Economic evaluation of typhoid: a review of typhoid cost-effectiveness studies

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Economic evaluation of typhoid- a review

Running title: a review of typhoid cost-effectiveness studies

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ABSTRACT

Introduction: To evaluate the potential economic value and likely impact of a hypothetical rapid test in its early stages of development requires the use of models. The model structure and the type of model (dynamic/static) to employ are key considerations. The aim of the review was to explore the literature on typhoid economic evaluations, and to explore the types of models that have been previously adopted in this setting for test-treat evaluations and to capture data on model inputs that may be useful for a de novo model.

Areas Covered: A systematic review was conducted to identify economic evaluations focused on typhoid in established literature databases. Eight studies were identified and included for narrative synthesis. The review has revealed that there have been relatively few economic evaluations that have focussed on typhoid fever, all of which have focused on the impact of interventions at the population level (vaccination) but not the individual level (test-treat strategies).

Expert commentary: Under certain circumstances**,** , either a static model or a transmission dynamic model may be appropriate in the evaluation of an intervention for typhoid fever. Typhoid test-treat modelling represents a grey area where further work is needed.

Key words: cost-benefit analysis; cost-utility analysis; cost-effectiveness analysis; economic evaluation; enteric fever; review; typhoid fever

1.0 INTRODUCTION

Typhoid fever is a faecal-oral transmissible disease caused by *Salmonella typhi* and *Salmonella paraty*phi (incubation period of 3-60 days) [1]. Humans serve as the only natural host and reservoir for typhoid fever pathogens, and transmission is via ingestion of food or water contaminated with faeces from infected individuals [2]. Typhoid fever remains an issue of concern in low- and middle-income countries (LMIC) because of unsatisfactory hygiene practices [3], and a lack of adequate diagnostic laboratory capacity to meet the daily challenge of differentiation of typhoid fever from other febrile conditions [2]. Consequently, efforts are being made to develop rapid diagnostic test kits for typhoid fever in LMIC settings [4]. And Ghana is an example of a country where concerted efforts are being made to develop a rapid test that is expected to be both clinically effective and cost-effective. The potential benefit of developing a rapid diagnostic test is that it will lead to early diagnosis and treatment (with appropriate effective therapy) to ensure the optimal management of patients on the typhoid test-treat pathway [5]. Furthermore, evaluating the economic value of the test-treat strategy may help to define the optimum target product profile (TPP) for a typhoid rapid diagnostic test. Where a TPP is defined as a strategic document which summarises the following: the technology under development, desired characteristics and features of the technology, studies and all activities necessary to demonstrate the performance, efficacy and safety of the technology and the features of the technology that give it a competitive advantage [6].

To evaluate the potential economic value and likely impact of a hypothetical rapid test in its early stages of development requires the use of models [7]. The model structure and the type of model (dynamic/static) to use are key considerations that are informed by the natural history of the disease, care pathway(s) and the type of intervention being evaluated [8]. Two main types of typhoid fever interventions exist: interventions targeted at typhoid treatment (such as test-treat strategies) and interventions targeted at typhoid prevention (such as vaccination) [1]. The underpinning tenet of typhoid fever infection prevention is better sanitation. However, in LMIC settings this remains problematic. Thus, the WHO recommends that vaccination can be considered for typhoid fever prevention in such settings where the disease is endemic. Vaccination acts by stimulating a host's immune response and operates both directly by reducing the number of susceptible individuals in the population and indirectly via 'herd immunity'. Dynamic models are well suited for capturing both effects and are appropriate when evaluating typhoid vaccine effectiveness [9]. However, in some situations, using a static model on the basis of only direct protection from vaccines may be a reasonable approximation, for example if vaccine-preventable new cases make a relatively little contribution to the rate at which susceptible individuals acquire the disease [10]. The outcome of typhoid fever is usually good when there is early accurate diagnosis and treatment with an effective antimicrobial therapy (fatality rate of <1%) [1]. However, relapse may occur even with appropriate antimicrobial therapy [11]. A notable feature of typhoid fever is chronic carriers (1-5% of patients become chronic carriers) who continue to shed the organism in their stool or urine, thereby sustaining the occurrence of the disease in endemic settings [1]. Furthermore, faecal shedding from short-term convalescent patients may also contribute to disease transmission in an endemic setting. Early accurate diagnosis and treatment of a case of typhoid fever (new case, short-term convalescent or chronic carrier) focused on curtailing shedding can potentially result in the prevention of some degree of onward transmission. However, the potential benefits of treatment following accurate diagnosis in preventing onward transmission of typhoid fever in an endemic area have been little studied compared to vaccination. And there is no evidence to inform the extent to which treatment contributes to the prevention of onward transmission or otherwise. The emphasis of typhoid testing and treatment in an endemic setting is the survival and quality of life of the person being tested rather than benefits to the population because of prevention of onward transmission. The evaluation of the direct benefits of testing and treatment to an individual can be served by a static model.

