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TOWARDS A MORE EFFICIENT AND EFFECTIVE PIPELINE OF TUBERCULOSIS MEDICATION: THE VALUE OF IDENTIFYING TRENDS AND INFLUENCING FACTORS

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ABSTRACT

Tuberculosis poses a significant risk to global health with estimated 1.7 million deaths worldwide in 2016. One key issue in tuberculosis management relates to the drug pipeline, with drug development not keeping pace with the rate at which the disease expands and changes. Identifying and addressing factors that inhibit tuberculosis research and development is essential. Research to identify trends in the drug pipeline and evaluate the relations between these trends and other influencing factors will strengthen the existing body of knowledge, enabling improved decision-making on investment in drug research and development, and structuring incentives to encourage investment.

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1. INTRODUCTION

Tuberculosis (TB) is the ninth biggest cause of death worldwide, affecting the lives of over 10,4 million people in 2016 [1]. An estimated four million people (40% of TB cases) are undiagnosed each year; this figure increases to 77% among individuals with drug-resistant TB (DR-TB) [2]. In most developing countries, diagnosed patients face drawn-out delays (up to 28–30 days) in receiving feedback confirming their TB status, thus prolonging the time during which they are without appropriate treatment or until they undergo the necessary drug-susceptibility testing (DST) [1]. Diagnosing TB is the first step in treating affected people and preventing the transmission of the disease [2]. According to the World Health Organisation, infection rates will only decrease if, firstly, the country and local-level uptake of the diagnostic tools available increases significantly, and, secondly, investment in basic scientific research and the diagnostic pipeline is increased considerably [2].

DR-TB is a growing threat: in 2016, 600 000 new cases of resistance to rifampicin (the most effective first-line TB drug) were diagnosed, and 490 000 of these cases were diagnosed as multidrug-resistant TB (MDR-TB) [1]. The 2017 treatment outcome data show a global success rate of 83% for TB treatment and 54% for DR-TB [1]. DR-TB treatment has a noticeably lower success rate than that of TB. The need for further advancement in the development of more effective, safer, affordable, accessible, shorter course and better tolerated treatment regimens is evident, and is being investigated by stakeholders and researchers as this is of paramount importance to reduce the global prevalence of this disease [3].

Despite research suggesting that the research and development (R&D) of TB drugs over the past few decades has not yielded any major breakthroughs, there has been noticeable progress in the TB treatment drug pipeline recently. Three drugs are currently in phase 3[4] of clinical development trials and are being distributed on a small scale to DR-TB patients [1]. Unfortunately, access to these drugs is restricted in developing countries, where the disease is most prevalent [3].

Dowdy [23] describes TB as an “epidemic at a crossroads”. According to Dowdy, “strains of DR-TB will emerge that are more transmissible and more difficult to treat”, yet there are more drugs and technologies to use against the disease than ever before [23]. There is evidence that DR-TB can effectively be reversed, unlike most other DR pathogens. Thus, the next decade can either be one in which the TB epidemic becomes an “unprecedented global epidemic” or one in which the “global burden will be unprecedentedly reversed” [23]. According to Dowdy, the difference between these two outcomes lies with the global TB control community, and whether there is enough political will to prioritise the mitigation of the disease [23].

The *end TB strategy* is related to the Sustainable Development Goals and aims to “eliminate TB by 2030” [4]. In order to achieve the global goal of ending TB, it is estimated that an annual amount of $2 billion should be invested in TB R&D globally. Currently, approximately $650 million is spent on global TB R&D per year, which indicates that there is a significant investment gap for the development of TB drugs [4]. According to the 2016 report on TB research funding, the lack of funding for TB is now a human rights issue in need of a political solution [2] & [4]. Lucica Ditiu, executive director of the Stop TB Partnership, states that the lack of funding for TB R&D is impacting everything related to the development of new drugs and technologies, with specific reference to: i) the rate at which new technologies become available to the market; ii) the state of the TB drug pipeline; iii) advocacy efforts; and iv) the possibility of reaching targets in global plans to end TB [4].

There is consensus in literature that investment in TB R&D is needed to increase the number of drugs that progress through the drug pipeline effectively [1] & [2]. Literature does not specify, however: i) why the private sector shows less interest in investing in TB compared to other diseases; ii) why TB drugs progress through the pipeline at a slower rate than drugs for other diseases; iii) the trends of drug R&D; and iv) what the major factors are that affect the drug movement of the TB drug pipeline. It is therefore argued in this paper that addressing the factors that affect the TB drug pipeline can contribute towards the advancement of effective progress of TB drugs through the R&D pipeline.

This article aims to investigate the trends and factors affecting the advancement of drugs in the drug pipeline and the TB drug pipeline in particular, in order to: i) highlight the value of identifying factors causing a loss of efficiency in the pharmaceutical R&D process; ii) enable informed decision-making about advancing drug

[4] Clinical development phases (1, 2 and 3) refer to the research studies, forming part of the drug R&D process, that determine whether a drug is safe and effective for human consumption. Each phase has different outcomes. The more advanced a drug is in the clinical trial phases, the higher the possibility for the drug to be accepted by regulatory agencies.

development; and iii) facilitate discussions concerned with directing investment in drug R&D to contribute towards increasingly effective and efficient output of drugs from the TB drug pipeline. The relationships between pipeline trends and factors affecting the pharmaceutical and TB drug pipeline is discussed and analysed to determine similarities or differences between the pipelines. Potential areas for future research are identified. Lastly, the value of future research in this field for the existing body of knowledge is briefly investigated to establish whether an understanding of the pipelines might improve the effectiveness and efficiency of, specifically, the TB drug pipeline.

2. METHOD

In order to address the aim stated above, this study investigates two drug pipelines; firstly, the pharmaceutical drug pipeline (diseases non-specific) and secondly, the TB drug pipeline (disease specific). These two drug pipelines will be addressed separately and subsequently compared to establish similarities and differences. Figure 1 depicts the research inquiry process followed to investigate each pipeline in order to ultimately establish the value of identifying those factors and trends that affect the pharmaceutical pipeline.

