Age and spatial spread Potentially population density	N/A	N/A
Modelling approach	Alternative mixing patterns are included in all three modelling approaches, however, based on the most frequent inclusion of age and social mixing in the context of the modelling approach, the following modelling approaches are recommended for usage of alternative mixing patterns:	Mathematical	✓	N/A
		Network		
		Simulation	✓	

If alternative mixing patterns are not deemed necessary at this stage of the modelling application, the default mixing pattern of homogeneous mixing is selected. If alternative mixing patterns are required, the following modelling considerations are used to inform the incorporation of alternative mixing pattern selection in Table F.13:

- Transmission mode (captured in Table F.4);
- Modelling scope (selected in Step 5);
- Population demographics (captured in Table F.8); and
- Modelling approach (selected in Step 6).

It is worth noting that the following population demographic factors play an important role in mixing patterns:

- Age distribution and age related susceptibility;
- Population density; and
- Spatial spread of contacts.

If additional detail is required at this stage of the modelling process, the modeller may amend the details of the population demographics (Table F.8) or the data source (Table F.9) in order to realistically incorporate the alternative mixing patterns.

Following the considerations and recommendations of this step of the framework, the selection of mixing patterns is documented in Table F.2.

Step 8. Select interventions

Depending on the mapping completed relating to the preparation steps (noted in Table F.1), intervention strategies may form part of the outbreak modelling selection. These intervention strategies relate to treatment or vaccination of individuals. If intervention strategies are required, the following modelling considerations are used to inform the incorporation of intervention strategies in Table F.14:

- Recommended strategies in relation to the transmission mode (captured in Table F.4);
- Data source (captured in Table F.9); and
- Modelling approach (selected in Step 6).

Treatment strategies

The disease transmission mode(s) is used to find potentially appropriate treatment methods in Table F.14. It is useful to note that the most frequently modelled treatment strategies relate to the reduction of contact between individuals (i.e. quarantine and hospitalisation). Similarly to previous modelling steps, the modeller has the freedom to select different or additional treatment strategies regardless

of the recommendations if these are a modelling application requirement and they are modelled realistically. Following the considerations and recommendations of this step, the treatment strategy exclusion or inclusion and selection is noted in Table F.2.

Vaccination strategies

The disease transmission mode(s) is used to find vaccination strategies relevant to the transmission modes in Table F.14. It is useful to note that the most frequently incorporated vaccination strategies are ring vaccination and a general vaccination of a proportion of the susceptible population. Additional vaccination strategies which are also available to incorporate are summarised in Table F.15.

Similarly to previous modelling considerations, the modeller has the freedom to select different or additional vaccination strategies regardless of the recommendations if this is a modelling application requirement and it is modelled realistically. Following the considerations and recommendations of this step, the vaccination strategy exclusion or inclusion and selection is noted in Table F.2.

Step 9. Select contextual factors

Depending on the decisions captured when mapping the modelling preparation (noted in Table F.1), contextual factors may form part of the outbreak modelling selection. These contextual factors relate to environmental or population demographic factors. If contextual factors are required, the following modelling considerations are used to inform the incorporation of contextual factors in Table F.16:

- Recommended environmental factors in relation to the transmission mode (captured in Table F.4);
- Recommended demographic factors in relation to the transmission mode (captured in Table F.4); and
- Data source (captured in Table F.9).

Environmental factors

The disease transmission mode(s) are used to find potentially relevant environmental contextual factors in relation to the transmission modes. Similarly to previous modelling considerations, the modeller has the freedom to include or model different or additional environmental factors regardless of the recommendations if this is a modelling application requirement and it is modelled realistically. Following the considerations and recommendations of this step, the environmental factor exclusion or inclusion and selection is noted in Table F.2.

Table F.14: Intervention consideration and selection guidance within the framework.

Category	Effect on decision		Treatment	Vaccination
Potential relevance of intervention strategies in relation to the transmission mode	When considering the inclusion of intervention strategies, the relevance of the treatment and intervention strategies in relation to the transmission mode are:	Direct contact	High	High
		Sexual contact	High	High
		Respiratory	High	High
		Body fluid	High	High
		Food-borne	Moderate	High
		Water contact	Moderate	High
		Vector-borne	Low	Low
Recommended strategies Intervention strategies in relation to the transmission mode:	The intervention strategies which are observed the most frequently in relation to the transmission mode are:	Direct contact	Quarantine Hospitalisation	A proportion of susceptible Ring
		Sexual contact	Quarantine	A proportion of susceptible Ring
		Respiratory	Quarantine Hospitalisation	A proportion of susceptible Ring
		Body fluid	Quarantine Hospitalisation	A proportion of susceptible Ring
		Food-borne	Disinfection	N/A
		Water contact	Disinfection Drug usage	A proportion of susceptible
		Vector-borne	Drug usage	N/A

Category	Effect on decision	Treatment	Vaccination
Data source	All six data sources are suitable in the context of intervention strategies, and the data source is not expected to play a role in the inclusion of intervention strategies. However, the ‘case data’ and ‘parameters from the literature’ data sources are observed in the highest proportion of modelling approaches which included treatment and vaccination strategies.		
Modelling approach	All three modelling approaches are suitable in the context of intervention strategy inclusion and the selection of a modelling approach is not expected to play a role in the inclusion of intervention strategies.		

Table F.15: Additional vaccination strategies.