The use of models in cost-effectiveness studies involves adapting an existing model or developing a new model. Identifying what has already been done in the particular field of interest is fundamental to the approach taken. Thus, there was the need for a review of previous typhoid economic evaluations to understand how the impact of typhoid interventions at the individual level has been explored using modelling in order to examine the value of a hypothetical rapid test for typhoid fever in Ghana.

Aim

The aim of the review was to explore the literature on typhoid economic evaluations, and to explore the types of models that have been previously adopted in this setting for test-treat evaluations and to capture data on model inputs that may be useful for a de novo model.

2.0 METHODS

The following databases were searched for studies published from inception to September 2017. No language restrictions were applied.

I. Medline
II. Excerpta Medica dataBASE (EMBASE)
III. Centre for Reviews and Dissemination [Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), and NHS Economic Evaluation Database (NHS EED)]
IV. PubMed

The reference list of the studies included in the review were also scanned for additional relevant articles. The list of articles used was managed through the reference management software, Endnote.

2.1 Search terms

The search strategy was customized for each database and searching was undertaken using the following terms, including truncation of terms where appropriate: economic evaluation, cost-benefit analysis (CBA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA), typhoid fever and enteric fever. Table 1 shows the complete search strategy for each database.

2.2 Inclusion criteria

Studies were included if they were

- Economic evaluations focussed on typhoid fever; or
- Systematic reviews of typhoid economic evaluations.

2.3 Exclusion criteria

Studies were excluded if they were

- Not in English; or
- Not conducted in an endemic setting; or
- Trial protocols or commentaries; or
- Letters or editorials.

2.4 Selection of articles for the review

After the removal of duplicates, a two-stage screening of titles and abstracts followed by an examination of the full text articles was undertaken against the inclusion criteria. All studies identified after the second stage of article selection were subsequently considered for data extraction. The article selection process was undertaken by two reviewers (SF and PB), and disagreements were resolved by consensus.

2.5 Data extraction

Data extraction was conducted for each included study to answer the following questions:

- What were the interventions evaluated (test-treat strategies; vaccination)?
- What was the economic evaluation approach adopted (CUA or CBA or CEA) and what was the outcome measure?
- What type of model was used (static model; transmission dynamic model)?
- What was the impact of the intervention on the transmission of infection between individuals?

2.6 Quality assessment

The methodological quality of the included studies was assessed using a modelling quality checklist modified from Philips et al. [12]. Each item on the checklist was rated under the following categories “yes”, “no”, “unclear” and “not applicable” by the extent of reporting. However, because the focus of this review was to explore the models used and not to comment on the validity of results and conclusions drawn from these studies, no study was rejected on quality grounds.

3.0 RESULTS

After de-duplication, 43 unique articles were identified for title and abstract screening. 15 titles and abstracts were potentially eligible for inclusion. After full text screening, 8 studies were included in the review. Fig 1 is the PRISMA flow diagram summarising the results of the screening process with reasons for exclusion noted.

3.1 Characteristics of included studies

A systematic review [10] and seven primary studies [13-19] were found. All primary studies identified had been included in the systematic review and no new primary publications were identified post the systematic review. The primary studies identified were published between 1992 and 2009 and the systematic review was published in 2015. Table 2 illustrates the characteristics of included primary studies.

