

BMJ Open Burden of seasonal influenza in sub-Saharan Africa: a systematic review protocol

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ABSTRACT

Introduction Measures of epidemiological burdens are an important contribution to estimating disease severity and determining the at-risk populations for seasonal influenza. In the absence of these data, it is extremely difficult for policy-makers to decide on how to distribute limited resources. This systematic review will synthesise the literature on reported burden of seasonal influenza (eg, morbidity and mortality) in sub-Saharan Africa.

Method and analysis We will include published epidemiological studies that capture the burden estimation of seasonal influenza between 1 January 2000 and 31 August 2018. Studies that have reported disease burden estimates associated to influenza-like illness, acute respiratory illness, acute lower respiratory illness, severe acute respiratory illness and severe or very severe pneumonia using laboratory-confirmed influenza cases will be included. We will perform a multiple electronic database search in PubMed, Embase, African Journals Online, Cochrane, Web of science, CINAHL and Google scholar for eligible studies. The reference lists of relevant studies will also be hand-searched for potentially eligible studies. The titles and abstracts of identified records will be screened independently by two authors. The full-text articles of potentially eligible studies will be assessed independently by two authors. Discrepancies will be resolved by discussion, and by a third author if the first two authors fail to come to a consensus. The measures of the burden of influenza will be aggregated using a meta-analysis for homogeneous studies and narrative synthesis if the studies are heterogeneous. The strength of the evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation approach.

Ethics and dissemination This systematic review will use publicly available data; and as such, no formal ethical review is required. Our findings will be published in a peer-reviewed journal and also disseminated through conferences and stakeholder meetings.

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INTRODUCTION

Seasonal influenza is a respiratory transmissible infection caused by different subtypes (types A, B, C and D) of influenza viruses. It is a public health problem, causing severe illness in about 3–5 million people and responsible for 290 000–650 000 deaths

Strengths and limitations of this study

- This systematic review will assess the epidemiological burdens of seasonal influenza without placing any restriction on language.
- The search for relevant studies will include both published and unpublished to minimise the risk for publication bias.
- The strength of the evidence in this review will be assessed using the Grading of Recommendations Assessment, Development and Evaluation approach.
- A wide variation in the case definition and diagnostic of influenza may lead to inaccurate estimates of the disease burden.
- The studies that will be included in this review are observational studies which are more prone to reporting biases and may overestimate the burden of the disease.

worldwide each year.¹ It further remains an important source of economic loss worldwide. The total economic loss in the USA due to the burden of influenza amounts to US\$87.1 billion every year.² Hospitalisation due to seasonal influenza leads to losses in working days due to sickness, reduction in quality of life due to secondary infections, increased school absenteeism and increased use of hospital resources.³

This condition affects individuals of all ages but complications are more common in those younger than 5 years of age, frail adults over 65, pregnant women and persons with chronic medical conditions. The age-specific mortality is highest in individuals over 65 years of age, accounting for 90% of deaths.⁴ Attack rates in susceptible populations, such as school-going children or those in nursing homes have been found to be as high as 40%–50%.⁵ Clinical influenza attack rates range from 34% to 67% and rate of hospitalisation varies, with children admitted to hospital with acute lower respiratory infection (ALRI), from which influenza virus is identified, varying from 0% to 15.6%.⁶ Severe



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ALRI would generally include pneumonia but also most commonly present itself as bronchiolitis in children. Mortality rates in children due to pneumonia are highest in Africa.⁷ The research on the global burden of paediatric influenza indicates that 99% of deaths in children under 5 years of age are due to lower respiratory tract infections.⁸

Although seasonal influenza produces lower level activity in space and time, its cumulative mortality from regular epidemics are greater overall than that of rare pandemics. For instance, cumulative seasonal influenza mortality accrued between 1957 and 1968 exceeded the mortality of the influenza pandemics of 1957 and 1968 in the USA. The influenza pandemics of the 1957 and 1968 caused about 98 000 excess deaths but seasonal influenza deaths were double the excess deaths between 1957 and 1968, excluding the pandemic years.⁹

Although much is known about the effects of seasonal influenza, including global estimates of burden of influenza, the majority of studies are derived from developed countries. The burden of seasonal influenza in Africa is not fully known. The purpose of this study is to synthesise the existing studies that have reported the burden of seasonal influenza in sub-Saharan Africa.