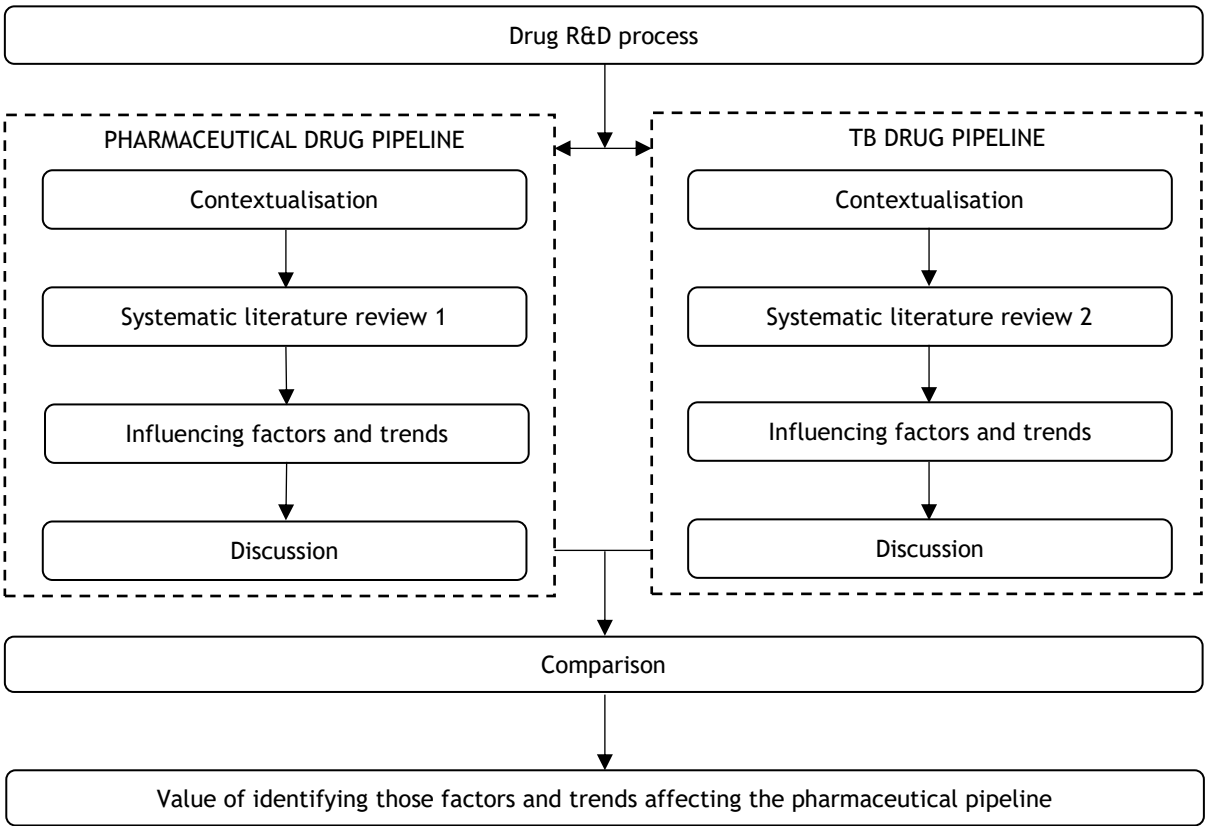

Figure 1: Research study method

As can be seen in Figure 1, the drug R&D process will be discussed first. Subsequently, both the pharmaceutical and TB drug pipelines will be discussed. Distinct systematic reviews of both pipelines (systematic review 1 and 2) will be conducted, resulting in the identification of two sets of influencing factors and trends relating to drug pipelines. A separate analysis of each pipeline and a comparison of the two pipelines will follow to establish relationships within the pipelines and similarities and differences between the two pipelines. The analysis will result in understanding the impact of various factors on the pipelines, and possible ways to improve pipeline efficiency and effectiveness, based on pipeline trends. Finally, the value of the study regarding the improvement of the TB pipeline will be presented, followed by an evaluation of how this information might be used to improve the impact on the pharmaceutical or TB drug pipeline.

3. DRUG RESEARCH AND DEVELOPMENT PROCESS

Drug R&D refers to the process followed from product discovery to the successful development of a drug. It includes all research conducted and review processes completed up to the introduction of the new drug.

The development of pharmaceutical drugs is an iterative, time consuming and costly process [5]. The process alternates between several factors, including: i) theoretical biology; ii) the appropriate use of animal assays to determine a compound's biological activity in the body; and iii) optimising the chemical compounds with medicinal chemistry [5]. The cost of R&D for each successful new drug was estimated to be $2.6 billion in 2016, as opposed to $1 billion in 2000 [6]. Costs include the cost of failures, thus the cost of all the drugs screened, tested and assessed but not necessarily approved. PhRMA [5] states that the development costs of drugs are still rising and become even higher when the cost of research after drug approval is considered. Drug development is a lengthy process, lasting up to fifteen years from initial discovery to product launch. The duration of the drug development process can be influenced by various factors, including the testing and analysis of the drug for safety and efficacy.

Drugs require approval from a recognised pharmaceutical regulatory agency, authorising the drug to be launched provided that it adheres to the international guidelines and standards set out for drugs [6]. One of the most well-known regulatory agencies is the Food and Drug Administration (FDA), the federal agency of the United States Department of Health and Human Services responsible for ensuring that organisations in the US, and a number of other countries, adhere to regulatory frameworks [7]. When a drug is FDA approved, it means the potential risk of the item is outweighed by its benefits, thus making it, legally, safe to use [7].

To discover and develop a new drug, researchers must understand the basic causes of a disease in terms of proteins, genes and cells [8]. The information emerging from the disease-cause analysis is known as 'targets' and identifies the potential factors that can be affected by drugs to diagnose, prevent or treat a disease [8]. The validation of the identified targets, discovering the right molecule to interact with the target, and testing for safety and efficacy are only a few of the tasks to be completed [8]. The drug development process occurs in five distinct phases, namely: i) drug discovery; ii) the preclinical phase; iii) clinical trials; iv) the review phase; and v) post-marketing surveillance. Each stage contributes to fine-tuning the developing drug so that it is in the best possible state for the target disease. Figure 2 illustrates the phases in drug R&D, the stipulated number of compounds (drug candidates) per phase, as well as the average duration of each phase.

