ABSTRACT

Background: Systematic reviews are source of questions for future Tuberculosis (TB) research. We did a systematic review of published systematic reviews on TB, to identify research priorities that are most frequently suggested in reviews.

Material and Methods: We searched EMBASE, MEDLINE, Web of Science, and the Cochrane Library for systematic reviews and meta-analyses on aspect of TB published between 2010 and 2015. In total, 85 systematic reviews were included in this review. We used the UK Health Research Classification System (HRCS) to classify the research questions and priorities. The three most common research topics were in the area of development and evaluation of treatments and therapeutic interventions (30%), detection, screening and diagnosis of TB (25%), prevention of disease (25%). The research priorities determined were mainly focused on evaluation of drug treatments for TB, drug-resistant TB and HIV/TB, on the discovery and evaluation of bacteriological TB tests and drug-resistant TB tests and prevention of disease.

Conclusions: Systematic reviews are a good source of key research priorities.

Keywords: Tuberculosis; Research; Systematic review.
INTRODUCTION

Research is particularly critical for developing new tools and approaches needed for eliminating TB by 2050.

The ultimate goal is to reach all populations, including people with TB/HIV co-infection or MDR-TB and children, with new and better methods of prevention, diagnosis and treatment.

We reviewed all the published systematic reviews and metaanalyses on TB (in all areas, including drugs, vaccines, diagnostics), to assess what research priorities have been identified in these reviews.

The objectives of our systematic review were to identify all systematic reviews and meta-analyses pertaining to any aspect of tuberculosis from 2010 to 2015, and to rank the research priorities that were identified.

MATERIAL AND METHODS

Searching MEDLINE, EMBASE, Web of Science, and the Cochrane Library were searched for systematic reviews and meta-analyses on TB. The search was limited to systematic reviews and meta-analyses published between January 1, 2010 and December 31, 2015.

RESULTS

There were a total of 800 records identified through the electronic database search. Following the first screening process, 715 records were excluded. Overall, there were 85 systematic reviews included in our analysis (1-84).

Characteristics of included TB Systematic Reviews

The 85 reviews were published in 60 different journals. The majority of reviews (60%) were published in journals with impact factors of five or less, and only six (6.6%) reviews were published in journals with a high impact factor (>9). However, a small proportion of the reviews (8.3%) were published in journals that did not have an impact factor. In addition, approximately 22% of the main authors were from the United States and 38% were from six other countries (China, India, UK, Switzerland, Canada, and Italy). The remaining 39.7% of authors were from 26 different countries. Approximately 91.7% of all reviews were not Cochrane reviews. Among the 11 Cochrane reviews, 7 of them focused on “evaluation of treatments and therapeutic interventions”.

Focus of TB Systematic Reviews

The four most common review categories, in decreasing order, were “Development and evaluation of treatments and therapeutic interventions” with 30% of systematic reviews, “Prevention of disease and conditions, and promotion of well-being” 25% of systematic review, “Detection, screening and diagnosis” 25% of systematic reviews, and “Aetiology” 15% of systematic reviews.
In the category “Development and evaluation of treatments and therapeutic interventions”, 07/30 (23.3%) studies focused on drug resistant tuberculosis treatment, 08/30 (26.6%) studies on evaluating different regimen combinations for tuberculosis treatment, and 13/30(43.3%) on TB/HIV treatment and 1/30 (0.03%) studies on treatment of latent tuberculosis infection (LTBI).

In the category "prevention of disease",19/25 (76 %) studies on evaluating vaccines and 5/25(20%) studies on isoniazid preventive therapy in MDRTB.

Within the category of “Detection, screening and diagnosis”,6/25 (24%) of the reviews focused on bacteriological diagnostics for active TB, and assessing the use of nucleic acid amplification tests (NAATs). In the category “Aetiology”, 30% of systematic reviews focused on biological/genetic risk factors such as genetic susceptibility and gene targets,60% of studies targeted surveillance and distribution of TB/HIV co-infection, MDRTB and HIV, and diabetes and TB, and 0.06% focused on travel risk for LTBI and nosocomial TB exposure.