Why is it important to do this review?

WHO recommends reinforcement of routine epidemiological and virological surveillance in order to ensure timely detection of outbreaks and management of cases.¹⁰ In 2002, WHO pledged to support the Integrated Disease Surveillance and Response (IDSR) systems which carry out monitoring and assessment of diseases, including the burden of seasonal influenza. Through surveillance systems, it is anticipated that hospitals and laboratories would document useful data for assessing the burden of seasonal influenza. However, there is a dearth of epidemiological information on seasonal influenza including its impacts (mortality, attack rates, susceptibility and hospitalisation) in sub-Saharan African countries. The aim of this review is to investigate the epidemiological burden of seasonal influenza and highlight its epidemiological patterns in sub-Saharan African countries. Our findings will contribute to the better understanding of the burden of seasonal influenza and will be useful in the planning for and response to seasonal influenza outbreaks in terms of prevention and treatment.

METHODS

Patient and public involvement

Patients were not involved in the design of this study.

ELIGIBILITY CRITERIA

Type of studies to be included

Epidemiological studies conducted in sub-Saharan African countries and published between 1 January 2000 and 31 August 2018 reporting on the burden of seasonal

influenza will be included. These dates coincides with the existence of the IDSR system in Africa. We will include published estimates from studies deriving their data from sentinel surveillance systems or healthcare facilities in which human influenza infection has been verified using a valid laboratory test such as a reverse transcriptase PCR (RT-PCR). Since influenza transmission occurs throughout the tropical and subtropical areas in Africa, we will consider studies with data reported weekly or monthly for at least a year. The peak periods in influenza in the tropics are between March and September but tend to vary from year to year depending on the type and subtype of human influenza in circulation.^{11 12} Studies that estimate the disease burden using modelling techniques will be excluded.

Participants

We will include studies that stratify influenza rates in the following age groups: 0 to <2 years, 2 to <5 years, 5 to <15 years, 15 to <50 years, 50 to <65 years and over 65 years. Where studies are unable to report age-stratified estimates within the proposed age groups, we will report rates as suggested in the studies. We will pull and group similar studies together according to the subgroup population based on WHO case definition of influenza. WHO case definitions vary across age groups and across study sites. All age-specific data for inclusion will be well defined in terms of numerators (case count) and denominators (population at risk). We will exclude all studies that use data reported between 31 January 2009 and 1 November 2010 including all studies where study duration overlaps or combines the pandemic and non-pandemic periods. The 2009 pandemic influenza was declared in April 2009 and by August 2010 it was declared over.¹³ This is based on the assumption that the pandemic virus (H1N1) was actively circulating for 6–8 weeks before and after the pandemic period.

Types of outcome measures

In order to be considered for inclusion, studies should explicitly report one or more epidemiological burden estimates. Burden estimates refer to mortality rates, attack rates, hospitalisation or admission rates, incidence rates or period prevalence rates associated with influenza-like illness (ILI) and severe acute respiratory illness (SARI). We will also adopt the following definition of the outcome measures. Mortality rate is defined as a measure of the number of deaths in a specific age group due to seasonal influenza divided by population of age group expressed in 1000 person-years. Overall attack rate refers to number of new cases of influenza during the specified time divided by the total number of specified population at start of time interval. Age-specific attack rate is calculated as a number of influenza illnesses among a specified age group divided by the total number of persons in that specified age population who were at risk to influenza at the start of the observation period. Hospitalisation rate is the number of influenza inpatient admissions discharged

over a specific time and geographical area divided by the population in that age group, expressed in terms of 1000 people days. Incidence rate is the number of new cases per population at risk in a given time period whereas period prevalence rate is a measurement of new and pre-existing of all individuals affected by the disease over a specified period of time divided by total number of people in that population. As far as prevalence estimates are concerned, we will only focus on period prevalence.

