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ABSTRACT

Introduction: Despite the availability of several commercial rapid diagnostic tests (RDTs) developed to detect typhoid fever, the cost-effectiveness in resource-limited settings is unclear. This review aimed to explore the literature on typhoid economic evaluations in order to assess the cost-effectiveness of using typhoid RDTs in resource-limited settings.

Areas Covered: A systematic review was conducted focusing on the identification of economic evaluations of typhoid RDTs to diagnose patients with suspected typhoid fever. Two studies were identified and included for narrative synthesis. Whilst highlighting a gap in the published literature, this review shows the use of typhoid RDTs to potentially be cost-effective in resource limited settings. Factors that appeared as significant in determining cost-effectiveness related to test characteristics (such as sensitivity, specificity and cost) and the prevalence of typhoid fever and should factor into any future evaluations.

Expert commentary: Concerted effort is needed in resource-limited settings with regards to medical device regulation to ensure that clinically effective and cost-effective typhoid RDTs are widely available and introduced into clinical practice. Typhoid modelling (with respect to typhoid testing and treatment strategies) represents an understudied area and further work is needed.

Keywords: Systematic review, cost–benefit analysis, cost–utility analysis, cost-effectiveness analysis, economic evaluation, enteric fever, typhoid fever, rapid diagnostic tests

1.0 INTRODUCTION

Typhoid fever is an acute bacterial infection caused by the bacteria *Salmonella typhi* and *paratyphi* [1]. Transmission occurs via the ingestion of food or water contaminated with faeces from infected individuals [2]. The World Health Organization (WHO) estimates global typhoid fever burden at 11-20 million cases annually, resulting in 128,000-161,000 deaths per year [3]. The case fatality rate of typhoid fever is 10–30% in the absence of treatment but drops to 1–4% with appropriate antibiotics [3]. Globally, typhoid fever remains an important cause of disease[4], especially in resource-limited countries [5]. Poor hygiene practices [6] and inadequate diagnostic laboratory capacity [2] have been noted as reasons for the continually high rates of infections in resource-limited settings.

The current gold standard method used for diagnosis is blood culture. However, this lacks sensitivity (40–75%) [7], meaning that the disease is often missed in patients resulting in lost opportunities for treatment. This in turn can lead to increased morbidity and mortality. Furthermore, blood culture requires trained laboratory personnel, equipment, supplies, and electricity, which may not be routinely available in many primary healthcare facilities in resource-limited countries. In addition, it can take 2 to 3 days before test results are returned leading to delays in diagnosis and possible complications such as perforation of the intestine and death if treatment is postponed or patients are lost to follow-up [8]. Low-cost diagnostic tests, such as the Widal test, are still widely used, however, the Widal test is limited by both a lack of sensitivity (44-77%) and may be geographically specific/unspecific (50-92%) depending on the epidemiology of other infections [9,10], making it an unreliable indicator for typhoid fever. Furthermore, typhoid fever clinically resembles other febrile conditions including malaria and is therefore easily misdiagnosed without laboratory confirmation [11], causing over-prescription of antimalarial therapies associated with a huge economic impact [12]. Therefore, the availability of a test that is accurate, simple, and affordable with a quick

time-to-result for the diagnosis of typhoid fever in resource-limited settings has an obvious attraction. Over the past decade, there has been over 20 commercially-available RDTs and their prototypes (including TUBEX, Typhidot, Typhidot-M, Test-it Typhoid, and other tests)[11]. However, despite the availability of commercial RDTs for typhoid fever [11], the cost-effectiveness in resource-limited settings is unclear.

Aim

The aim of this systematic review was to assess the cost-effectiveness of using RDTs to diagnose typhoid fever in patients with suspected typhoid fever in resource-limited settings. Specifically:

- To report the results of existing economic evaluations of typhoid RDTs in terms of cost-effectiveness.
- To gain insights, through the studies identified, into the relevant factors that influence the cost-effectiveness of the use of typhoid RDTs.