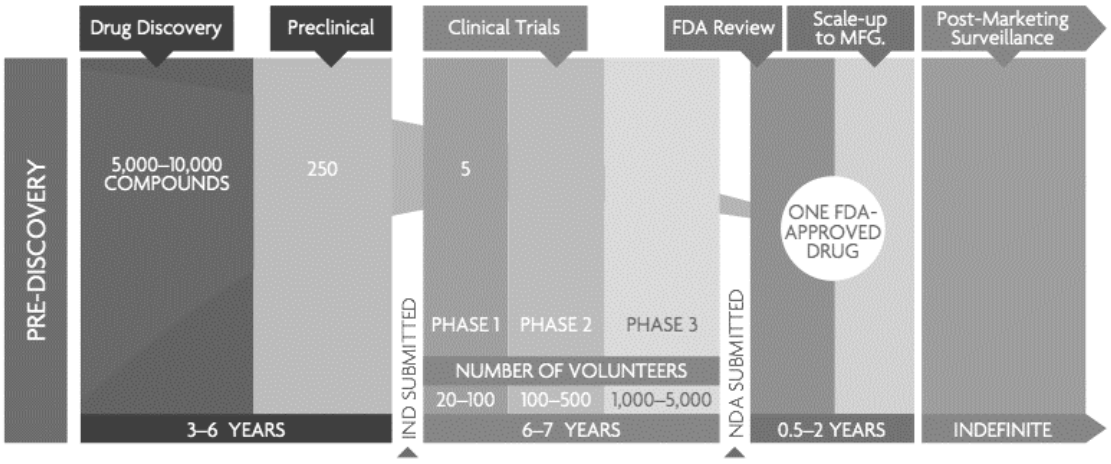

Figure 2: Drug R&D process ***[8]***

The primary aims of the review process in drug R&D are to ensure that: i) drugs are safe for human consumption; ii) drugs are effective in treating the disease targeted; iii) drugs are affordable for users; and iv) the benefit of the new drug outweighs the potential risk [8]. The benefit versus risk ratio is determined by the FDA, or another regulatory agency, scrutinising the data collected in the preclinical and clinical findings. The drugs need to meet

the safety and efficacy standards set by regulatory bodies. Currently only 12% of candidate drugs (drugs in the R&D process) receive FDA approval [9].

Although scientific advances enable a greater understanding of diseases at molecular level, it is evident that scientific, technical and regulatory challenges still exist in the R&D process [5]. According to PhRMA [5], an in-depth analysis of the R&D process could clarify why the successful development of drugs takes so long.

4. PHARMACEUTICAL DRUG PIPELINE

This section focuses on the pharmaceutical sector. Firstly, it discusses the context of the pharmaceutical pipeline. Then a systematic literature review is conducted, and factors and trends that influence the pipeline are identified. Finally, any similarities or differences between the factors and trends are analysed and evaluated.

4.1 Contextualisation: The pharmaceutical drug pipeline

The drug pipeline refers to the set of drugs that a pharmaceutical company, or the entire pharmaceutical industry, in the process of discovering, research or development at a given point in time [10]. The drug pipeline encompasses the amount of active R&D taking place, thus serving as a form of reference to the extent of interest, investment and resource allocation in a specific drug or disease [11]. In the pharmaceutical industry, the drug pipeline includes all the processes from initial drug discovery to the introduction of the product for public consumption [10].

The drug pipeline does not end when the drug development process has been completed and the drug approved for launch; ongoing research and data collection form part of post-approval studies [9]. These studies are conducted for as long as the product is used by patients and include the examination of the drug and its effects on drug users; these insights can also be used to expand treatment options in future drug development [9].

The pharmaceutical pipeline is under tremendous pressure when the significant number of events, processes, stakeholders, circumstances and regulations influencing the outcome are considered. Great advances in science, technology and management practices in drug development have been made over the past 60 years; yet the number of new drugs approved per billion US dollars spent on drug development has decreased about 80-fold [12]. The time and cost challenges are well known for their impact on the drug industry. Another contributor to the loss of efficiency in the drug pipeline is the 'curse of attrition' [13]. This refers to the considerable number of drugs being rejected in clinical trial phases, as the drug progresses through the compulsory trials and processes [13]. The low success rate of compound development is further impaired by the amount of funds lost once a drug is rejected at such an advanced stage of development [13].

The pharmaceutical industry strives to decrease the number of drug compounds exiting the R&D system without being approved, thereby minimising lost investment costs, research effort and time. An ideal scenario would entail a more extensive safety and efficacy test being initiated in earlier phases of the drug R&D process. The elimination of unsafe and ineffective compounds in an earlier phase would mean that less development effort goes to waste.

4.2 Systematic literature review

Numerous research studies have been aimed at pinpointing factors that contribute to the loss of efficiency in the pharmaceutical R&D process [27]. The value of identifying these factors lies within the opportunity to potentially address the identified factors in the R&D process, thus limiting the negative effect that it might have on the pharmaceutical pipeline. This study, however, aims to identify the factors that have a direct influence on the drug R&D process, thus affecting the state of the drug pipeline. A systematic literature review has been used to determine such factors.

4.2.1 Systematic literature review method

The literature review search was done in the Scopus[5] literature database. The objective was to establish the factors that lead to a lack of efficiency in the pharmaceutical drug pipeline. Answering the following two research questions (RQs) will contribute to addressing the primary objective of the study effectively.

[5] Scopus is the database of Elsevier, and the world's largest abstract and citation database of peer-reviewed literature. Scopus provides global interdisciplinary and scientific information across all research fields. Scopus is free to use [27].

- *RQ 1: What factors influence the overall drug pipeline of the pharmaceutical industry?*
- *RQ 2: What trends can be identified in the development of drugs over the past 10 years?*

Keywords for the search were derived from the two research questions and arranged in a logical manner. A search was completed with the search line: ("clinical trial" OR ((pharmaceutical OR drug*) W/5 (r&d OR pipeline OR development)) W/5 (factor* OR challeng* OR influenc* OR improv* OR affect*)).

4.2.2 Systematic literature review results

The search, using the keywords mentioned above, gave an output of 16 309 possibly relevant documents. The document set was further limited by type to journal sources only, excluding 1 017 articles. The document type was limited to articles, leading to 8 623 articles in total. The publication date was limited to a range from 2008 to 2017, resulting in a total of 5 504 documents. Finally, all articles written in languages other than English were excluded, resulting in set of 5 099 documents.