3.2 Quality assessment of included studies

On examining the methodological quality of included studies by rating each item on the checklist under the categories “yes”, “no” and “unclear” depending on the extent of reporting, it was found that 38% of the checklist items were categorised as “yes”, 27% as “no” and 35% as “unclear. No item on the checklist was categorised under “not applicable”. All of the studies stated clearly the decision problem and specified the objectives of the model which were consistent with the stated decision problem. However, in all the studies, it was unclear if the structure of the model was consistent with a coherent theory of the health condition under evaluation. All the studies but one [17], gave a clear definition of options under evaluation but none of them did evaluate all feasible and practical options. No justification was given in any of the studies for the exclusion of feasible options. And it was noted that the chosen model type (static model) was inappropriate given the intervention (vaccination) that was evaluated in all the studies. Table 3 presents the details of the quality assessment.

3.3 Summary of study findings

All primary studies focussed on typhoid vaccine cost-effectiveness. None of the studies considered test-treat cost-effectiveness and evaluations that were based on field studies were found to share common authorship through collaboration with the Disease of Most Impoverished (DOMI) program. It was noted that static models were used in all studies with no economic evaluation based on transmission dynamic modelling. Only one study was found to include indirect protection quantitatively, albeit using hypothetical values for herd immunity rather than estimates from dynamic modelling [16]. In that study, it was shown that vaccine cost-effectiveness was impacted by the level of indirect protection. While the other studies acknowledged the importance of herd immunity, it was noted to be excluded from their analysis. The absence of evidence was cited as the reason for exclusion. The analysis by Poulus et al. [18] conducted from the public sector perspective, showed that a vaccination programme targeted at children under 5 years would be cost-saving. Conducting the same analysis from the societal perspective showed that there was net benefits in other age groups if vaccine cost was moderate and vaccination was carried out in a high incidence setting. Two studies showed that, while vaccination with Vi-polysaccharide in both adults and children was unlikely to be cost-effective in a general population setting from the public sector perspective, such an intervention was likely to be cost-effective in a high incidence setting [14,15]. In these studies the main drivers of cost-effectiveness established through sensitivity analysis were vaccine cost, vaccine duration of protection, case fatality rate and vaccine effectiveness. No indirect protection was assumed; therefore the effect of herd immunity on cost-effectiveness could not be appraised. It was noted that vaccination is effective in reducing the incidence of typhoid. However, short or medium-term vaccination programs are unlikely to be effective in the elimination of the disease without measures aimed at reducing the ongoing force of infection (such as asymptomatic carriers).

4.0 DISCUSSION

This review has examined previous typhoid economic evaluations, with particular focus on how test-treat modelling for typhoid had been approached. The review has shown that there have been relatively few economic evaluations that have focussed on typhoid fever, all of which have focused on typhoid vaccine cost-effectiveness.

Vaccination operates by conferring both direct and indirect effects in its role of preventing onward transmission. Thus, to capture both effects fully, transition dynamic models (which are better suited to capturing these effects) were required. However, as noted, none of the economic evaluations conducted was based on transmission dynamic modelling and indirect protection was omitted in the analysis. Thus, it was not possible to appraise the indirect effect of vaccination in their analysis. The implication is that this may lead to underestimating or overestimating the true benefits of vaccination and may result in inappropriate decision making. Therefore, in order for economic evaluations of typhoid vaccines to be useful to policy making, transmission dynamic modelling should be integrated into cost-effectiveness analysis when estimating their true value.

None of the studies focussed on typhoid test-treat strategies. Thus the review shows that, the impact of typhoid interventions at the individual level has not been explored using modelling. However, in the evaluation of interventions that primarily seek to improve direct health outcomes (such as test-treat strategies) without necessarily impacting disease transmission, static models could be a plausible option to consider since the focus is to capture principally the direct outcomes of the intervention [20]. Although it might be argued that typhoid fever is an infectious disease and transmission dynamic modelling will be better suited for its evaluation, the role of treatment in preventing onward transmission in typhoid fever has been little explored. And there is no evidence informing the extent to which it contributes to the prevention of onward transmission or otherwise compared to vaccination where its role in reducing the incidence of typhoid (directly and indirectly) has been demonstrated in this review.. Therefore a static model may suffice to evaluate the cost-effectiveness of an intervention for typhoid fever where the emphasis is on improving individual health outcomes (such as test-treat strategies) rather than benefits to the population as a result of treatment preventing onward transmission. Indeed, there are examples of studies in other infectious disease areas where static models have been used to evaluate the cost-effectiveness of rapid diagnostic testing and treatment strategies because the focus was to improve direct health outcomes without necessarily impacting disease transmission [21, 22]. The goal of several recent studies in the field of typhoid economic evaluation has been to identify strategies and associated epidemiological conditions under which interventions will be cost-effective. A parameter that has frequently been found to be a major driver of cost-effectiveness has been “incidence”, and most studies have focussed on the estimation of incidence thresholds to guide policy decision making. However, covariates such as the case fatality rate, antimicrobial resistance, and access to quality healthcare have been shown to be critical but uncertain parameters that have been shown to drive the incidence threshold [23]. While static models have their shortcomings, they can certainly be used to assess the importance of these parameters on driving the conclusions from models such as these.

