

## Review

# Less research on tuberculosis than HIV and malaria when research agendas are poorly coordinated: a systematic review of research outputs from Cambodia



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## SUMMARY

**Objective:** Coordination of health interventions and research is often weak during periods of political transition and unprecedented aid inflows, which Cambodia has recently experienced. Although HIV, tuberculosis (TB), and malaria have been a focus of international funding, TB has received much less. This study compares the numbers and methodologies of studies conducted on TB, malaria, and HIV in Cambodia, identifying evidence gaps and future research needs.

**Methods:** Three electronic databases and the grey literature were searched for studies on HIV, TB, and malaria published between January 2000 and October 2015. Information about the disease focus and methodology was extracted from the studies included.

**Results:** A total of 2581 unique studies were screened and 712 were included in the analysis. The results of this review demonstrated that despite increasing numbers of publications, there have been fewer studies on TB (16%) than HIV (43%) and malaria (41%). Observational epidemiological studies outnumbered other methodologies (44%) for all three diseases.

**Conclusions:** Despite substantial investments, important research areas appear to have been neglected in Cambodia; specifically, studies on TB and studies involving economic, qualitative, interventional, and genomics methods. The inter-disease disparity in published research in Cambodia identified, considered alongside disease burden, suggests that an increase in TB research may be needed to inform control strategies.

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## 1. Introduction

The setting of health research agendas in developing countries is a complex and often neglected process, and coordination across stakeholders is even more difficult in post-conflict settings experiencing unprecedented influxes of international funding.<sup>1,2</sup> Cambodia is an example of such a situation; the country experienced a genocide in the second half of the 1970s and

substantial political and military conflict for the following decade.<sup>3</sup> In the 1990s, Cambodia became a focus for international aid and interest in rehabilitation<sup>2</sup>, with the three major infectious diseases of HIV, tuberculosis (TB), and malaria being a key focus. From 1998 to 2007, the total amount of aid donated for health programmes in Cambodia was estimated at US\$800 million.<sup>4</sup>

The influx of international donor funding, along with strong economic growth in recent years,<sup>5</sup> has been associated with notable progress in controlling the major infectious diseases.<sup>6</sup> The prevalence of HIV among adults (aged 15–49 years) decreased from 2% in 1998 to 0.7% in 2012, and there was a decrease in the prevalence rate of TB from 1230 cases per 100 000 population in 2005 to 715 cases per 100 000 population in 2013.<sup>7,8</sup> The incidence

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of malaria also decreased from 71 814 cases in 2009 to 24 135 cases in 2013.<sup>9</sup>

Although the control of HIV, TB, and malaria has been the focus of donor aid, TB has received much less funding. The Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund) has been the principal donor to HIV, TB, and malaria control in Cambodia, with more than US\$383 million disbursed between 2003 and 2016. Of this, 58.1% went towards HIV projects, 31.7% to malaria, and only 10.2% to TB.<sup>10</sup> The distribution of donor aid to Cambodia may be influencing research conducted on TB, HIV, and malaria, as found elsewhere;<sup>11</sup> indeed evidence from the only systematic review to be conducted on health research in Cambodia – covering a number of conditions – indicates that there may be unequal representation of disease areas in terms of research publications.<sup>12</sup> The aims of this study were to compare TB research output with those for malaria and HIV and to analyse differences in research methods applied, in order to identify evidence gaps and future research needs.

## 2. Methods

Scoping reviews are systematic literature reviews used to summarize a range of evidence in terms of the volume, nature, and characteristics of the primary research.<sup>13</sup> They are particularly useful when the topic has not been reviewed previously and when the studies are likely to be heterogeneous in nature. Scoping reviews have some similarities to systematic literature reviews, in that they use defined and thorough methods to collate and analyse all the relevant literature pertaining to a specified research question. One main difference between the review techniques is that a scoping review aims to map the whole body of literature on the topic area in question and therefore considers a large and broad selection of literature, whereas the systemic review has a more focused set of results relating to the research question being answered. A key characteristic of scoping reviews is that they usually include publications with a range of methodologies and study designs and do not involve data synthesis from the individual papers.<sup>14</sup>

This scoping review of research published in the last 15 years on major communicable diseases (TB, HIV, malaria) in Cambodia was conducted based on the well-established methodological framework for scoping reviews designed by Arksey and O'Malley in 2005,<sup>15</sup> and included the following stages: (1) identifying the research question, (2) identifying relevant studies, (3) study selection, (4) charting the data, (5) collating, summarizing and reporting the results.