In order to reduce the number of documents in the document pool further, it was decided to use the top 200 cited documents from the set of 5 099. To correct for the bias inherent in only selecting the top cited documents, all documents published from 2015 to 2017 were also included in the document pool. This resulted in a document pool of 200 (top cited) + 2 049 (published 2015-2017). Eleven documents were duplicates in the two sets, which gave a total of 2 238 preliminary, relevant documents.

The titles of all 2 238 documents were scanned for relevancy to the two research questions. Consequently 147 documents were deemed relevant. The abstracts of these 147 documents were reviewed and resulted in the final selection of 97 documents with information relevant to both RQ1 and RQ2. The abstracts of these documents were analysed from two perspectives. Firstly, the abstracts were comprehensively investigated to establish factors that correlate with RQ1 (see Section 4.3). Secondly, the abstracts were explored to identify trends that correspond with RQ2 (see Section 4.4).

4.3 Results: Influencing factors

The preliminary identification of influencing factors was conducted by investigating the abstracts of the 97 documents and identifying factors that correlate with RQ1. In total, 39 factors were identified. The range of occurrence varied from a single occurrence to 13 occurrences across the 97 articles. Table 1 shows the most prominent factors present in the articles included in the dataset.

Table 1: The top occurring influencing factors identified in the preliminary analysis of the document pool

No.	*Influencing factor*	*Occurrence*
1.	Policy & regulatory issues	13
2.	Set-up of clinical trials; randomisation in trials (RCT); trial methodology & choice of metrics	13
3.	Recruitment and retention of participants; enrolment & minority representation; little clinical trial awareness of potential participants	11
4.	Complexity of trials; deal with multiple endpoints; better operational framework; clinical trial activation difficulty	10
5.	Clinical trial risk	7
6.	Lack of transparency; accountability; accessibility of clinical trial information	7
7.	Quality of clinical trial; improve use of innovative clinical trial tools; quality of pre-clinical trials	7

8.	Physician participation; relationships between stakeholders; collaboration; data sharing & intellectual property	6
9.	Lack of capacity and funding; lack of ROI	5
10.	Ethical obstacles and issues	5

The top four factors found to influence the pharmaceutical pipeline occurred in 10% or more of the document pool selected for this systematic review. All four factors are briefly discussed below.

1. Policy and regulatory challenges refer to any challenge encountered in ensuring, establishing or completing the regulations laid out by the regulatory drug agencies of the pharmaceutical industry. These challenges might exist because of national or international policies and are often influenced or enforced by government.
2. Clinical trial set-up refers to the way in which the clinical trials are organised, planned or arranged. The set-up determines how the activities of the trial phases will operate and what each step will entail.
3. Participants of clinical trials refers to the patients on whom tests are being conducted. Participants usually volunteer for clinical trials and might be provided with some sort of incentive to participate.
4. The complexity of clinical trials refers to the difficulty of completing and performing the actions required for the trials. It refers to the operational challenges experienced in carrying out the necessary protocols in all aspects of the clinical trials.

4.4 Results: Pharmaceutical pipeline trends

Trends in the pharmaceutical pipeline indicate a general direction in the development of or changes to the pipeline. Of the 97 abstracts reviewed, eight mentioned trends in the pharmaceutical drug pipeline. Four trends in drug R&D and pipelines are identified and investigated in this section, namely: i) R&D productivity; ii) investment capital and returns in the pharmaceutical sector; iii) clinical trial registration; and iv) the cost of clinical trials.

4.4.1 R&D productivity

The productivity of pharmaceutical R&D can be measured by various methods. According to Lendrem [14], productivity is measured by evaluating the number of new therapeutic drugs (NTDs) per billion dollars R&D spent per annum; Schulze et al. [15] evaluated the number of peak sales value of NTDs instead. The method of measurement used by Landrem [14] includes the effect of inflation-adjusted R&D costs.

The productivity evaluation, as mentioned by Landrem [14], concluded that escalating R&D costs is a dominant feature influencing the productivity of R&D during the period 1990 to 2013. The rise in operating costs, according to Hammer and Champy [16], might be a result of a change in focus during the 1990s to maximise the development speed of drug R&D. The cycle times of successful molecules were halved from 1990 to 2001, but this led to an immense increase in development costs, ultimately affecting the entire drug development process. The productivity of R&D remained relatively constant over the period 1990 to 2013, but decreased drastically when inflation was considered. The increase in the inflation-adjusted R&D costs offered an explanation for the market decline in overall R&D productivity [14].

4.4.2 Investment capital and returns in the pharmaceutical sector

The investment capital in this sector has decreased over time in response to many factors. These factors include preclinical scientific breakthroughs [17], clinical trial data, regulatory oversight, healthcare policies, pricing, technology and other economic changes related to drug discovery and development [18]. According to Thakor et al. [18], the most direct driver of capital flow in and out of the industry is the performance of pharmaceutical investments, thus providing attractive returns on the investments made. Some sources state, however, that not all pharmaceutical companies are struggling to realise returns, and that healthcare venture capital outperformed all other venture sectors over the past decades [18]. The annual returns of the pharmaceutical sector for the period 1980 to 2015 exceeded that of the stock market by 3%. The pharmaceutical portfolio also outperformed the market portfolio, where $1 invested in pharmaceutical companies in 1980 would be worth $114, compared with $44 if invested in the market at the same time [18].

Each investment holds a certain amount of risk and volatilities in returns [18]. The Sharpe ratio, a measure of an investment's return per unit of total risk, for the pharmaceutical sector was higher than that of the average

market. The high Sharpe ratio indicates that the risk-adjusted returns of the pharmaceutical sector were better than the average market for the period 1980 to 2015.

4.4.3 Clinical trial registration

The registration of clinical trials is necessary to increase their ethical and scientific value [19]. More than half of clinical trials are never published and are reported selectively, resulting in a waste of resources and decision-making based on biased evidence, such as exclusive groups of patients used to participate in trials [19]. According to Viergever and Li [19], the number of registered clinical trials increased substantially between 2004 and 2013, from 3 297 to 23 384. Table 2 indicates the number of clinical trials registered, based on regional income groups.