Name of strategy	Strategy	Advantages	Disadvantages
Ring	Identify individuals with disease infection, then trace contacts for vaccination.	Minimises the required amount of vaccine doses	Highly effective contact tracing required to limit disease transmission
Targeted	Vaccination of an entire population within a specific city or district	Effective strategy if used in an eradication campaign to contain geographically localised disease transmission	Only effective in the context of prior high levels of herd immunity
Mass	Vaccination of an entire population in a country	Effective at preventing and protecting against disease transmission across large areas	Quick vaccination of large quantities of individuals are required to be effective
Prophylactic	Preventative vaccination before disease outbreak	Very effective at stopping spread of disease when used for an entire population	High long term cost when used to protect an entire population
Pulse	Repeated intervals of vaccination targeting a specific age range or a group of susceptible individuals	Relative low levels of vaccination are required to ensure disease eradication	Timing of pulses critical in the effectiveness of the strategy

Table F.16: Contextual factor consideration and selection guidance within the framework.

Category	Effect on decision		Contextual factors	
			Linked to disease propagation	Modelled
Potential relevance of environmental factors in relation to the transmission mode	When considering the inclusion of environmental contextual factors, the relevance to the transmission mode are:	Direct contact	Low	
		Sexual contact	Low	
		Respiratory	Moderate	
		Body fluid	High	
		Food-borne	High	
		Water contact	High	
		Vector-borne	Very high	
Recommended environmental factors to consider: Environmental factors in relation to the transmission mode	The environmental contextual factors which are observed the most frequently in relation to the transmission mode are:	Direct contact	N/A	Seasonality
		Sexual contact	N/A	
		Respiratory	Climate & seasonality & rainfall	Seasonality
		Body fluid	N/A	Seasonality
		Food-borne	Climate & rainfall	
		Water contact	Climate & temperature & rainfall	
		Vector-borne	Climate & temperature & rainfall	
Potential relevance of demographic factors in relation to the transmission mode	When considering the inclusion of population demographic contextual factors, the relevance of the to the transmission mode are:	Direct contact	Very high	
		Sexual contact	Low	
		Respiratory	Very high	
		Body fluid	High	
		Food-borne	Moderate	
		Water contact	Very high	
		Vector-borne	Moderate	

Category	Effect on decision		Contextual factors	
			Linked to disease propagation	Linked to disease propagation
Recommended demographic factors to consider: Population demographic factors in relation to the transmission mode	The population demographic contextual factors which are observed the most frequently in relation to the transmission mode are:	Direct contact	Age & population density & migration & spatial spread	
		Sexual contact	N/A	
		Respiratory	Age & population density & migration & spatial spread	
		Body fluid	Age & population density & migration & spatial spread	
		Food-borne	Spatial spread & socio economic	
		Water contact	Spatial spread & socio economic	
		Vector-borne	Spatial spread & socio economic	Age & spatial spread
Data source	The only two data sources which were used in the context of all contextual factors were case data and parameters from the literature. Population estimates and travel data are only used in the context of population demographic factors.			

Population demographic factors

The disease transmission mode(s) are used to find relevant population demographic contextual factors in relation to the transmission modes. Similarly to previous modelling considerations, the modeller has the freedom to include or model different or additional population demographic factors regardless of the recommendations if it is a modelling application requirement and is modelled realistically. It is useful to note that the most frequently included demographic factors are spatial spread of individuals, population density, migration and age stratification of individuals within the population. Following the considerations and recommendations of this step, the population demographic exclusion or inclusion and selection is noted in Table F.2.

Step 10. Validate model

Following the modelling application selection and implementation, the model is validated to ensure that the modelling application and modelling results accurately reflect the disease outbreak. The following questions guide the validation process:

- Does the model answer the research question (i.e. modelling rationale and modelling goals)?
- Is the model comprehensible (i.e. ability to analyse and examine the model)?
- Is the model believable (i.e. an accurate reflection of reality)?
- Does the model fit the data (i.e. verify the model operation)?

The selection of a fitting method is left to the discretion of the user.

A checklist is available for use in Table F.2 to ensure the validation questions are considered and addressed, in addition to noting the selection of a fitting method.

F.3 Case study

F.3.1 Case study design considerations

The following case types are used to guide the case study design, namely:

- **Exploratory**, when the case study is used to analyse events with no particular single set of outcomes;
- **Descriptive**, when an event or phenomenon is described according to the occurrence in a real-life context; and
- **Instrumental**; when the case study is of secondary interest and is used to gain insight to a problem or aid in refinement of a theory.

The above mentioned guidelines are well-suited to explore and describe the intended use of the framework.

F.3.2 Case study

The fairly recent global Zika outbreak is used as the studied disease in the case study. The following hypothetical situation is constructed to demonstrate the functioning of the framework in supporting the modelling process:

A major outbreak of Zika virus is in progress in Brazil, with the virus currently being transmitted beyond the country borders. There are no prophylactic vaccines available for use and no confirmed disease treatment, apart from supportive treatment. It is suspected that multiple transmission routes exist. Furthermore, the disease has not been modelled extensively in the past.

The modeller is tasked with selecting a modelling approach to investigate relevant factors which may suggest the prevalence of the disease in the area. As few modelling approaches are completed in the past, the influence of relevant factors are first considered, prior to establishing a disease transmission model. Confirmed clinical case data for large cities are available to the modeller.

F.3.3 Framework walkthrough

In this section, a high-level walkthrough of the framework through each of the steps is presented, as the modeller would use and consider inclusions in a modelling approach

Step 0. Documentation

This steps runs concurrently throughout the modelling process, and the user is reminded that documentation of:

- Step 1 – 4 is done according to the template of Table F.1; and

- Step 5 – 10 is done according to the template of Table F.2.

The completed preparation documentation and outbreak selection documentation is captured to Table F.23 and Table F.24, respectively and is presented at the end of the section.