2.0 METHODS

The systematic review protocol was registered with the international prospective register of systematic reviews (PROSPERO), in accordance with PRISMA guidelines (PROSPERO CRD42021253072). In May 2021 we searched CAB Abstracts (Ovid), Cochrane library (Wiley), Embase (Ovid); Global Health; Global Index Medicus-(WHO), MEDLINE(Ovid), Web of Science core collection, International HTA database (INAHTA), and NHS EED for studies that conducted economic evaluations of diagnostic tests for typhoid.

The searches were developed using the concepts: typhoid and generic testing terms, as well as a second approach searching specifically for named typhoid diagnostic tests and peer reviewed by a senior Information specialist using the PRESS checklist [13]. The search strategies were customized for each database using a combination of database subject headings and index terms

including these key terms (enteric fever or typhoid or paratyphoid) AND (diagnostic tests, Widal or TUBEX or Typhifast) AND the Academic Unit of Health Economics Information Specialists economic evaluation strategies [14]. See search strategies in the Appendix. The searches were not limited by date or language. Searching was not limited by language to make it more inclusive.

2.1 Inclusion criteria

Studies were required to meet all the inclusion criteria outlined in Table 1 in order to be included in this review. All published literature which relates to the cost-effectiveness of typhoid RDTs were considered for inclusion. Only studies with full texts available in English were included in the final set of studies because of a lack of expertise to translate non-English language studies.

We excluded studies not published as a full text manuscript or conference paper (e.g., all abstracts, review, editorials and opinion pieces were excluded); however; any relevant reviews were flagged, and their citations checked for relevant studies not already captured in the review. The reference lists of included studies were also screened. Studies that do not diagnose typhoid in patients were excluded.

2.2 Data management and screening

Records were stored and deduplicated in Endnote software and reviewed using the web app, Rayyan [15].

A two-stage screening of titles and abstract, followed by full text review was undertaken independently (i.e., blinded to the other reviewer's decisions) by two reviewers (SF and GS). At the initial title and abstract screening stage, citations considered relevant by either reviewer were included in the full text review. At the full text review stage, disagreements between

reviewers as to article inclusion (as outlined in Table 1) were resolved via discussion with a third reviewer (NK).

2.3 Data extraction

A data extraction form was developed and piloted in Microsoft Excel 2016. For each of the included studies, data extraction was conducted to answer the following questions:

- Is the use of typhoid RDTs for the diagnosis of typhoid fever cost-effective in resource-limited settings?
- What are the relevant factors that influence the cost-effectiveness of the use of typhoid RDTs in resource-limited settings?

Data extraction included key items related to design of study, study population, type of economic evaluation, form of economic evaluation, perspective, location, currency and price year, intervention(s), comparator(s), methodology, measurement of health outcomes, time horizon and discount rate, base case findings and results of sensitivity and scenario analysis. Data extraction was undertaken independently and in duplicate (SF and GS) with any disagreements between reviewers resolved by a third reviewer (NK).

2.4 Quality assessment

The methodological quality of each included study was assessed independently and in duplicate (SF and GS) using a modelling quality checklist modified from Philips et al. [16]. Each item on the checklist was rated using the categories ‘yes’, ‘no’, ‘unclear’, and ‘not applicable’ allowed by the extent of reporting.

3.0 RESULTS

The database searches identified 1293 records. Once duplicates were removed, there were 741 records eligible for title and abstract screening. Ten studies were potentially eligible for inclusion after title and abstract screening. Following the full text screening, two studies were included in this review. The PRISMA diagram below (Figure 1) illustrates the results of the screening process with reasons for exclusion noted.

3.1 Characteristics of included studies

The identified studies included in the review were published between 2018 and 2020. One study conducted an early economic evaluation [17] and the other, traditional economic evaluation conducted at the late phase of product development [18]. The patient population considered in one study was febrile children who attended a healthcare centre [18] and the other study considered individuals presenting with symptoms suggestive of typhoid. In both studies, decision tree models were used for cost-effectiveness modelling based on hypothetical cohorts. Table 2 illustrates the characteristics of the included studies.

3.2 Quality assessment of included studies

The methodological quality of included studies as rated using the categories “yes”, “no” and “not applicable” found that 64% of the checklist items were categorised as “yes”, 19% as “no” and 17% as “not applicable”. No item on the checklist was categorised as “unclear”. Both included studies clearly stated the decision problem and specified the objectives of their model which were consistent, in our opinion, with the stated decision problem. However, in one study the primary decision maker was not explicitly stated [18] and the other did not specify the sources of the information used to develop the model structure [17].