Case definitions of ILI and SARI

We will adopt WHO case definitions for ILI and SARI used between 1999 and 2018. The 1999 WHO case definition of ILI was defined as ‘a sudden onset of fever, a temperature $>38^{\circ}\text{C}$ and a cough or sore throat in the absence of another diagnosis’.¹⁴ In 2018, ILI was defined as ‘an acute respiratory illness (ARI) with measured temperature of $\geq 38^{\circ}\text{C}$ and cough, with onset within 10 days’.¹⁵ In 1999, SARI definition did not exist but in 2009 it was officially defined as ‘a sudden onset of fever $>38^{\circ}\text{C}$, cough or sore throat, shortness of breath or difficulty breathing and requiring hospitalisation. For those less than 5 years of age, pneumonia was used as criteria including cough or difficulty breathing’.¹⁶ The 2018 definition of SARI (including ARI, ALRI and severe or very severe pneumonia) was ‘an ARI with a history of fever or measured fever of $\geq 38^{\circ}\text{C}$ and cough, with onset within the past 10 days, requiring hospitalisation’.¹⁵ We will pull studies that report laboratory-confirmed influenza in patients with pneumonia that matches the International Classification of Disease, Ninth Revision codes (ICD-9 codes; 488.01, 488.11 and ICD-10 codes; J09.01, J09.11, J10.0). WHO case definitions for ILI and SARI have changed many times, in 2011, 2014 and 2018 in order to facility valid comparison of disease occurrence over a period of time, and increase the sensitivity and specificity in reporting.

Search method for identification of studies

We will construct a comprehensive search strategy using keywords and Medical Subject Headings (MESH) terms in PubMed, Embase, African Journals Online, Cochrane, Web of science, CINAHL and Google scholar for relevant studies. We will conduct a database search followed by hand-searching of reference sections of all relevant studies. The MeSH terms influenza (human) OR inter-pandemic influenza, sentinel or virological surveillance, mortality, morbidity, hospitalisation, admission rates, clinical attack rates, ILI (outpatients), SARI, ALRI and Africa will be used to combine searches systematically. The search strategy for PubMed is shown in **box 1**, but we plan to modify and run slightly different search strategy across the different databases. We will not place any restriction on language but will limit our search to studies in sub-Saharan Africa.

Selection of studies

All the identified titles and abstracts will be examined independently for potential eligibility by two authors (Ezs