Three electronic databases – PubMed, Embase, and Index Medicus for the South East Asia region (IMSEAR) – were searched in accordance with the specifications of each database. The search strategies were executed on October 27, 2015, and search limits were applied to include only those studies published from January 1, 2000. Search terms were intentionally broad in order to capture the breadth of literature. The search was conducted in two stages. For the first search, the terms “Cambodia” AND “health” were applied, and for the second search, the term “Cambodia” was combined with any of the following disease-specific terms to identify papers not identified by the first search: “HIV” OR “AIDS” OR “Tuberculosis” OR “TB” OR “Malaria”. In addition, the following grey literature sources were also searched through website archives: the World Bank and the World Health Organization (WHO). Relevant additional papers that were not identified in the searches were added at this stage.

Following the removal of duplicates, two-stage screening against inclusion and exclusion criteria was executed independently by two reviewers (RJ, SW), sifting first by title and abstract, followed by full-text sifting of potentially eligible papers. Studies

were included if they discussed or analysed any aspect related to HIV, TB, or malaria in Cambodia, and were published in English on or after January 1, 2000. All types of research publications, including review articles, were included. Letters to the editor, correspondence, and news articles were excluded. Included publications had to report data generated within Cambodia; those focusing on Cambodian nationals not living within Cambodia were excluded.

The full-texts of publications meeting the inclusion criteria were obtained and the studies were categorized by two reviewers (RJ, SW) independently in duplicate using a standardized data extraction tool. Information was extracted from each study about the disease area (or areas) of focus and the study methodology. If a paper covered more than one disease area it was included in multiple categories, whereas only one category was selected to best describe the methodology. Papers were classified into the following methodologies based on standard definitions of study design:<sup>16,17</sup> qualitative, mixed methods (applying qualitative and quantitative methods), observational epidemiology, interventional epidemiology, genomic and transmission studies, economic (including economic modelling studies), and literature reviews. The final category, ‘other’, included all those publications that did not fit into one of the first seven categories, and contained case reports, papers describing testing diagnostic techniques, comparisons of diagnostic or treatment protocols, drug treatments, disease vectors, and non-economic modelling studies.

Any disagreements between reviewers during the screening of papers for inclusion or data extraction were discussed and resolved with a third independent reviewer (MK), if required.

This review did not involve any primary research with human subjects and therefore did not require ethical approval.

## 3. Results

A total of 4577 citation hits were retrieved from the first and second literature searches, and 2581 remained after the removal of duplicates. Six articles from the search of the relevant grey literature were also included in the screening. Of the combined search results 1742 were excluded by title/abstract sifting, leaving 839 papers deemed suitable for full-text review. Of these, 58 were excluded because they were letters, personal views, or news articles, 35 did not focus on data from Cambodia, 30 were not specific to the three diseases in question, and four were not in English. Seven hundred and twelve of the articles were retained for inclusion in the final analysis (Figure 1).

The results demonstrated a steady increase in the number of publications during the past 15 years (Figure 2).

The comparison across disease areas showed that from January 2000 to October 2015, 124 articles (16%) were published on TB, notably fewer than the 331 (43%) published on HIV and 315 (41%) on malaria (Figure 2).

The analysis of study methodologies (Figure 3) showed that observational epidemiological studies greatly outnumbered all other methodologies; 335 (44%) articles used an observational epidemiological study design and 66 (9%) were interventional studies. Twenty-five (3%) of the included articles were qualitative studies and 54 (7%) were classed as mixed method. Seventy papers (9%) were genomic studies, 16 (2%) were economic analyses (including economic modelling), 96 (12%) were literature reviews, and the remaining 108 (14%) were classed as ‘other’ (Figure 3).