Both studies provided clear definition of options under evaluation but neither evaluated all feasible and practical options. Furthermore, neither study provided any justification for the exclusion of feasible options, and it was noted that heterogeneity was not dealt with by running

the model separately for different subgroups. See Appendix for details of the quality assessment.

3.3 Summary of the results of existing economic evaluations of typhoid RDTs in terms of cost-effectiveness

One study conducted a cost-effectiveness analysis [18] and the other study conducted a cost-utility analysis [17]. The primary measurement of health outcomes in the study which conducted a cost-effectiveness analysis was treatment success at 7 days, therefore, the incremental cost-effectiveness ratio (ICER) was reported as cost per additional treatment success [18]. The measurement of health outcomes in the study which conducted a cost-utility analysis was the QALY, therefore, the incremental cost-effectiveness ratio (ICER) was reported as cost per QALY gained [17]. In both studies no discounting was applied to future costs and outcomes because of the short time horizon used.

Different assumptions were used across the two studies. For example, different assumptions were made about the time horizon. One study used a time horizon of 7 days [18] and the other study used a time horizon of 180 days. A time horizon of 7 days was chosen because the authors consider treatment success at day 7 to be a useful measure of diagnosis since it represents the effect of correct diagnosis and subsequent treatment choice which is commonly used to assess efficacy. A time horizon of 180 days was chosen in the other study because the authors considered it to be a more appropriate timeframe over which patients would benefit from the impact of both testing and treatment for typhoid fever [17]. Increasing the time horizon to 180 days also allows other feasible options with a longer treatment time (compared to the 34 days considered in the analysis) to be added to the model. In terms of the patient population

modelled, one study assumed patients presenting with suspected typhoid who subsequently do not have typhoid then had malaria because this was the most probable differential diagnosis [17]. In the other study, a febrile child was considered to only have typhoid with malaria excluded [18]. It is worth highlighting that despite the different assumptions used, both studies made the assumption of no co-infections and health workers perfectly adhering to test results and treatment protocols.

In terms of cost-effectiveness in the base case results for both studies, the use of typhoid RDT was cost-effective compared to the comparators they were evaluated against. In one study, the base case results showed that immunoglobulin M lateral flow assay (IgMFA) is more expensive but also more effective than presumptive clinical diagnosis without an RDT. The IgMFA detected 5.87 more true positives than clinical diagnosis (38.45 versus 43.17). The incremental cost of the IgMFA was estimated at US$5700 resulting in an ICER to detect one additional correct diagnosis of typhoid fever as US$972. In the same study the ICER for one additional treatment success (their primary health outcome, IgMFA had 3.61 more treatment successes versus clinical diagnosis) was estimated to be US$1579. In the other study, the base case results show that, at certain price and accuracy pairs for the hypothetical test (HT-test), the HT-test has the potential to be more effective compared with the Widal test in terms of QALYs gained and cost effectiveness.

3.4 Summary of the relevant factors that influence the cost-effectiveness of the use of typhoid RDTs

Both studies performed and reported on at least some form of deterministic sensitivity analysis and reported a probabilistic sensitivity analysis.

Across both studies, factors that appeared as significant in determining cost-effectiveness related to test sensitivity, specificity, cost and the prevalence of typhoid fever. One study

reported that the relative sensitivity of IgMFA versus clinical diagnosis, the cost of IgMFA, and the prevalence of typhoid fever or multi-drug resistant (MDR) strains were the key drivers for the ICER [18]. When the sensitivity of IgMFA was changed (from 59% used in the base case) to 42% (lower 95% CI value), the ICER was estimated to be US$1776 resulting in 3.21 less cases of treatment success than versus clinical diagnosis. The ICER changes to US$285 with perfect sensitivity resulting in treatment of 20.05 more successful cases. The cost of IgMFA was US$70 higher per treatment success versus the clinical diagnosis. With the typhoid fever prevalence set at 4.5% (lower 95% CI value), the ICER was estimated to be US$2292. When using a higher prevalence of 9.0% (upper 95% CI value), the estimated ICER was US$1147. Having a prevalence of 25% for MDR strains (50% prevalence at base case), the ICER increased to $2219, whereas a much higher prevalence of MDR strains (90%), IgMFA was cost-effective ($1081 per an additional treatment success). The other study reported that, for the HT-test to perform better, in terms of QALYs gained and cost effectiveness, than the existing test (Widal) it is necessary for it to have a high specificity (at least 70%) and should not be priced more than US$4.