Step 1. Select modelling rationale

As stated in the case study, no extensive modelling has been completed for the Zika virus. In the context of the modelling task, which is to investigate the drivers of disease prevalence, the 'investigate causal relationships' modelling rationale is selected and noted in Table F.23. The importance of a selection of modelling considerations in the context of the selected modelling rationales are described in Table F.17 (this is an excerpt of only the relevant information from Table F.3) and used in Step 2 and Step 3.

Table F.17: Modelling rationale selection.

Selected modelling rationale	Modelling approach	Mixing patterns	Intervention and control	Contextual factors
Investigate causal relationships	Strong	Context	Context	Strong

Step 2. Map disease characteristics

From the GIDEON database, the vectors and vehicles of disease transmission are as follows:

- Vector: mosquitoes; and
- Vehicle: sexual contact, saliva, blood transfusion, breast-feeding.

Using Table F.5 the transmission modes are determined and noted in Table F.18. From the literature, the incubation period is also noted. This is used to potentially inform realistic transmission parameters.

The selected modelling rationales recommend the contextual inclusion of intervention strategies, if this is a modelling requirement. Based on the case study, no vaccines are available to use against Zika infection and no treatment other than supportive treatment is available (noted in Table F.19). In view of the modelling goal that does not require intervention strategies in the modelling approach, Table F.14 and Table F.15 are not used to extract intervention strategy recommendations and the exclusion of intervention strategies from the modelling approach is noted in Table F.23.

Table F.18: Disease characteristics.

Category		Transmission modes present (✓ / ✗)	Modelling assumptions	Additional information
Incubation period (days)	Lower	N/A	3	Symptoms typically last for 2-7 days
	Upper		14	
Disease transmission mode	Direct contact	✓	Not used in model	GIDEON vehicle breast feeding, assumed very rare
	Sexual contact	✓	Not used in model	Not a model requirement
	Respiratory			
	Body fluid	✓	Not used in model	Transfusion of blood
	Food-borne			
	Water contact			
	Vector-borne	✓		Primary transmission mode investigated

Table F.19: Disease intervention strategies and modelling assumptions.

Category	Accounted for (✓ / ✗)	Modelling assumptions	Additional information
Availability of vaccine	✗		No vaccine currently available. Investigation of theoretical vaccine not currently a priority
Treatment options	✗		No current treatment available

Step 3. Map contextual characteristics

Based on the selected modelling rationales, contextual characteristics are a strong requirement for the modelling approach, as one of the overarching modelling tasks are the investigation of factors

which could potentially explain disease prevalence. Based on the transmission mode, the relevant factors are extracted from Table F.16. The user may select both population demographics (noted in Table F.21) and environmental factors (noted in Table F.20), however, only the vector-borne transmission route is studied in this modelling approach and not the other transmission routes which relate to contact between humans (i.e. sexual contact). Only environmental factors are, therefore, included in the modelling approach and noted in Table F.23. As more information on the disease dynamics become available, future work could include detailed incorporation of population demographic factors.

Table F.20: Environmental factors contextual factors.

Category	Accounted for (✓ / ✗)	Modelling assumptions	Additional information
Seasonality	✓		Correlation to climatic factors?
Climatic factors	✓	Temperature and rainfall	Potential drivers of disease prevalence
Additional factors	✗		

Table F.21: Population demographic contextual factors.

Category	Accounted for (✓ / ✗)	Modelling assumptions	Additional information
Age structure	✗		No data on age related disease prevalence. Additionally not a modelling requirement
Spatial spread	✗		Not studied in detail and not a modelling requirement
Mixing	✗		
Migration	✗		
Socio-economic	✗		
Additional factors	✗		

The selected modelling rationales recommend the contextual inclusion of alternative mixing patterns, if this is a modelling requirement. If population demographics are studied in more detail, alternative

mixing patterns could form part of the modelling approach. In this modelling application, however, alternative mixing patterns are not a modelling requirement and the exclusion thereof from the modelling approach is noted in Table F.23.

Step 4. Determine resources

The monthly case data of reported clinical cases are available to the modeller. This is important to note, especially considering that Zika and Dengue share similar symptoms, and the availability of monthly case data therefore enables the modeller to ensure that only Zika disease instances are considered. Furthermore, monthly climate data on rainfall is documented and availability of this data is noted by the user. The data source considerations are noted in Table F.22.

Table F.22: Mapping quality and source of data.

Category	Data source used (✓ / ✗)	Modelling assumptions	Additional information
Case data	✓	Monthly data on confirmed clinical cases Monthly climate data	As the incubation period of the disease is between 3-14 days, monthly data is suitable in order to investigate the effect of climatic variables on disease prevalence
Parameters from literature	✗		
Population estimates	✗		
Travel data	✗		
Assumed	✗		
None	✗		

Step 5. Select modelling scope

The information provided in Table F.10 is used to guide the selection of the modelling scope, based on the modelling rationale, the transmission mode, and the data source. Based on the modelling rationale selection, the recommended scopes include a country, provincial and small region scope. In relation to the transmission mode (vector-borne), the recommend scope is a provincial or small region scope. As case data is available for the modelling approach, all modelling scopes apart from

a general scope are available to select. In this context, however, the data source relates to a small region. This could be aggregated to construct a provincial model, however, the modeller selects a small region scope. This selection is noted in Table F.24, in addition to the line of reasoning for this selection.

Step 6. Select modelling approach

The information provided in Table F.11 is used to guide the selection of a modelling approach, based on the modelling rationale and the transmission mode. Based on the modelling rationale selection and the disease transmission mode, a mathematical approach is frequently used. With further considerations, the simulation approach is not practical, as actors are not modelled in the approach. A similar line of reasoning eliminates the selection of network modelling. In the mathematical approaches, regression is selected, as this is the most suitable method to investigate the effect of the climate variables. Although a simulation approach is proportionately used the most frequently for the selected modelling scope, Table F.11 states that all three modelling approaches are suited for the modelling scopes. Additionally, compartmental classification is not included, as individual disease states are not modelled. The modelling approach selection is noted in Table F.24, in addition to the line of reasoning for this selection.