An examination of the study methodologies disaggregated by disease category indicated that malaria had the greatest diversity in terms of research methodologies, with a lower proportion of the malaria publications using observational methodologies and a higher proportion of publications describing interventional and literature review studies. In particular, genomics research was

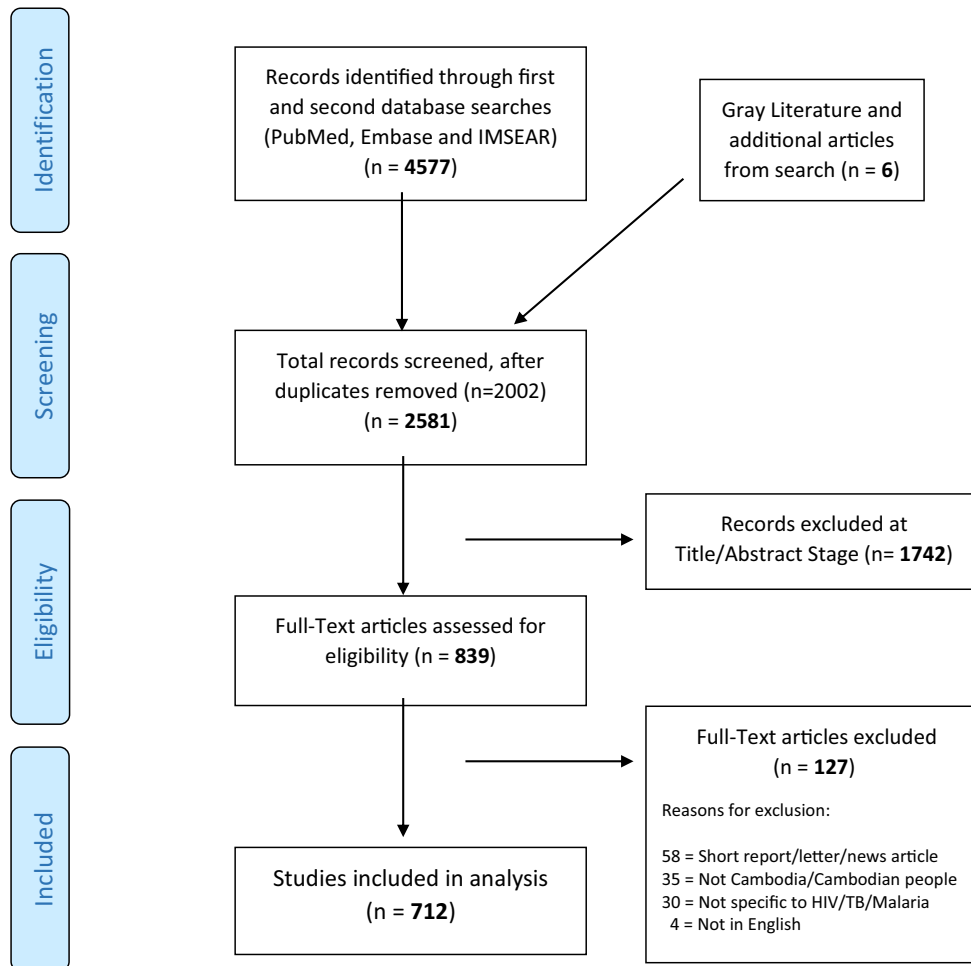


Figure 1. Flow diagram of the publication search and inclusion/exclusion process.