4.0 DISCUSSION

This review has examined previous economic evaluations focused on the cost-effectiveness of using rapid diagnostic tests for the diagnosis of typhoid fever in patients with suspected typhoid fever, with particular focus on whether the use of typhoid RDTs is cost-effective and what the relevant factors that influence the cost-effectiveness are. This review identified only two published economic evaluation studies on the cost-effectiveness of typhoid RDTs despite the availability of several commercial RDTs for typhoid fever [11].

It is noted from the review that both studies concluded that the use of typhoid RDTs is cost-effective. However, an explicit statement on the cost-effectiveness of the use of typhoid RDTs

in resource-limited settings cannot be made here because of the limited number of studies identified, difference in patient population evaluated, difference in diagnostic tests evaluated and difference in the evaluative approaches used, all of which can potentially impact on the cost-effectiveness of the use of typhoid RDT's. What this shows though is that the application of typhoid RDTs in resource-limited settings has the potential to be cost-effective. Although both studies concluded that the use of typhoid RDTs is cost-effective, different assumptions were made across the studies in their analysis. Plausible reasons for the difference in assumptions is the potential difference in typhoid care pathways in both settings. An informative economic model requires knowledge of care pathways if it is to appropriately represent a simplification of the disease, persons not having the disease and misclassifications, and be fit for the purpose of aiding decision-making [19]. In both analysis models were built to represent the existing care pathway (current practice) in the different settings, thus the differences in model structure and assumptions used. For example, the antimicrobial given when a test was positive for typhoid fever was azithromycin for 5 days in the study by Saito et al. [18] whereas ciprofloxacin for 14 days was given in the study by Frempong et al. [17]. Furthermore, the comparator test was different in the studies.

In both studies, it was noted that the models were not run separately for different subgroups. Consequently, it is not possible to comment on what the cost-effectiveness would be if a different patient population to the ones used in the analysis were considered. Considering all patient subgroups gives an indication of the patient group in which the application of the test will be optimal. Another issue worth highlighting is the assumption of health workers perfectly adhering to test results and treatment protocol. In reality, health workers may not perfectly adhere to test results and treatment protocols if they don't have confidence in the test result. They may completely ignore test results and prescribe treatment in all patients who have a negative test result or prescribe treatment in a proportion of patients with a negative test result

or in some instances, request further testing . Non-adherence leads to these added complexities which should ideally be captured and explored if the true value of the test is to be established. Omitting these scenarios from the analysis may lead to misleading conclusions on the cost-effectiveness on the application of the test.

The cost of the test, the relative accuracy of the test, and the prevalence of typhoid fever were found to be the significant factors that influence cost-effectiveness. A test price of US$ 3.58 was used in the study by Saito et al. [18] and Frempong et al. [17] estimated that the test should not be priced more than US$4. This gives an indication of the potential price range for a typhoid RDT to be cost-effective in a resource limited setting. Although it must be highlighted that other factors such as the willingness to pay threshold used might influence the maximum price that can be charged for the test in any setting. This information might be useful for test developers who might consider developing new typhoid RDTs whether it will be feasible to produce and sell the test around this price range and still make profit.