Step 7. Select mixing patterns

According to Table F.23, alternative mixing patterns of individuals are not considered in this modelling approach. Individuals are assumed to mix homogenously and the selection of homogenous mixing is noted in Table F.24, in addition to the line of reasoning for this selection.

Step 8. Select interventions

According to Table F.23, intervention strategies are not considered in this modelling approach. Therefore, the exclusion of intervention strategies from the modelling approach is noted in Table F.24, in addition to the line of reasoning for this exclusion.

Step 9. Select contextual factors

According to Table F.23, only environmental contextual factors are considered for inclusion in this modelling approach. Therefore, the inclusion of environmental factors in the modelling approach is noted in Table F.24, in addition to the line of reasoning for the selection of environmental and the exclusion of population demographic factors as noted in Table F.20 and Table F.21, respectively.

Step 10. Validate model

In this stage, the modeller reviews the modelling approach according to the four questions presented in the validation category in Table F.24. In addition to addressing these questions, the fitting method used in the modelling approach to ensure that the model is a realistic representation of the disease outbreak is noted, together with the line of reasoning for the selection of the fitting method and the results of the fitting method.

F.3.4 Conclusion

A theoretical case study is presented with background information on a disease outbreak. This demonstrates how a user would use the framework to systematically document the decision relating to the inclusion of relevant factors and considerations as well as the selection of a modelling approach. This systematic documentation process ensures that the most relevant modelling considerations are incorporated in the modelling approach, while considering the context of the given disease outbreak. Much of the selection would relate to the context of the disease outbreak and no hard and fast rules are presented which are applicable to all scenarios. Instead, suggestions are made based on relationships observed in literature, to guide the decision-making process and propose feasible options.

Table F.23: Outbreak preparation documentation.

Modelling rationale	Selected (✓ / ✗)	Treatment included (✓ / ✗)	Vaccination included (✓ / ✗)	Environmental factors included (✓ / ✗)	Demographics included (✓ / ✗)	Alternative mixing patterns included (✓ / ✗)
Model disease dynamics	✗	✗	✗	✓	✗	✗
Investigate causal relationships	✓					
Investigate super spreading events	✗					
Forecasting disease instance	✗					
Develop model and analyse behaviour	✗					
Test interventions	✗					

Table F.24: Outbreak modelling documentation.

Category		Selection (✓)	Methods and/or categories selected	Modelling assumptions	Additional comments
Modelling scope	General		N/A		Selection based on recommendations in relation to the transmission mode and modelling rationale. Case data may be aggregated to model on a provincial scope, however, small region is selected. Additionally, the data supports the use of this modelling scope.
	Global				
	Intercountry				
	Country				
	Provincial				
	Small region	✓			
Modelling application	Mathematical	✓	Regression	Most suited approach to investigate causal relationships	Selection based on recommendations in relation to the transmission mode and modelling rationale.
	Network				
	Simulation				
	Compartmental classification		Not used	Not used	Individual disease states are not modelled
Mixing patterns	Homogeneous	✓	Homogeneous		Detailed mixing not required
	Alternative				
Intervention and control	None	✓			
	Treatment				No treatment strategies available
	Vaccination				No vaccines available, investigation of theoretical vaccine not currently a priority
Contextual factors	None				
	Environmental	✓		Correlations between factors and prevalence	Rainfall and temperature suspected to affect disease dynamics
	Demographics				Not studied in detail
Validate model	Does the model answer research question?	✓	N/A		
	Is the model comprehensible?	✓			
	Is the model believable?	✓			
	Does the model fit the data?	✓			
	Fitting methods used:	✓	Least squares	Commonly used for this mathematical approach	Correlation: 0.8 rainfall 0.4 temperature
Future work		✓	Investigate effect of population density and migration on disease prevalence		Test theoretical vaccine to prepare for availability of newly developed vaccine

F.4 Validation and feedback

The validation questionnaire which is used for feedback and complete the validation of the framework is produced in Table F.25. The framework is validated against a selection of close ended questions relating to purpose, functionality and performance measures, in addition to open ended questions. This is presented in a separate PDF document titled ‘ValidationQuestionnaire’ with interactive fields for answer selection and feedback comments.

Table F.25: Validation questionnaire.

Close ended questions						
	Questions	Criteria				
		Disagree strongly	Disagree moderately	Indifferent	Agree moderately	Agree strongly
Purpose	The framework is able to assist modelling practitioners in the context of a disease outbreak.					
		Comments:				
Function	The framework is capable of informing the user of the most relevant modelling considerations.					
		Comments				
	The framework is capable of guiding selection of modelling considerations.					
		Comments:				
	The most relevant steps in the modelling process are presented in the framework.					
		Comments:				
	The framework steps are clear and concise.					
		Comments:				
	The framework steps are easy to follow.					
		Comments:				
Performance	The framework modelling steps follow each other logically.					
		Comments:				
	The contextualization of the outbreak characteristics are useful to guide the modelling process.					
		Comments:				
	The framework ensures thoroughness in the modelling process.					
		Comments:				
	The documentation step of the framework serves as a useful checklist for the modelling process.					
		Comments:				
	The documentation step of the framework is useful to assist future modelling efforts.					
		Comments				
	I would recommend the framework use in a modelling context where a rapid response is required and there are no / few previous instances where the disease has been modelled in literature.					
		Comments:				

Open ended questions	
Criticism and concerns?	
Additional feedback or comments?	
Checklist	
Close ended questions completed	
Open ended questions completed	
Form saved prior to closing	

Appendix G (Chapter 6)

Supporting information to Chapter 6 is presented within this appendix. This includes additional information extracted from the GIDEON database, the questionnaire template constructed for feedback responses and the completed validation questionnaires following the semi-structured interviews.