*Table 2: Clinical trial registrations based on income groups, adapted from **[19]***

Region (country income groups)	***Number of trials registered in 2005-2013***	***Percentage of all clinical trials registered in 2005-2013***
High-income countries	143 137	82.5
Upper middle-income countries	24 937	14.4
Lower middle-income countries	8 229	4.7
Low-income countries	1 433	0.8
Not specified	6 319	3.6

It is evident from the information presented in Table 2 that high-income countries have the highest number of registered trials, representing 82.5% of all the clinical trials registered globally. In comparison, low-income countries conduct only 0.8% of the total number of clinical trials registered.

The registration of clinical trials has improved transparency in pharmaceutical research by increasing access to information across the globe [19]. Challenges still exist though [1]. These include: i) the quality of data available; ii) the accessibility of all clinical trial data; and iii) data searchability, data aggregation and linking data [19].

4.4.4 The cost of clinical trials

The cost of each clinical trial completed is influenced by a range of factors. The factors identified in Section 2.3, amongst other things, affect the cost of the trial. Sertkaya et al. [20] evaluated all direct cost components and constructed a list. Their study [20] established that the average cost of each of the various stages are as depicted in Table 3.

*Table 3: Average cost per clinical trial phase, adapted from **[20]***

Phase number	***Average range of clinical trial cost***
Phase 1	$1.4 million to $6.6 million
Phase 2	$7 million to $19.6 million
Phase 3	$11.5 million to $52.9 million

The top three cost drivers, as established by Sertkaya et al. [20], were clinical procedure costs (15-22%), administrative staff costs (11-29%), and site monitoring costs (9-14%). It is important to note that these findings are based on trials funded by pharmaceutical and biotechnological organisations and not governments, academic institutions or other organisations [20].

4.5 Discussion of results

The factors and trends identified can be evaluated based on the effect that they have on one another, and on how certain factors influence the trends within the pipeline.

The productivity of drug R&D is a result of several factors, including the cost of R&D (as mentioned in Section 4.4.1). Policies and regulations (influencing factor 1) potentially reduce the amount of NTDs introduced into the market. This does imply, however, that the process of eliminating unsafe and ineffective compounds from the pipeline is meticulous, resulting in reduced risk for potential drug users. The complexity and difficulty of trials (factor 4) mean that more time is required to conduct accurate studies. The quality of the trials also plays a role in the time it takes to complete the necessary procedures and whether it is necessary to repeat the study because of inadequate, inaccurate or insufficient data. The recruitment and retention of participants (factor 8) in the drug development process has a direct effect on the length of a study. It might take longer than planned to recruit all the participants necessary for the study, or the participants might be unable to complete the study, making the study unacceptable to regulatory authorities.

The amount of investment capital and the returns of the pharmaceutical industry relies on the amount of risk (factor 5) involved in the drug development process. For each disease this risk differs. Clinical trial registration requires organisations to be transparent (factor 7) about the procedures of the clinical trials and the trial outcome and information. Lastly, the cost of clinical trials is affected by almost all aspects of the drug development process. The longer the process, the higher the cost of drug development. The attrition of drug compounds during the R&D process also plays a major role in the cost – funds are lost when compounds pursued for many years fail to qualify as safe and effective drugs.

The state of the pharmaceutical pipeline is undoubtedly dependent on all the factors mentioned in Table 1. The trends identified in Section 4.4 discusses the impact of those factors with one another and the status quo of the pipeline.

5. PHARMACEUTICAL TB DRUG PIPELINE

This section describes the pharmaceutical TB drug pipeline. Firstly, various views on the TB drug pipeline are discussed. The current state and number of drugs in the pipeline are evaluated. A systematic literature review was conducted to determine influencing factors and trends in the TB drug pipeline. The results of the literature review are analysed at the end of the section.

5.1 Contextualisation: The pharmaceutical TB drug pipeline

Inspecting the drug pipeline of a specific disease differs from viewing the overall pharmaceutical pipeline. An overview of the TB drug pipeline incorporates characteristics of the disease and how those characteristics affect the drug development process.

5.1.1 Different views of the TB drug pipeline

According to the *2017 Pipeline Report* [2], the overall TB drug pipeline can be divided into four explicit pipelines. The four pipelines are the: i) diagnostics; ii) prevention; iii) treatment; and iv) diagnostics and treatment for children pipelines. Each of the pipelines has different aims and objectives in the way it addresses the TB epidemic. These various TB drug pipelines are discussed below.

I. Diagnostics pipeline

The TB diagnostics pipeline includes the development of all technologies, tools and tests to identify and specify TB and the type of TB of the person tested. TB diagnostic tests include patient diagnosis and drug-susceptibility testing [2]. TB diagnostics also include treatment monitoring technologies, which are necessary to establish whether treatment regimens are effectively improving or worsening the patient's condition.

II. Prevention pipeline

Mycobacterium tuberculosis (MTB) is the causative agent of TB. According to a study completed in 2015 [21], 1.7 billion individuals are infected with MTB. However, it is only when the MTB infection progresses to

the active, transmissible state that a person is said to have TB. For most people, an MTB infection will not progress to the active state; for others, certain life events (aging, pregnancy) or immune-compromising conditions might lead to an active TB infection [2].

The TB prevention pipeline primarily entails the R&D of vaccines or other innovation therapies. According to Behr et al. [22], the two primary goals of TB vaccine development is to, firstly, find a vaccine to boost the current vaccination available to prevent active TB in adults infected with MTB and, secondly, to find a novel vaccine to replace existing vaccination for infants. Behr et al. [22] consider it important to pursue the parallel development of vaccines not only to prevent active TB from developing, but also to develop a vaccine to prevent sustained infection by MTB.

III. Treatment pipeline

The bacterial species MTB is treated with a combination of antibiotics [2]. Several antibiotics are used as first-line medicines to treat the infection. The extensive overuse and misuse of antibiotics since their introduction in the 1950s have led to a rise in DR-TB infections [23]. The DR infections occur because of inadequate or interrupted treatment or can be transmitted from one person to another.