Box 1 Search Strategy

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((('africa'[MeSH Terms] OR 'africa'[All Fields]) AND (((('epidemiology'[Subheading] OR 'epidemiology'[All Fields] OR 'incidence'[All Fields] OR 'incidence'[MeSH Terms]) OR ('epidemiology'[Subheading] OR 'epidemiology'[All Fields] OR 'prevalence'[All Fields] OR 'prevalence'[MeSH Terms])) OR ('mortality'[Subheading] OR 'mortality'[All Fields] OR 'mortality'[MeSH Terms])) OR ('hospitalisation'[All Fields] OR 'hospitalisation'[MeSH Terms] OR 'hospitalisation'[All Fields])) OR ADMISSION[All Fields] OR (('influenza, human'[MeSH Terms] OR ('influenza'[All Fields] AND 'human'[All Fields]) OR 'human influenza'[All Fields] OR 'influenza'[All Fields]) AND ASSOCIATED[All Fields] AND ILLNESS[All Fields])) AND (((('influenza, human'[MeSH Terms] OR ('influenza'[All Fields] AND 'human'[All Fields]) OR 'human influenza'[All Fields] OR 'influenza'[All Fields]) AND LIKE[All Fields] AND ILLNESS[All Fields]) OR (SEVERE[All Fields] AND ACUTE[All Fields] AND ('respiratory tract infections'[MeSH Terms] OR ('respiratory'[All Fields] AND 'tract'[All Fields] AND 'infections'[All Fields]) OR 'respiratory tract infections'[All Fields] OR ('respiratory'[All Fields] AND 'infections'[All Fields]) OR 'respiratory infections'[All Fields])) OR (('virology'[MeSH Terms] OR 'virology'[All Fields] OR 'virologic'[All Fields]) AND ('epidemiology'[Subheading] OR 'epidemiology'[All Fields] OR 'surveillance'[All Fields] OR 'epidemiology'[MeSH Terms] OR 'surveillance'[All Fields])) OR (('laboratories'[MeSH Terms] OR 'laboratories'[All Fields] OR 'laboratory'[All Fields] AND CONFIRMED[All Fields])) OR (('outpatients'[MeSH Terms] OR 'outpatients'[All Fields] OR ('out'[All Fields] AND 'patients'[All Fields]) OR 'out patients'[All Fields]) AND VISIT[All Fields])) OR ('reverse transcriptase polymerase chain reaction'[MeSH Terms] OR ('reverse'[All Fields] AND 'transcriptase'[All Fields] AND 'polymerase'[All Fields] AND 'chain'[All Fields] AND 'reaction'[All Fields]) OR 'reverse transcriptase polymerase chain reaction'[All Fields] OR ('rt'[All Fields] AND 'pcr'[All Fields]) OR 'rt pcr'[All Fields])) AND (((('SEASONAL'[All Fields] AND ('influenza, human'[MeSH Terms] OR ('influenza'[All Fields] AND 'human'[All Fields]) OR 'human influenza'[All Fields] OR 'influenza'[All Fields])) OR ('influenza, human'[MeSH Terms] OR ('influenza'[All Fields] AND 'human'[All Fields]) OR 'human influenza'[All Fields])) OR (INTER[All Fields] AND ('pandemics'[MeSH Terms] OR 'pandemics'[All Fields] OR 'pandemic'[All Fields]) AND ('influenza, human'[MeSH Terms] OR ('influenza'[All Fields] AND 'human'[All Fields]) OR 'human influenza'[All Fields] OR 'influenza'[All Fields])) OR (('laboratories'[MeSH Terms] OR 'laboratories'[All Fields] OR 'laboratory'[All Fields]) AND CONFIRMED[All Fields] AND ('influenza, human'[MeSH Terms] OR ('influenza'[All Fields] AND 'human'[All Fields]) OR 'human influenza'[All Fields] OR 'influenza'[All Fields])) OR (ACUTE[All Fields] AND ('respiratory tract infections'[MeSH Terms] OR ('respiratory'[All Fields] AND 'tract'[All Fields] AND 'infections'[All Fields]) OR 'respiratory tract infections'[All Fields] OR ('respiratory'[All Fields] AND 'infections'[All Fields]) OR 'respiratory infections'[All Fields])) OR (('influenza, human'[MeSH Terms] OR ('influenza'[All Fields] AND 'human'[All Fields]) OR 'human influenza'[All Fields] OR 'influenza'[All Fields]) AND ASSOCIATED[All Fields] AND ACUTE[All Fields] AND LOWER[All Fields] AND ('respiratory tract infections'[MeSH Terms] OR ('respiratory'[All Fields] AND 'tract'[All Fields] AND 'infections'[All Fields]) OR 'respiratory tract infections'[All Fields] OR ('respiratory'[All Fields] AND 'infections'[All Fields]) OR 'respiratory infections'[All Fields]))))
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and AM). Discrepancies will be resolved by consensus and if necessary by arbitration by a third author (CSW). The full texts of potentially eligible studies will be retrieved, and screened independently by two authors (Ezs and

AM). Disagreements between the first two authors will again be resolved by discussion and consensus and by arbitration by a third author (CSW) if necessary.