G.1 Disease characteristics as extracted from the GIDEON database

Disease

Zika

Agent

Virus, Flaviviridae, Flavivirus: Zika virus

Reservoir

Human, Mosquito, Monkey

Vector

Mosquito

Vehicle

Sexual contact, Saliva, Blood transfusion, Breast-feeding

Incubation Period

5d - 8d (range 2d - 15d)

Diagnostic Tests

- Viral isolation (blood)
- Serology
- Nucleic acid amplification.

Typical Adult Therapy

Supportive

Typical Paediatric Therapy

As for adult

Clinical Hints

- A mild dengue-like illness with conjunctivitis and a pruritic maculopapular rash that starts on the face and spreads to the rest of the body;
- Joint pain is common
- Myalgia, retroorbital pain and leg edema may occur
- May be associated with Guillain-Barre syndrome and congenital neurological defects

G.2 Validation questionnaire

The validation questionnaire is presented in Table G.1 on the following page.

Table G.1: Validation questionnaire.

Close-ended questions						
	Questions	Criteria				
		Disagree strongly	Disagree moderately	Indifferent	Agree moderately	Agree strongly
Purpose	The framework is able to assist modelling practitioners in the context of a disease outbreak.					
		Comments:				
Function	The framework is capable of informing the user of the most relevant modelling considerations.					
		Comments				
	The framework is capable of guiding selection of modelling considerations.					
		Comments:				
	The most relevant steps in the modelling process are presented in the framework.					
		Comments:				
	The framework steps are clear and concise.					
		Comments:				
	The framework steps are easy to follow.					
		Comments:				
Performance	The framework modelling steps follow each other logically.					
		Comments:				
	The contextualization of the outbreak characteristics are useful to guide the modelling process.					
		Comments:				
	The framework ensures thoroughness in the modelling process.					
		Comments:				
	The documentation step of the framework serves as a useful checklist for the modelling process.					
		Comments:				
	The documentation step of the framework is useful to assist future modelling efforts.					
		Comments				
	I would recommend the framework use in a modelling context where a rapid response is required and there are no / few previous instances where the disease has been modelled in literature.					
		Comments:				

Open-ended questions	
Criticism and concerns?	
Additional feedback or comments?	
Checklist	
Close-ended questions completed	
Open-ended questions completed	
Form saved prior to closing	

G.3 Completed validation questionnaires

The questionnaires from the validation interviews as completed by the SMEs are presented in no particular order below in Table G.2 – Table G.6.

Table G.2: Completed questionnaire 1.

Close-ended questions						
	Questions	Criteria				
		Disagree strongly	Disagree moderately	Indifferent	Agree moderately	Agree strongly
Purpose	The framework is able to assist modelling practitioners in the context of a disease outbreak.				✓	
Function	The framework is capable of informing the user of the most relevant modelling considerations.				✓	
	The framework is capable of guiding selection of modelling considerations.				✓	
	The most relevant steps in the modelling process are presented in the framework.				✓	
	The framework steps are clear and concise.		✓			
	The framework steps are easy to follow.		✓			
Performance	The framework modelling steps follow each other logically.			✓		
	The contextualization of the outbreak characteristics are useful to guide the modelling process.				✓	
	The framework ensures thoroughness in the modelling process.				✓	
	The documentation step of the framework serves as a useful checklist for the modelling process.				✓	
	The documentation step of the framework is useful to assist future modelling efforts.				✓	
	I would recommend the framework use in a modelling context where a rapid response is required and there are no / few previous instances where the disease has been modelled in literature.				✓	

Comments to close-ended questions	
Question	Comment
N/A	
Open-ended questions	
Criticism and concerns?	I found the document a bit unclear: for example, "biological problem" and "disease" and "infectious disease outbreak" are used interchangeably. As another example, it is never clearly stated that a literature review was performed to identify the various relevant characteristics so when reference was made to the literature review, I was not sure what that was or why it was done. The interventions considered are Treatment and Vaccination. However, one must also consider Prevention and Mitigation during a disease outbreak. Prevention, for example, might include social distancing.
Additional feedback or comments?	I have marked the document with specific comments throughout and sent it back to the candidate.

Table G.3: Completed questionnaire 2.

Close-ended questions						
	Questions	Criteria				
		Disagree strongly	Disagree moderately	Indifferent	Agree moderately	Agree strongly
Purpose	The framework is able to assist modelling practitioners in the context of a disease outbreak.				✓	
Function	The framework is capable of informing the user of the most relevant modelling considerations.					✓
	The framework is capable of guiding selection of modelling considerations.					✓
	The most relevant steps in the modelling process are presented in the framework.					✓
	The framework steps are clear and concise.				✓	
	The framework steps are easy to follow.				✓	
Performance	The framework modelling steps follow each other logically.					✓
	The contextualization of the outbreak characteristics are useful to guide the modelling process.					✓
	The framework ensures thoroughness in the modelling process.					✓
	The documentation step of the framework serves as a useful checklist for the modelling process.					✓
	The documentation step of the framework is useful to assist future modelling efforts.					✓
	I would recommend the framework use in a modelling context where a rapid response is required and there are no / few previous instances where the disease has been modelled in literature.					✓

Comments to close-ended questions	
Question	Comment
The framework steps are easy to follow.	The large number of tables (although very helpful) did sometimes disrupt the reading flow, making it difficult to follow.
The documentation step of the framework is useful to assist future modelling efforts.	Yes. The final table provides a concise summary of what was done, assumptions made, etc., making it very useful for future work.
I would recommend the framework use in a modelling context where a rapid response is required and there are no / few previous instances where the disease has been modelled in literature.	I would even recommend the framework for use in a modelling context that does not require a "rapid response" - it could serve as a checklist to evaluate your modelling efforts and how it agrees with what is typically done in literature.