IV. Diagnostics and treatment for children pipeline

Childhood TB has unique challenges with regard to diagnosis, prevention and treatment, as the disease differs considerably from TB in adults [24]. The BCG vaccine is primarily used by to prevent TB in children but is not fully protective and is not recommended for HIV-infected children. According to the 2017 WHO report, only 38% of TB-infected children are diagnosed and reported to national authorities each year [1]The diagnosis of childhood TB is complicated by the disease having non-specific symptoms. In most cases, children present smear-negative results, even though they are infected with the disease [24].

This research study focuses on the treatment pipeline: the current state of drugs in R&D intended to treat TB. This study does not distinguish between drugs aimed at treating adults or children, but rather views the pipeline from a systems perspective.

5.1.2 The current TB pipeline

There are a significant number of challenges in the management of TB on a global scale [3]. A considerable number of organisations, stakeholders, researchers and advocates are working on developing drugs to mitigate the effect that TB has on patients. Yet a more effective, shorter, safer and more easily tolerable treatment regimen is needed to manage the disease effectively [3]. The current TB drug pipeline, as reported in March 2018, consists of 14 candidate drugs for drug-susceptible, drug-resistant and latent TB. The 14 drugs are all in clinical stages of development; two drugs are in early stage development, nine are novel and in clinical trial phases 1 and 2, three have been approved and are in clinical trial phase 3 [3]. In addition to these drugs, other immune-based and host-directed treatment arrays are also under development [3]. The drug development industry has made extraordinary progress with the approval of two novel anti-TB drugs, bedaquiline and delamanid, in 40 years [25]. Figure 3 depicts the recent drug development pipeline for medicines currently progressing through clinical trials.

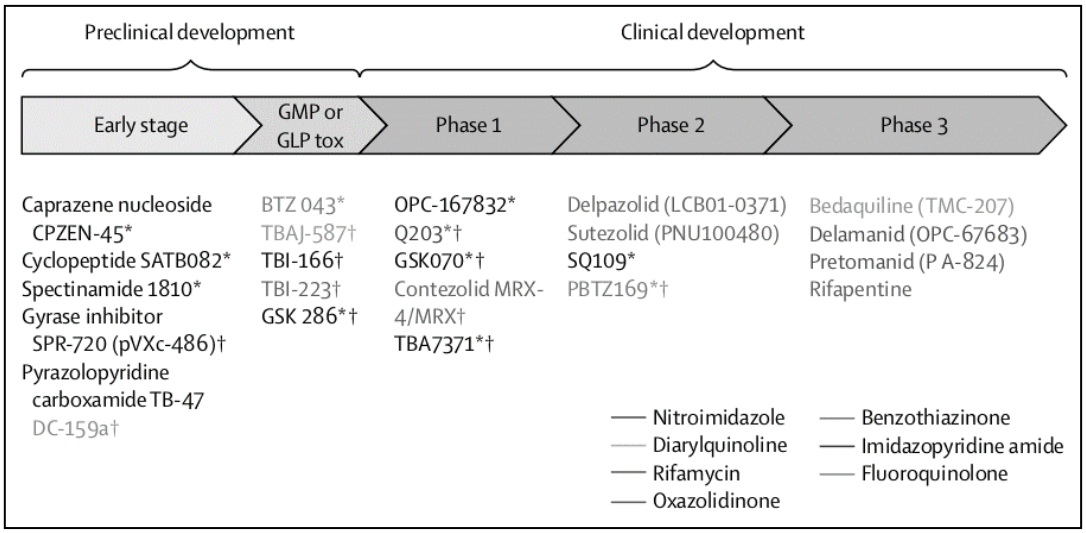

*Figure 3: New global TB drug development pipeline **[3]***

5.2 Systematic literature review process

The objective of this literature review was to establish what existing literature says about factors that lead to the lack of efficiency in the TB drug pipeline, in particular. The trends experienced in the TB drug pipeline were investigated to determine the state of the current pipeline. This systematic review was conducted to replicate the platform created with the previous systematic review, making a comparison between the two pipelines possible.

5.2.1 Systematic literature review method

As in the systematic literature review described in Section 4.2, the document search was completed in Scopus. The RQs presented in Section 4.2.1 were adjusted to form new RQs that would apply to the TB drug pipeline instead of the pharmaceutical drug pipeline. Addressing these two RQs will assist in comprehending the TB drug pipeline.

- *RQ 3: What factors influence the TB drug pipeline?*
- *RQ 4: What trends can be identified in the development of TB drugs over the past 10 years?*

The search line was as follows: (Tuberculosis OR tb) AND ("clinical trial" OR ((pharmaceutical OR drug*) W/5 (r&d OR pipeline OR development)) W/5 (factor* OR challeng* OR influenc* OR improv* OR affect*)).

5.2.2 Systematic literature review results

The search resulted in a total of 230 documents. The sources were limited to journals and conference proceedings, leading to 219 documents in the pool. Conference proceedings were added to this systematic review, and not to the systematic review in Section 4, because the document pool for this search was much smaller, since including TB narrowed the search extensively. The document type was then limited to articles and conference papers, leading to 121 documents. The publication date, as in the previous search, was limited to the last ten years (excluding 2018), resulting in 80 documents. The document pool was finally restricted to only English-language publications, leading to a total of 77 documents. The titles of the documents were scanned to find articles that mention anything that relates to RQ3 & 4. A total of 33 documents were found to be applicable to the RQs. The abstracts of these 33 documents were screened from two perspectives; firstly, to determine the factors influencing the TB drug pipeline (RQ3) and, secondly, to identify trends in the TB drug pipeline (RQ4).

5.3 Results: Influencing factors

With the first review of the 33 article abstracts, a total of 24 factors influencing the TB drug pipeline, thus relevant to RQ3, were identified. Table 4 shows the eight most frequently occurring factors identified.