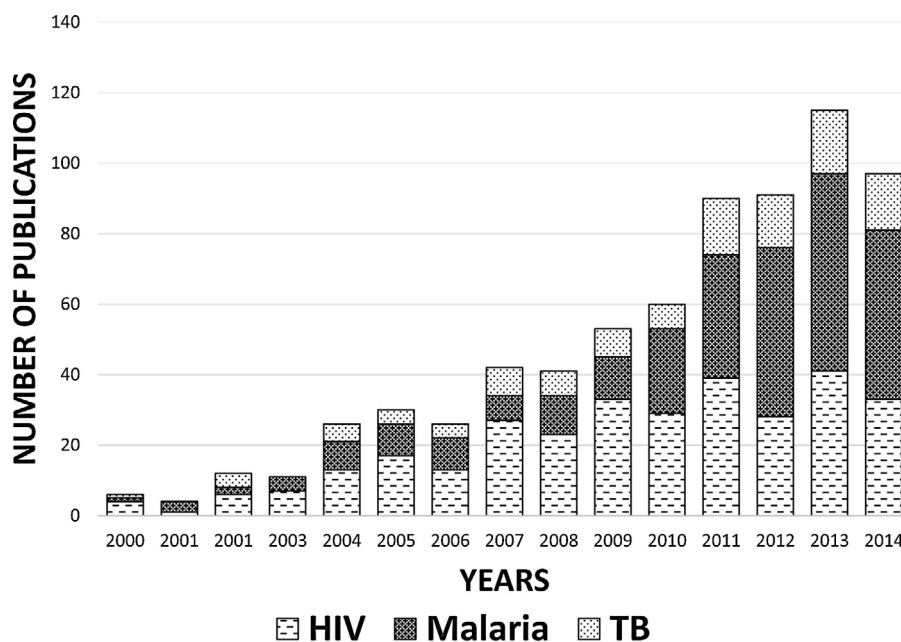
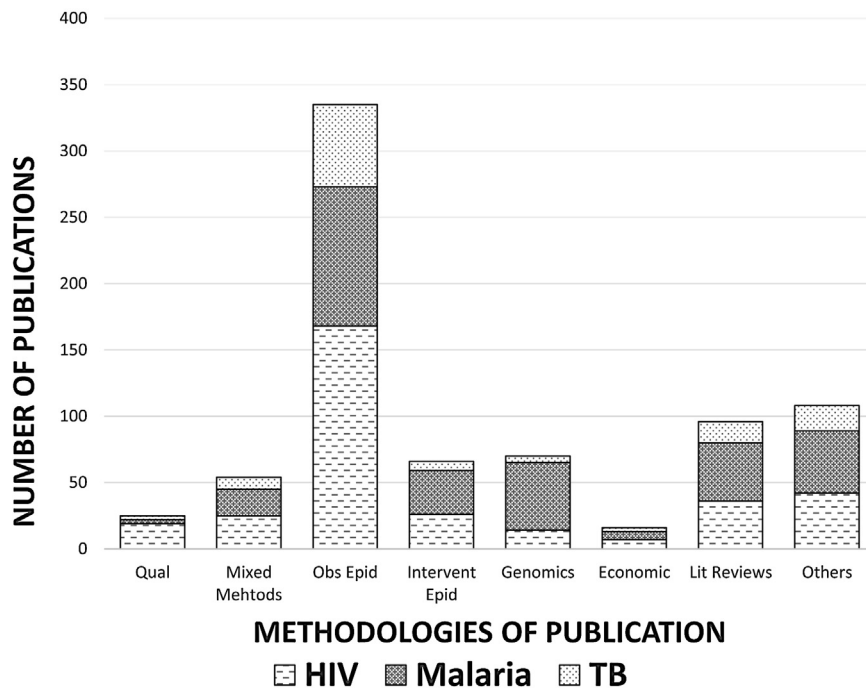


Figure 2. Research on HIV, TB, and malaria in Cambodia published in international journals from 2000 to 2014.



**Figure 3.** Distribution of the research study methodologies for HIV-, TB-, and malaria-related publications in Cambodia between January 2000 and October 2015.

dominated by malaria at 17%, compared to only 4% of TB and HIV studies using genomics methods. For all three diseases, there were very few economic analyses, with only 2% of the publications using economic analysis methodologies.

#### 4. Discussion

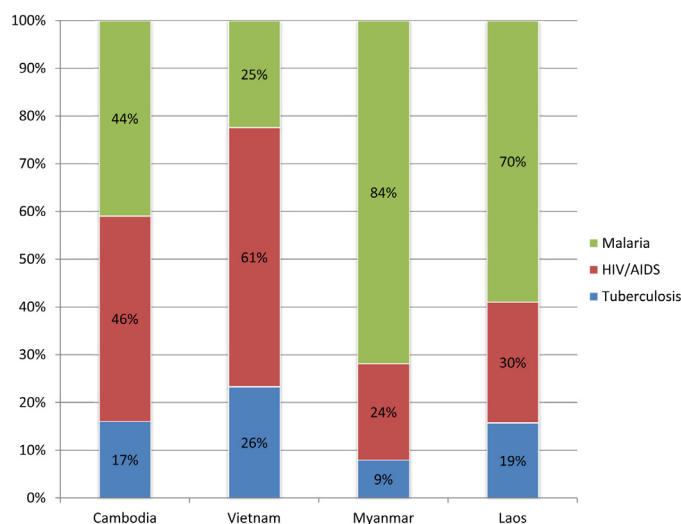
Reducing the burden of HIV, TB, and malaria in Cambodia has been challenging. The Cambodian health system, weakened after years of conflict, experienced a rapid influx of aid, which made the establishment of research agendas difficult. This scoping review, which analyses trends in scientific research into HIV, malaria, and TB in Cambodia, revealed that while there has been a steady increase in research publications in the past 15 years, there has been much less published research on TB compared to HIV or malaria.