Open-ended questions	
Criticism and concerns?	Only that which I mentioned in the comments above.
Additional feedback or comments?	Not sure whether this is possible, but this could make a very useful online application/tool where the user could make their selections/choices in the tables and type their assumptions and additional comments. The application can then recommend, for example, a modelling scope (Table F.10) based on previously selected rationale, transmission, etc. As an output the application can provide a summary table (similar to Table F.24).

Table G.4: Completed questionnaire 3.

Close-ended questions						
	Questions	Criteria				
		Disagree strongly	Disagree moderately	Indifferent	Agree moderately	Agree strongly
Purpose	The framework is able to assist modelling practitioners in the context of a disease outbreak.					✓
Function	The framework is capable of informing the user of the most relevant modelling considerations.					✓
	The framework is capable of guiding selection of modelling considerations.					✓
	The most relevant steps in the modelling process are presented in the framework.					✓
	The framework steps are clear and concise.				✓	
	The framework steps are easy to follow.				✓	
Performance	The framework modelling steps follow each other logically.					✓
	The contextualization of the outbreak characteristics are useful to guide the modelling process.				✓	
	The framework ensures thoroughness in the modelling process.				✓	
	The documentation step of the framework serves as a useful checklist for the modelling process.					✓
	The documentation step of the framework is useful to assist future modelling efforts.					✓
	I would recommend the framework use in a modelling context where a rapid response is required and there are no / few previous instances where the disease has been modelled in literature.				✓	

Comments to close-ended questions	
Question	Comment
N/A	
Open-ended questions	
Criticism and concerns?	The key concern I have with the framework is that it is heavily dependent on the modeller's choices; i.e. what the modeller selects to include in the selection criteria vs. what should be included given the specific case. However, during the validation discussion, this was debated and it seems like that the framework is robust enough that sections that is heavily reliant on the modellers preferences are not the areas that provide the most significant guidance in terms of the outcome. My suggestion therefore would be that the candidate carefully evaluate and discuss the sensitivities of the framework.
Additional feedback or comments?	I think this is a very valuable framework, especially given the vast number of possibilities within the disease modelling space - this framework will not only guide users in specific cases, but will also contribute towards the establishment of a coherent stock of knowledge where trends in disease modelling could in turn be observed and provide feedback into frameworks such as this to continuously improve our abilities to contribute towards effectively dealing with communicable diseases.

Table G.5: Completed questionnaire 4.

Close-ended questions						
	Questions	Criteria				
		Disagree strongly	Disagree moderately	Indifferent	Agree moderately	Agree strongly
Purpose	The framework is able to assist modelling practitioners in the context of a disease outbreak.				✓	
Function	The framework is capable of informing the user of the most relevant modelling considerations.				✓	
	The framework is capable of guiding selection of modelling considerations.					✓
	The most relevant steps in the modelling process are presented in the framework.					✓
	The framework steps are clear and concise.					✓
	The framework steps are easy to follow.				✓	
Performance	The framework modelling steps follow each other logically.				✓	
	The contextualization of the outbreak characteristics are useful to guide the modelling process.					✓
	The framework ensures thoroughness in the modelling process.				✓	
	The documentation step of the framework serves as a useful checklist for the modelling process.				✓	
	The documentation step of the framework is useful to assist future modelling efforts.			✓		
	I would recommend the framework use in a modelling context where a rapid response is required and there are no / few previous instances where the disease has been modelled in literature.				✓	

Comments to close-ended questions	
Question	Comment
The framework is able to assist modelling practitioners in the context of a disease outbreak.	I agree that the modelling knowledge of a novice with suffice. However, I think some health systems knowledge (at least vocabulary will also be required).
The framework is capable of informing the user of the most relevant modelling considerations.	I assume that our understanding of the "most relevant" modelling considerations are the same.
The contextualization of the outbreak characteristics are useful to guide the modelling process.	Yes, this is very important, since you assume novice modelling experience and not necessarily health systems knowledge.
The documentation step of the framework is useful to assist future modelling efforts.	Difficult to say if the context of the future modelling efforts are not known.
I would recommend the framework use in a modelling context where a rapid response is required and there are no / few previous instances where the disease has been modelled in literature.	This is somewhat of a leading question, but I do agree.

Open-ended questions	
Criticism and concerns?	Are the decisions supported by this framework really of such a frequent and repetitive nature that it warrants the development of this framework?
Additional feedback or comments?	I think the framework has also value not only for the practitioner so guide the model building process, but also as frame of reference for future research projects.

Table G.6: Completed questionnaire 5.