**Research Priorities**

The category “Evaluation of treatments and therapeutic interventions” was the most frequent. It focused on TB/HIV drug treatments (48.3%), new TB drugs and active tuberculosis regime (45.1%).

New drugs are required to shorten and simplify treatment; There are 8 new drugs in Phase II or Phase III trials.2 new drugs(bedaquiline and delamanid) have been approved and recommended by WHO for use in the treatment of MDR-TB. Novel regimens including these or other new drugs are studied for a shorter, novel shorter treatment combinations that could be safety used to prevent development of TB latently infected patients are tested.; The drug pipeline appears static in phase I of clinical development. Recent attention has focused on development of the new drugs bedaquiline, delamanid, pretromanid, sutezolid and SQ 109 and their evaluation in clinical trials.

Within the “Prevention of disease and conditions” the main TB priorities were: the development of vaccine candidates (44.4%) and investigating diet/BMI/diabetes mellitus as TB risk factors (30.5%).

Within the category “Aetiology” category, the main TB research priorities were: socioeconomic risk factors (38%), research designer and methodologies (28.5%), biological and endogenous risk factors (19%), surveillance and distribution (14.2%).

There are 16 vaccines candidates in clinical trials, including recombinant BCG vaccines, attenuated Mycobacterium tuberculosis strains, recombinant viral-vectored platforms, protein/adjuvant combinations and mycobacterial extracts. Most candidates are about to enter Phase II or IIb trials.

In the category, “Detection, screening and diagnosis”, the top research priority was the evaluation of bacteriological TB diagnostic tests in 4/25 (16.0%) reviews.
Other frequently cited TB research priorities were: evaluation of immunological TB diagnostic tests (2/15 [13.0%]); discovery and development of new TB diagnostic tests (1/15 [6.5%]); and development of new bacteriological MDR-TB diagnostics (1/15 [6.6%]). More than 50 new TB tests are in various of development. Rapid molecular diagnosis and drug susceptibility testing using automated nucleic acid amplification have been introduced. Technologies under development include innovative and complex molecular platforms for simultaneous detection of multiple mutations for drug resistance. The Xpert MTB/RIF assay (Cepheid Inc) is an automated polymerase chain reaction-based test that can identify MTB DNA in clinical specimens and detect rifampicine resistance. An optimized version of the Xpert MTB/RIF is being developed. Truenat MTB test (Molbio Diagnostics, India) undertaken in India found sensitivity and specificity to be similar to that of the Xpert MTB/RIF assay. Easynat reported high sensitivity and a specificity compared with culture of 66.7% with 10% of smear cases found to be positive.

**DISCUSSION**

Our systematic search showed that a fairly high number of systematic reviews were published on TB during the period of 2010 to 2015. The findings of our review need to be interpreted along with two recent systematic reviews by Rylance and Nicolau colleagues. These authors found that the top priority areas for research were new TB drug development, diagnosis and diagnostic tests, epidemiology, health services research, basic research, and vaccine development and use. In our review of 85 TB systematic reviews, the top three categories for the focus of the research priorities were “Evaluation of treatments and therapeutic interventions”, “Detection, screening and diagnosis”, “Aetiology”. The findings of our review need to be interpreted with recent reviews by Rylance and Nicolau. TB diagnosis and treatment were among the most important research priorities in both reviews. One possible reason of why TB diagnosis research ranked high on their list could be that their review focused on years 2005 to 2010, a period when major advances have been made in TB diagnostics, especially with IGRAs becoming a very popular subject of research.

Our study has several limitations. The findings may not be representative of the general output from the TB research community.

The inclusion of eligible studies was limited by the fact that we only reviewed articles in two other languages besides English.

In summary, our systematic review of published systematic reviews on TB helped identify several key priorities for future TB research. This exercise was useful to describe the landscape of TB research and the overarching TB research themes arising from systematic reviews and meta-analyses conducted over the last 5 years. Their scope is, however, limited, since systematic reviews themselves are influenced by current hot topics or new technologies.
References