Table 4: Top 8 factors influencing the TB drug pipeline

No.	*Influencing factor*	*Occurrence*
A.	Drug resistance	6
B.	Developing countries	5
C.	Resource-constrained (limited) setting	5
D.	Complex structure of MTB within host; different physiological states of bacterium	4
E.	Access to drugs; implementation of current & new treatment; low exposure	3
F.	Lack of finances	2
G.	Not enough DST technology	2
H.	Uncertain predictive value of preclinical animal models	2

The top three factors are briefly discussed below:

A. For TB, drug resistance refers to the characteristic of the disease that develops in many patients as a result of their not taking the medicine as scheduled, or by the DR-TB being transmitted from one person to another. The effect of drug resistance on the TB drug pipeline was mentioned in six of the 33 articles (18%) scanned in the systematic review. Patients infected with DR-TB are resilient to the first-line drugs used to treat the disease, as mentioned in Section 1.
B. Developing countries refers to the setting in which the disease occurs most often. Treating diseases in developing countries present challenges that do not necessarily occur in developed countries, thus making it a valid characteristic to consider with regard to the state of the drug pipeline.
C. Resource-constrained setting refers to the capability of the region in which TB occurs to perform the necessary actions and allocate the required funds to have a positive influence on the development of drugs.

5.4 Results: TB drug pipeline trends

With the second review of the 33 article abstracts, three major trends surfaced in two articles. Additional literature was included to describe the trends in the TB drug pipeline effectively. Each of the three trends are described in this section.

5.4.1 Funding trends by research category

TB is being addressed by organisations globally. Unfortunately, the funding available to combat TB does not seem to receive the attention needed to effectively mitigate the disease. The global plan to stop TB recommends an annual $2 billion investment to accomplish the goal of ending TB by 2030 [2]. At present, the effective investment in TB R&D is approximately $650 million per year. Figure 4 indicates the total TB R&D funding for the period 2005 to 2015.

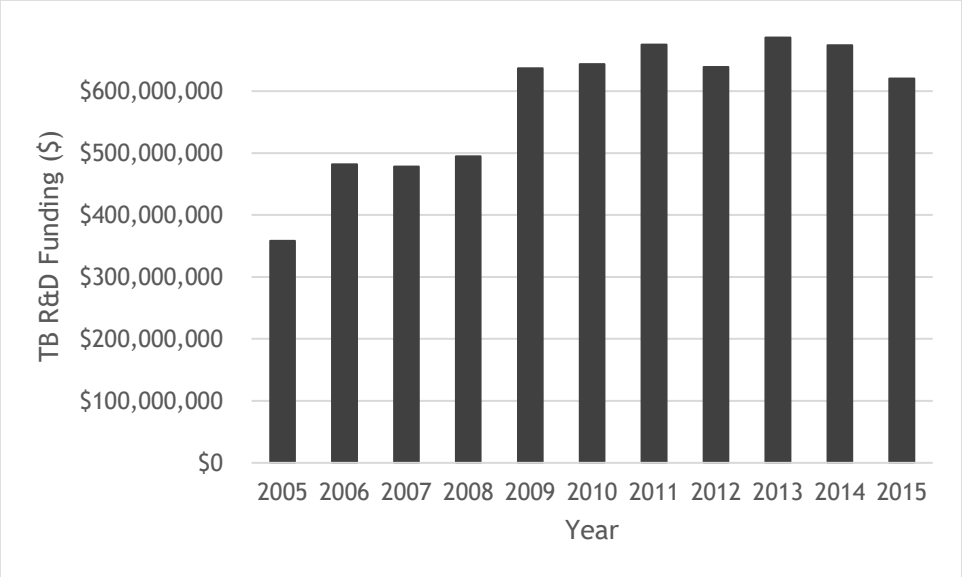

Figure 4: Total TB R&D funding, 2005-2015, ***[4]***

Funding per research category per year gives an indication of the focus of investors in TB R&D over the past 10 years. The drug development received the most funding, achieving a maximum of $268 million in 2013, but decreasing with over $30 million to a less desirable $232 million in 2015 [4]. Diagnostics reached its funding peak with $111 in 2014 million, but decreased to $81 million in 2015; operational research achieved a maximum of $88 million in 2011, decreasing to $61 million in 2015 [4]. These figures indicate the decreased market interest in TB.

5.4.2 Number of drug approvals

The FDA approval of drugs for treating TB has been notably slow over the past 40 years [3]. The exception, however, is the approval of the two novel drugs bedaquiline and delaminid. At the time of writing, a third drug, pretomanid, is undergoing phase 3 clinical trials along with the two drugs mentioned previously [3].

5.4.3 TB disease burden

Measuring the effectiveness of the drugs, innovations and technologies launched is challenging. One way in which the success of the strategies used to end TB can be measured is by assessing the overall disease burden. Globally the TB mortality rate (measured per 100 000 population) decreased by 37% between the years 2000 and 2016 [1].

5.5 Discussion of results

The amount of funding invested in TB drug R&D and the overall drug pipeline depends greatly on the return on investments in TB drug R&D [4]. The number of drug approvals for TB is influenced by the complex structure of MTB within the host (influencing factor D). The different physiological states of the bacterium (factor D) also lead to a greater variety of scenarios in which the drug compounds in development should act. The number of drug approvals is also affected by the strict policies and regulations put in place to ensure that only safe and effective drugs are introduced into the market.

The disease burden of TB is subject to most of the factors listed in Table 4. Drug resistance (factor A) causes the disease to be less treatable with the drugs on the market. Because the disease is most prevalent in developing countries (factor B) with a constrained amount of resources (factor C), it decreases the likelihood that the impact of the disease can be mitigated effectively. When the access to drugs of patients infected with TB is limited (factor E), the effective treatment of those patients becomes unviable. The disease burden cannot be lessened if there is no easy access to the right types of drug for patients. Improving the availability of DST technology (factor G) will improve the ability of clinics to determine whether someone is infected with DR-TB or not, thus providing the patient with the right type of medicine.

6. COMPARISON BETWEEN PHARMACEUTICAL AND TB DRUG PIPELINES

It is apparent that there are similarities and differences between the pipeline of the pharmaceutical industry and the TB drug pipeline. It is important to note that the pharmaceutical pipeline serves as a reference to which the TB drug pipeline is compared.

6.1 Evaluation of influencing factors

The top eight factors in the pharmaceutical sector focus mainly on improving the efficiency and productivity of the drug pipeline by ensuring that the drugs progressing through the clinical trial phases are approved as fast as possible and identifying reasons if this does not happen. The factors that occurred the most in the TB drug pipeline indicate something about the nature of the disease, the complexity of the disease itself and the state of the setting in which most TB cases occur. The only factor found in both pipelines is the lack of funding (factors 9 and F in tables 1 and 3, respectively).