Data extraction and management

Two study authors (EZS and AM) will extract data independently from eligible studies using a prestructured and tested data collection form. The information collected using this form will include details on the year the study was conducted, setting, study design, methods, participants and outcomes, source of funding and risk of bias. The two authors will compare the extracted data and discrepancies will be resolved by consensus or by a third author (CSW) if relevant. In the event where there are missing data from included studies which we deem important, we will contact the authors of the studies involved.

Risk of bias (quality) assessment

Two independent reviewers will retrieve, screen and assess the risk of bias in the identified studies using the risk of bias tool by Hoy *et al.*¹⁷ In context of surveillance, biases are often present at the sampling stage of SARI/ALRI/ILI case counts of which many eligible cases are excluded resulting in selection bias. In addition, diagnostic assays used to identify cases may lead to misclassification bias. For example, RT-PCR identifies more cases than immunofluorescence assays.

Data and sensitivity analysis

A descriptive analysis of the study outcomes will be undertaken if studies are not eligible to be pooled for burden estimates. This will include studies with burden estimates that are not representative of the catchment population. Eligible studies will be stratified by type of population (ie, community or hospital setting, etc), surveillance type (ie, active or passive surveillance) and type of influenza case definitions (including whether it is based on 1999, 2014 or 2018 case definition) in order to compare similar designs. We will also stratify the burden estimates for ILI and SARI by age or risk group. In an event, there is multiple reporting in a study we will combine all the studies or use the study with the most complete dataset.

Quantitative estimates, that is, annual incidence, period prevalence and mortality of influenza, and 95% CIs will be obtained from all eligible studies and pooled for a statistical meta-analysis by use of STATA software version 15 if we find that studies are similar. If burden estimates are reported by week or month, we will calculate yearly burden estimates based on methods provided in WHO manual for estimating disease burden associated with seasonal influenza.¹⁸ Where studies provide relevant data for the catchment population, we will pool burden proportions of all cases sampled among SARI cases from whom clinical specimen were tested by week/month/year by dividing the total number of SARI cases by month/week/year and multiplying it by 100%. We will adjust for true total number of influenza-associated SARI cases per week/month/year by scaling up the number of influenza positive SARI cases by the

proportion of SARI cases tested. To estimate the proportion of ILI cases attributable to laboratory-confirmed influenza illness without population denominators require data on case counts (ie, number of ILI cases positive for influenza virus using laboratory tests) divided by number of ILI cases from whom clinical specimens were collected for diagnostic testing multiplied by 100. To estimate number of influenza-associated ILI, we will adjust the proportion influenza-associated ILI by week, month or year multiplied by total number of ILI cases by week, month or year. Step-by-step formulas are presented in WHO manual for estimating disease burden associated with seasonal influenza.¹⁸

We will use a meta-analysis to aggregate estimate measures. The random-effects models and fixed-effects models of regression coefficients will be used for pooled data analysis. If necessary, all studies of good methodological quality will be combined. We anticipate heterogeneity in the pooled studies due to different case definitions for SARI/ILI and origin of data (active and passive surveillance), thus, heterogeneity will be tested using the χ^2 test and I^2 test statistic. We will consider a significance level of $\alpha=0.1$ for χ^2 test and I^2 statistic of $>50\%$ to reflect significant heterogeneity. Heterogeneity and non-heterogeneity will be tested by deliberately dropping studies with high risk of bias from the analyses one at a time. If statistical heterogeneity is present, a subgroup analyses will be undertaken to examine the source of the poor data quality. We will include case definitions of influenza, passive or active studies, representation of the catchment area, age, gender, seasonality (tropical or subtropical), duration and type of study as covariates in the meta-analysis. Where there is significant heterogeneity, meta-analysis will not be performed. Only studies with similar risk of bias assessment will be pooled in a meta-analysis. We will define country burden disease estimates yielded from passive sentinel surveillance data (eg, ILI) as a lower threshold and upper threshold for active sentinel surveillance data (eg, SARI). Passive sentinel surveillance substantially yields lower estimates compared with active surveillance data. A forest plot on all data points and random-effects estimates will be generated to give insight to the analyses. The reviewers will assess the strength of the evidence according to the Grading of Recommendations Assessment, Development and Evaluation approach.¹⁹ This approach rates the strength of the evidence by taking into account five factors: methodological quality, directness of evidence, heterogeneity, precision and risk of publication bias.