In the study by Frempong et al. [17] specificity was found to be key to the cost-effectiveness argument whereas sensitivity was found to be key to the cost-effectiveness argument in the study by Saito et al. [18]. In the study by Frempong et al. [17], this was explained by the prevalence of typhoid fever and what happens to false positives and false negatives following the test–treat pathway for a suspected typhoid case. From the models, false positive results are worse for patients than false negative test results because of the extra testing and delays in receiving effective treatment that patients undergo before they are eventually cured. Thus, it should be recommended that a high specificity is required in order to avoid these unnecessary testing and treatment strategies associated with these pathways. The prevalence of the disease in the population is a key driver for cost-effectiveness as shown in the study by Saito et al. [18]. They showed that at a prevalence of 4.5% for typhoid fever (the lower 95% CI value), the ICER was estimated to be US$2292, whilst at the upper CI value of 9.0% the estimation was

US$1147. The prevalence of disease differs for different patient groups hence the need to consider different subgroups in order to establish the patient group in which the application of the test will be optimal. Running the model for a different population (in this case, adults instead on children) might have a different impact on cost-effectiveness. The two studies identified highlight that typhoid modelling (with respect to typhoid testing and treatment) represents an area that has been relatively understudied and further work is needed.

Despite the availability of several commercial RDTs for typhoid fever [11], surprisingly, only two economic evaluations were identified. This might be explained by considering the wider context of medical device regulation in resource-limited settings. Regulation of medical devices in resource-limited settings is weak and is particularly problematic with diagnostic tests [20]. Health technology assessments are rare because there is a lack of proper systems and structures in place to ensure adequate evaluation of the clinical and cost-effectiveness of tests before they are introduced in clinical practice [21]. Although there is a proliferation of typhoid RDTs, only two economic evaluations were identified. As little regulatory controls exist, these may be sold with little or no evidence of their effectiveness and cost-effectiveness. Concerted efforts are needed to ensure that clinically effective and cost-effective typhoid RDTs are introduced into clinical practice.

Another plausible explanation for the dearth of cost-effectiveness evidence might be because cost-effectiveness studies can often be undertaken by industry or industry sponsored and manufacturers may not readily make available results of their analyses.

5.0 Expert Commentary

Whereas pharmaceutical products are widely regulated, less attention has been placed on the regulation of other medical devices, particularly diagnostic tests. However, medical devices, like pharmaceuticals, also carry a degree of risk and could cause problems in specific

circumstances when treatment is based on test results. This highlights the need for governments to put in place policies to address all elements related to medical devices, ranging from access to high quality, affordable products, through to their safe and appropriate use and disposal. Although most countries in resource-limited settings have a legal mandate to regulate medical devices there is limited capacity to implement and enforce that regulation. The two economic evaluations identified in this study might be a clear indication of the lack of medical device regulation in resource-limited settings (particularly, with respect to typhoid fever) which results in less incentive to undertake such studies prior to implementation of such tests and highlight the need for more work to be done in this area. The two studies identified also highlight that typhoid modelling (with respect to typhoid testing and treatment) represents a relatively understudied area and further work is needed.

6.0 Five-year view

Given the disease burden of typhoid fever, there remains the need to develop rapid diagnostic tests for resource-limited settings. The validation and evaluation of such tests should include a demonstration of the value of such tests (clinical effectiveness and cost-effectiveness) before their introduction into routine clinical practice. It is our hope that an increased effort in generating evidence in resource-limited settings as would be required by medical device regulators would help to ensure that clinically effective and cost-effective typhoid RDTs are available and introduced into clinical practice.

7.0 Key issues

- Despite the availability of several commercial RDTs for typhoid fever, the cost-effectiveness in resource-limited settings is unclear and understudied.
- There are currently two published economic evaluation studies on the cost-effectiveness of typhoid RDTs.

- There is potential for the application of typhoid RDTs to be cost-effective in resource limited settings.
- Significant factors in determining cost-effectiveness related to test characteristics (such as sensitivity, specificity and cost) and the prevalence of typhoid fever. These should be prominent in future evaluations and furthermore incorporate and explore the impact of test result adherence on cost-effectiveness.
- Typhoid modelling (with respect to typhoid test and treat strategies) represents an understudied area and further work is needed.
- Concerted effort is needed in resource-limited settings with regards to medical device regulation to ensure that clinically effective and cost-effective typhoid RDTs are available and introduced into clinical practice.

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Declaration of interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Author contributions

All study authors meet the criteria for authorship as outlined by the journal policy.

Complying with ethics of experimentation

Ethical approval was not needed.

Consent

Participatory consent was not needed.

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