There is significant uncertainty in many aspects of the transmission and epidemiology of typhoid fever that makes any typhoid related economic evaluation somewhat complex. In order to improve the value of typhoid economic evaluations, there is the need for a concerted effort to develop a single robust model that can assist researchers globally. This could then serve as a standard robust quantitative and analytical tool that can be used for modelling the disease, thereby ensuring standardisation in modelling approaches. Furthermore, the availability of such a model will assist the scientific community to accelerate the exploration of the disease to better understand the dynamics of the disease in a population over time. This will help to determine and formulate health policies and identify optimum intervention strategies that can lead to the eradication of the disease. Another advantage of having such a model is that, it will increase confidence in modelling results that are used to inform policy decision making. Despite these advantages, the dynamics of typhoid fever may vary between settings and a single model may not fit all. However, we believe that the benefits of having such a model would be substantial and any work in this field is a step in the right direction.

Clearly, under certain circumstances, a static model or a transmission dynamic model may be appropriate in the evaluation of an intervention for typhoid fever. Typhoid test-treat modelling represents a grey area where further work is needed.

5.0 Expert commentary

In an increasingly resource constrained environment, informed decision making about health care resource allocation is key. Decision analytic modelling is increasingly being used as a framework for economic evaluation to support such decision making. However, if it is to be fit for purpose for decision making then the structure of the model and the type of model is vitally important. Depending on the role of a typhoid intervention in preventing onward transmission or otherwise of the disease, a static model or a transmission dynamic model may be appropriate in its evaluation. For interventions targeted at preventing typhoid onward transmission at the population level (such as vaccination), transmission dynamic models are appropriate and must be integrated into economic evaluations to maximize the value of such analysis, but, this is currently not the case. For interventions targeted at typhoid treatment (such as test-treat strategies) where the focus is to evaluate the direct impact of the intervention on the quality of life of the individual, static models may be appropriate for their evaluation and this represents a grey area where further work is needed. Typhoid modelling is an area that has been relatively understudied and typhoid vaccine cost-effectiveness evaluations predominate currently in this field.

6.0 Five-year view

The growing demand to develop rapid diagnostic tests for typhoid fever in LMIC settings is likely to be associated with an increased need to demonstrate the value of tests (clinical effectiveness and cost-effectiveness) before their introduction into clinical practice. It is expected that this will lead to an increased interest to understand how the impact of typhoid interventions at the individual level should be evaluated using modelling. Consequently, this will lead to an increase in the effort to develop rigorous guidelines or methodologies in this field to assist researchers.

7.0 Key issues

- Under certain circumstances, a static model or a transmission dynamic model may be appropriate in the evaluation of an intervention for typhoid fever.
- For interventions targeted at preventing typhoid onward transmission at the population level (such as vaccination), transmission dynamic models are appropriate and must be integrated into economic evaluations to maximize the value of such analysis.
- For interventions targeted at typhoid treatment (such as test-treat strategies) where the focus is to evaluate the direct impact of the intervention on the survival and the quality of life of the tested individual, static models may be appropriate for their evaluation.

- The review has shown that there have been relatively few economic evaluations that have focussed on typhoid fever, all of which have focused on typhoid vaccine cost-effectiveness.
- None of the economic evaluations conducted was based on transmission dynamic modelling and indirect protection was omitted in the analysis.

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