Reporting of this review

We wrote this protocol following the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) Protocols guidelines. PRISMA focuses on ways in which authors can ensure the transparent and complete reporting of systematic reviews and meta-analyses.²⁰ The findings of this review and any amendments will be reported according to the PRISMA statement.

Ethics and communication

Our findings will be published in a peer-review journal and subsequently disseminated to policy-makers through conferences and stakeholder meetings.

Discussion and study limitations

There is a lack of epidemiological and laboratory surveillance data on the burden of seasonal influenza in Africa.²¹ This lack of information specifically attack rates, susceptibility and hospitalisation may undermine the role of seasonal influenza vaccination programme specifically in terms of how it should be implemented. Careful understanding of seasonal influenza, through continuous collection of surveillance and monitoring data of influenza activity taking place at any time of the year, will assist policy-makers in preparing for and to strengthening capacity for seasonal influenza surveillance and reporting. The overall understanding of the burden of seasonal influenza in African settings will subsequently provide information for treatment, prevention and control strategies of seasonal influenza such as giving the vaccines to high-risk groups first. We also hope that strengthening surveillance systems for seasonal influenza that report on the burden of viruses will rapidly help detect and send early signals of an impending new or severe influenza activity in humans. Seasonal influenza burden estimates that provide baseline data can provide valuable information with which to compare annual influenza outbreaks with unusual outbreak events.¹⁸ This information can serve as a predictive indicator for new events such as an influenza pandemic and systematically aid pandemic planners to plan for additional capacities and resources (stockpile of antivirals and antibiotics, etc) needed to deal with a severity of a new pandemic activity.²²

We anticipate several limitations in our study related to bias in influenza reporting and estimating burden of the disease. First, pooled data from studies will be limited to respiratory infections such as ILI and SARI. As such there is possibility of underestimating influenza-related burden caused by other clinical manifestation such as myocardial event triggered by influenza infection. Second, ILI surveillance data do not have a known population denominators and many people in the communities or catchment areas may not report influenza-associated disease, thus making it difficult to extrapolate, for example, incidence rates. Assuming enough information is provided in the studies, we will adjust the estimates by using the methodology provided in a similar study²³ to ours. Third, while we will take precautions to review studies for quality and relevance, often bias resulting from case definitions (error in coding cases), diagnostic sampling and diagnostic assays are inevitable in eligible studies, thus difficult to determine precisely the disease burden estimations once we pool data for analyses. We deliberately intend to use different WHO case definitions of SARI and ILI. However, the implication of this is that much older version of case definition is highly sensitive to children under the age of 5 and less sensitive to older children and adults. Further

implication of the use of different case definitions is that pooled estimates may not be a reflection of true influenza burden in the population. We intend to reconcile the different case definitions (eg, SARI cases) in different studies by matching them to hospitalised severe ALRI and pneumonia and influenza (ie, ICD-9 and ICD-10) making sure there are comparable between themselves and help in harmonisation and interpretation of data.

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Contributors CSW, ABW, EZS, AM, AP and RB contributed to the conceptualisation of the review. EZS wrote the manuscript draft. EZS and ABW developed the search strategy. All authors revised and edited the manuscript draft and search strategy. All authors approved the manuscript.

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Competing interests None declared.

Patient consent Not required.

Ethics approval This systematic review and meta-analysis will use the publicly available data as such no formal ethical review was required.

Provenance and peer review Not commissioned; externally peer reviewed.

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