It is evident that the TB drug pipeline cannot be examined without taking the circumstances and characteristics of the disease into account. These circumstances and characteristics include: i) the number of cases reported per year; ii) the success rates of drug treatments; iii) the regions in which this disease is most prevalent; iv) the complexity of treatment; and v) the length of the treatment course.

6.2 Evaluation of pipeline trends

Although there is a lack of funding and investment in both pipelines, it is evident that the funding gap in the TB drug pipeline is much greater than the funding gap in the general pharmaceutical industry, indicating that the investment gap is most likely not as prominent for the R&D of other drugs.

The productivity of the development of TB drugs differs significantly compared to productivity in the pharmaceutical pipeline. The number and rate of TB drug approvals are much lower and slower than those in the pharmaceutical drug pipeline. This indicates the difficulty in finding an effective cure for TB and DR-TB, as a result of disease complexity and drug resistance.

The prevalence of TB in developing countries gives rise to smaller returns on investment compared with the R&D for other diseases. It is assumed that pharmaceutical organisations or private investors aim to maximise their returns on investment. Consequently, TB R&D investment is not seen as a first option and funds are rather invested elsewhere.

7. THE VALUE OF THE IDENTIFICATION AND ANALYSIS OF TRENDS AND INFLUENCING FACTORS IN THE PHARMACEUTICAL AND TB DRUG PIPELINES

The value of the factors and trends identified in this study, and ways in which the identification of influencing factors and trends in drug pipelines might contribute towards more effective investment and better decision-making, are discussed in this section.

7.1 The ability of trend analysis to enable decision-making in TB R&D investment

The trend and influencing factor analysis of the general pharmaceutical industry identified characteristics of the industry and sector in terms of market attractiveness, productivity and costs that would not be possible otherwise. Comparing the TB and general pipelines identifies gaps in the TB drug pipeline that do not exist in the general sector. The identification of these gaps serves as a platform to improve the TB drug pipeline. The TB drug pipeline undoubtedly requires more funding and investment to mitigate the disease effectively. Questions arise on how additional funding options will be made available or how investors will be encouraged to invest in this disease – keeping in mind that TB mostly occurs in developing countries with limited resources and relatively low returns on investment, and with the infection evolving day by day into an even more drug-resistant strain.

It should be noted that all drug pipelines are similar, but that variance is caused by the disease itself. The disease, its characteristics, most popular region of occurrence, challenges, complexity, and all other factors affect the drug pipeline. TB has exceptional characteristics, as it is currently the infectious disease that kills the most people in the world.

Identifying trends in the TB drug pipeline not only identifies the characteristics of the disease, but also provides a platform to present to stakeholders and potential investors, encouraging contributions and influencing future investment decisions.

7.2 Encouraging investment in TB R&D with the use of incentives

Decision-making on investment in TB drugs includes the consideration of incentives [25]. Burki [25] remarks that, even if funds were to be sufficient, other incentives should be available to keep the sector sustainable, as the high development costs will not lead to profitable returns. Parys suggests that push (grants) and pull (the transferable priority review voucher scheme run by the FDA and advancement prizes for achieving a specified goal) mechanisms are the best way to encourage private companies to invest in the disease [25].

Médicins Sans Frontières (MSF) proposed a new model for TB R&D based on push and pull mechanisms, with pooled intellectual property as an addition. The model is primarily aimed at separating the selling price of drugs from the R&D process costs [25]. The proposed MSF model, is intended to reduce the duplication of R&D efforts by different stakeholders, ensures open collaborative research, reduces the risk of compounds being rejected, and accelerates drug combination development [25] & [26]. To MSF's disappointment, the WHO rejected the proposal in December 2013, and it was thus not pursued any further.

7.3 The benefit of an in-depth understanding of the TB drug pipeline

Understanding the drug pipeline, and more specifically the TB drug pipeline, creates the opportunity to forecast and strategise decision-making more accurately. Forecasting in pharmaceutical pipelines enables stakeholders to make more informed predictions of the unpredictable market, and to allocate funds more efficiently to areas lacking the required growth. The complete understanding of the drug pipeline presents the opportunity to adjust the overall drug development strategy to align with the goals of effectively mitigating the disease.

8. CONCLUSION AND FURTHER RESEARCH

The drug pipeline is a complex and interconnected system. Thirty-nine factors influencing the pharmaceutical drug pipeline have been identified through a systematic literature review. The foremost factors are regulations and policy, the set-up of clinical trials, and circumstances regarding the participants of clinical trials. Trends identified in the pharmaceutical industry include the relative stagnation of productivity (in terms of NTDs launched) and a decline in capital investment in the sector. The transparency of clinical trials has increased, as more trials have been registered over the past decade. The cost of clinical trials has sky-rocketed – clinical procedures, administrative staff and site monitoring costs are responsible for between 37% and 65 % of total trial costs.

The complete / total TB drug pipeline can be divided into four distinct sub-pipelines. This study focused on the treatment pipeline only. The R&D in TB drugs has only recently made progress, with the approval of two novel drugs for the first time in 40 years. Twenty-four factors influencing the TB drug pipeline have been identified. The foremost factors are the increasing drug resistance of the infection, and the fact that disease occurring primarily in developing countries with limited resources. The trends most visible in the TB drug pipeline include the seeming shortage of private investment in TB R&D, and a lack of productivity (when based on drug approvals).

The conclusion is that the realisation of returns in the pharmaceutical industry depends on the type of drug being developed and on certain characteristics of the disease being targeted. In the case of TB, the characteristics include the high prevalence of the disease in developing countries, making it unattractive as a potential investment. Looking at investment trends, it can be deduced that investments in diseases occurring mostly in resource-constrained countries hold greater risks for stakeholders, compared to diseases in developed countries with more funds available.

Future research opportunities exist within the pharmaceutical R&D pipeline to identify characteristics that improve the market attractiveness of certain diseases in comparison with others. Research should be done to determine the features of diseases and the similarity of those features in various diseases that currently experience a lack of capital investment. Current and alternative finance mechanism schemes should be investigated to potentially improve the interest of private investors in diseases with unattractive characteristics.

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