Close-ended questions						
	Questions	Criteria				
		Disagree strongly	Disagree moderately	Indifferent	Agree moderately	Agree strongly
Purpose	The framework is able to assist modelling practitioners in the context of a disease outbreak.					✓
Function	The framework is capable of informing the user of the most relevant modelling considerations.					✓
	The framework is capable of guiding selection of modelling considerations.				✓	
	The most relevant steps in the modelling process are presented in the framework.					✓
	The framework steps are clear and concise.					✓
	The framework steps are easy to follow.				✓	
Performance	The framework modelling steps follow each other logically.					✓
	The contextualization of the outbreak characteristics are useful to guide the modelling process.					✓
	The framework ensures thoroughness in the modelling process.				✓	
	The documentation step of the framework serves as a useful checklist for the modelling process.					✓
	The documentation step of the framework is useful to assist future modelling efforts.					✓
	I would recommend the framework use in a modelling context where a rapid response is required and there are no / few previous instances where the disease has been modelled in literature.					✓

Comments to close-ended questions	
Question	Comment
The framework is able to assist modelling practitioners in the context of a disease outbreak.	Good framework for guiding a novice
The framework is capable of guiding selection of modelling considerations.	Some experience may be required, but good guidance provided.
The framework steps are easy to follow.	Given the person has some experience, yes. For non-experienced person, it may not be easy…but possible.
The framework ensures thoroughness in the modelling process.	This is dependent on the level of expertise of the person applying the framework?
I would recommend the framework use in a modelling context where a rapid response is required and there are no / few previous instances where the disease has been modelled in literature.	It is guiding and not overly specific - this will be helpful.

Open-ended questions	
Criticism and concerns?	
Additional feedback or comments?	I do not have much experience in this field, but find that it provides good guidance throughout the process of contextualizing aspects regarding the disease outbreak and then also modelling it well. I find the validation step valuable and also believe that applying this framework will support documenting the complete approach. At first I thought the environmental factors and the modelling approaches where a bit vague, but the framework-designer had a good response to why this so. For example, only stating mathematically does not say much as there are so many methods, but apparently from the literature, the methods used are already limited, and going in too much detail will not be helpful. I would also have considered war-stricken areas as it could affect the considerations regarding providing vaccinations / how to go about 'treating' disease. Also, it might increase probability of transmission with e.g. mosquito / flies attracted by blood? but I understand that the data on this might be too little.

Open-ended questions	
Additional feedback or comments?	The case study was good, I would have maybe tried to apply one more disease transmission method - or motivate better why only one was applied. The case study did however convey that the framework can be successfully implemented and steer the process logically. The specifics of modelling and decisions made are left to the person using the framework. This is also good, as it can be applied to various settings. All in all - I thought the framework is done thoroughly, can be successfully implemented and potentially a valuable addition to the literature and practice.

Appendix H (Disease dataset references)

The literature instances for each disease which forms part of the infectious disease modelling dataset is referenced within this appendix in according to the sections as noted in Table H.1.

Table H.1: Sections in Appendix H in which the literature instances that are included in the dataset are referenced for each disease selected in the structured literature review.

Disease	Section in which the literature instances are referenced
Diphtheria	§H.1
Measles	§H.2
Mumps	§H.3
Pertussis	§H.4
Polio	§H.5
Rotavirus	§H.6
Rubella	§H.7
Cholera	§H.8
Dengue	§H.9
Ebola	§H.10
H1N1	§H.11
Malaria	§H.12
SARS	§H.13
Smallpox	§H.14

H.1 Diphtheria

(Sornbundit et al. 2017; Trisilowati & Fitri 2014)

H.2 Measles

(Bai & Liu 2015; Bharti et al. 2010; Bhattacharyya & Ferrari 2017; Chiogna & Gaetan 2004; Coudeville 2003; Finkenstadt & Grenfell 2000; Garba et al. 2017; Getz et al. 2016; Goufo et al. 2014; Lima 2009; Liu et al. 2015; Ma et al. 2017; Maitani & Ishikawa 2012; Momoh et al. 2013; Neal & Xiang 2017; Pang et al. 2015; Rozhnova & Nunes 2010; Sharmin & Rayhan 2012; Stone et al. 2000; Thompson & Badizadegan 2017; Trentini et al. 2017; Verdasca et al. 2005; Word et al. 2010; Xia et al. 2004; Zekri & Clerc 2002)

H.3 Mumps

(Lee & Kim 2010; Li et al. 2016; Liu et al. 2017; Polgreen et al. 2010; Porter & Oleson 2016)

H.4 Pertussis

(Bento & Rohani 2016; Campbell et al. 2016; Dafilis et al. 2014; De Greeff et al. 2009; Dottori & Fabricius 2015; Huang et al. 2017; Pesco et al. 2015; Roberts 2000; Rohani et al. 2010; Rostamy & Mottaghi 2016; Rozenbaum et al. 2012; Safan et al. 2013; Sanstead et al. 2015; Verdasca et al. 2005; Yeung et al. 2017; Zeng et al. 2016)

H.5 Polio

(Blake et al. 2014; Khan & Khan 2016; Mayer et al. 2013; Okuonghae et al. 2015; Sutradhar 2008; Tebbens et al. 2005; Wilder-Smith et al. 2015; Yaari et al. 2016)

H.6 Rotavirus

(Darti 2016; Omondi et al. 2015; Paynter 2016; Pitzer et al. 2009; Shim et al. 2006; Van Gaalen et al. 2017)

H.7 Rubella

(Buonomo 2011a; Buonomo 2011b; Iannelli & Manfredi 2007; Jazbec et al. 2004; Maltz & Fabricius 2016; Metcalf et al. 2012; Sfikas et al. 2007; Thompson & Badizadegan 2017)