Even though TB is the leading cause of death in Cambodia among the three diseases studied,<sup>18</sup> the number of publications on TB was found to be substantially lower than the numbers on HIV and malaria. In 2012, TB was the second leading cause of death in Cambodia, with HIV in fifth place and malaria no longer in the top 10.<sup>18</sup> This analysis showed that TB research has also been the most homogeneous in terms of methodology, with economic, interventional, qualitative, and genomic studies – which may help to address the challenges in TB control – poorly represented. A recent survey assessing TB prevalence in Cambodia noted that, despite declines over the past decade, Cambodia still has one of highest TB prevalence rates in the world, and that a large proportion of patients remain undiagnosed under the current TB control system.<sup>19</sup> Cost-effective strategies to identify undiagnosed (often asymptomatic) patients and reduce transmission are thus needed in Cambodia. The disparity in HIV, TB, and malaria research in Cambodia identified by this review, considered alongside the disease burden, suggests that an increase in TB research may be needed to inform control strategies.

Furthermore, a recent global analysis has indicated that even within TB research, specific policy-relevant topics may be neglected.<sup>20</sup> Indeed, with research funding for TB declining in

recent years, funding for operational research has consistently been a Cinderella area of research.<sup>21</sup> Research priority setting in low- and middle-income countries (LMICs) has become an increasingly important issue, owing to concerns that alignment with donor policies can distort national research agendas in LMICs.<sup>22,23</sup> International agencies and non-governmental organizations (NGOs) have research agendas occasionally perceived by local ministers and policy developers as not aligned to their countries' health needs.<sup>11</sup> Whilst the attribution of research directly to measurable improvements in public health is challenging and often non-linear, investment in research and the production of research outputs (such as publications) is a reasonable measure of domestic and international political commitment to disease control. For TB, perhaps unlike HIV and malaria, donor support for research seems to be lacking. Fewer publications from TB research than from HIV and malaria research appears to occur not only in Cambodia, but also in other countries in the region such as Vietnam, Myanmar, and Laos; a preliminary search on PubMed, using the same search terms and dates as for the Cambodia analysis, revealed that there were fewer TB than HIV and malaria publications in all countries (Figure 4).

This review showed that observational epidemiological studies dominated all three diseases, with limited evidence available from studies applying other methodologies such as economic analyses, qualitative investigations, interventional designs, and genomics. Economic analysis, including but not limited to cost-effectiveness analyses, will be particularly important for decision-making on resource allocation in the near future as funding is reduced during Cambodia's transition from a low- to a middle-income country. The number of genomic studies published was also found to be relatively small, particularly for HIV and TB; such studies can, for example, provide insights on pathogen interaction, emergence of drug resistance, and vaccine effectiveness.<sup>24</sup> Finally, ethnographic and other qualitative investigations will help to develop an in-depth understanding of help-seeking behaviours, as well as approaches for engaging communities and healthcare workers, which is essential for developing locally appropriate and sustainable disease control strategies.



**Figure 4.** Publications with TB/HIV/Malaria in the title or abstract in Cambodia (total 712), Vietnam (total 792), Myanmar (total 450) and Laos (total 123).

A limitation of this study is that unpublished reports from implementation programmes could not be included. Being a scoping review, it was beyond the remit of this study to assess the quality or conclusions of the publications included, although further reviews and meta-analyses on subsets of the studies to appraise and summarize the evidence generated may be useful. An analysis of the impact of the published research on evidence-based policy-making would also provide important insights, especially as a previous review has reported a relatively low level of actionable recommendations being made in the Cambodia health research literature.<sup>12</sup>

In conclusion, it is well documented that the coordination and strategic planning of health sector rehabilitation and public health research is weak during periods of political transition and unprecedented aid inflow.<sup>2</sup> This analysis of HIV, TB, and malaria research activities during the past 15 years in Cambodia revealed that several important research areas may have been neglected; studies on TB and studies involving economic, qualitative, interventional, and genomics methods are under-represented. Ultimately, a coherent research strategy, with the explicit aim of informing policy and practice with defined public health aims is necessary. This should, as is often the case, address research questions that are ‘interesting’ or ‘feasible’, but also result in a programmatic approach to research that harnesses the strengths of multiple disciplines and a number of projects that are timely, feasible, relevant, and linked in a coherent manner to impact upon the public health goals of domestic stakeholders. Work has been conducted recently to develop a national operational research strategy for malaria,<sup>25</sup> and it is suggested that the instrument for development of such a research strategy should be a national committee supported by the donor and research community, as this will ensure that research addresses critical information gaps for policy decisions.

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