H.8 Cholera

(Abrams et al. 2013; Alexanderian et al. 2011; Andrews & Basu 2011; Augustijn et al. 2016; Azaele et al. 2010; Bakhtiar 2016; Baracchini et al. 2016; Berge et al. 2017; Bertuzzo et al. 2016; Brauer et al. 2013; Cai et al. 2017; Cash et al. 2008; Codeço 2001; Collins & Duffy 2016; Collins & Govinder 2016; Crooks & Hailegiorgis 2013; Cui et al. 2014; De Magny et al. 2008; Gani & Swift 2009; Gazi et al. 2010; Hove-Musekwa et al. 2011; Javidi & Ahmad 2014; Kelly et al. 2016; Khan et al. 2015; Koelle 2009; Koepke et al. 2016; Leckebusch & Abdussalam 2015; Lemos-Paiao et al. 2017; M.-T. Li et al. 2013; Matsuda et al. 2008; Mukandavire et al. 2011; Nishiura et al. 2017; Njagarah & Nyabadza 2014; Ohtomo et al. 2010; Osei et al. 2012; Panja et al. 2016; Pascual et al. 2008; Pasetto et al. 2017; Paz 2009; Perez-Saez et al. 2017; Posny et al. 2016; Posny & Wang 2014; Rahmi et al. 2016; Rebaudet et al. 2016; Righetto et al. 2013; Robertson et al. 2013; Samadder et al. 2014; Sebastian et al. 2015; Shuai & Van den Driessche 2015; Shuai & Van den Driessche 2013; Sun et al. 2017; Tian et al. 2013; Tuite et al. 2011; Wang & Liao 2012; Wang & Modnak 2011; Wang et al. 2016; Wang & Wang 2017; Wang & Cao 2015; Wang & Wei 2013; Yang & Qiu 2014; Zhou & Cui 2011; Zhou & Cui 2013; Zhou et al. 2017)

H.9 Dengue

(Adde et al. 2016; Amaku et al. 2016; Anggraeni et al. 2017; Anno et al. 2015; Astuti et al. 2017; Atique et al. 2016; Barmak et al. 2016; Cheng et al. 2017; Gu et al. 2016; Kang & Aldstadt 2017; Lee et al. 2017; Li et al. 2017; Lizarralde-Bejarano et al. 2017; Lopez et al. 2016b; Lopez et al. 2016a; Martınez-Bello et al. 2017; Mathulamuthu et al. 2016; Morin et al. 2015; Munoz et al. 2016; Qi et al. 2015; Ren et al. 2017; Rocha et al. 2016; Sardar et al. 2015; Sharmin et al. 2015; Sumi et al. 2017; Talagala 2015; Thiruchelvam et al. 2017; Wu & Wong 2017; Zhang et al. 2016)

H.10 Ebola

(Ahmad et al. 2016; Ajelli et al. 2016; Al-Darabsah & Yuan 2016; Area et al. 2015; Area et al. 2017; Azizah et al. 2017; Bai et al. 2016; Berge et al. 2016; Browne et al. 2015; Burch et al. n.d.; Camacho et al. 2015; Chen 2015; Conrad et al. 2016; Dike et al. 2016; Do & Lee 2016; Espinoza et al. 2016; Goufo et al. 2016; Grigorieva & Khailov 2015; Hu et al. 2015; Irwan et al. 2017; Khaleque & Sen 2017; Kramer et al. 2016; Kucharski et al. 2015; Kucharski et al. 2016; Lau et al. 2017; Leander et al. 2016; Legrand et al. 2007; Lewnard et al. 2014; Li & Mohebbi 2015; Merler et al. 2015; Ndanguza et al. 2013; Pell et al. 2016; Rachah & Torres 2015; Rachah & Torres 2016; Rainisch et al. 2015; Ristic & Dawson 2016; Roy & Upadhyay 2017; Salem & Smith 2016; Sanchez & Sanchez 2015; Sato et al. 2015; Shen et al. 2015; Siettos et al. 2015; Siettos et al. 2016b; Siettos et al. 2016a; Tithi & Hasan 2015; Tsanou et al. 2017; Tulu & Tian 2017; Tulu et al. 2017; Valdez et al. 2015; Vinson et al. 2016; Webb & Browne 2016; Xia et al. 2015; Yan 2015; Zhang et al. 2015)

H.11 H1N1

(Andradóttir et al. 2011; Apolloni et al. 2013; Balcan et al. 2009; Chen 2010; Chong & Zee 2012; Eames 2014; Flahault et al. 2009; Ge et al. 2011; González-Parra et al. 2014; Hu et al. 2012; Imran et al. 2016; Jin et al. 2011; Lam et al. 2011; X. Li et al. 2013; Maeno 2016; Ming et al. 2016; Mostaço-Guidolin et al. 2012; Ponnambalam et al. 2016; Rathore et al. 2012; Rausanu & Grosan 2014; Song et al. 2015; Tan et al. 2013; Upadhyay et al. 2014; Weng & Ni 2015; Yarmand et al. 2013; Zhong 2017)

H.12 Malaria

(Abboubakar et al. 2016; Adeola et al. 2017; Arifin et al. 2015; Forouzannia & Gumel 2015; Laguna et al. 2017; Lingala 2017; Ngonghala et al. 2016; Turner et al. 2015; Xue & Scoglio 2015)

H.13 SARS

(Fujie & Odagaki 2007; Gao et al. 2012; Gumel et al. 2006; Hsieh et al. 2006; Hsieh et al. 2007; Huang 2010; Huo n.d.; Jinping et al. 2004; Kong et al. 2016; Lai et al. 2013; Maeno 2016; Maeno 2010; Maki & Hirose 2013; Masuda et al. 2004; McLeod et al. 2006; Meyers et al. 2005; Mkhatshwa & Mummert 2011; Naheed et al. 2014; Small et al. 2006; Tang et al. 2009; Tse & Small 2010; Walker et al. 2010; Wang & Ruan 2004; Xu et al. 2014; Yoneyama et al. 2010; Zhou et al. 2004; Zhu & Zhou 2008)

H.14 Smallpox

(Adivar & Selen 2011; Brouwers et al. 2010; Del Valle et al. 2013; Grais et al. 2003; Hall et al. 2007; Huo n.d.; Kretzschmar et al. 2004; McKinley et al. 2013; Mizumoto et al. 2013; Porco et al. 2004; Ren et al. 2013)