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A review of typhoid fever transmission dynamic models and economic evaluations of vaccination

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ABSTRACT

Despite a recommendation by the World Health Organization (WHO) that typhoid vaccines be considered for the control of endemic disease and outbreaks, programmatic use remains limited. Transmission models and economic evaluation may be informative in decision making about vaccine programme introductions and their role alongside other control measures. A literature search found few typhoid transmission models or economic evaluations relative to analyses of other infectious diseases of similar or lower health burden.

Modelling suggests vaccines alone are unlikely to eliminate endemic disease in the short to medium term without measures to reduce transmission from asymptomatic carriage. The single identified data-fitted transmission model of typhoid vaccination suggests vaccines can reduce disease burden substantially when introduced programmatically but that indirect protection depends on the relative contribution of carriage to transmission in a given setting. This is an important source of epidemiological uncertainty, alongside the extent and nature of natural immunity.

Economic evaluations suggest that typhoid vaccination can be cost-saving to health services if incidence is extremely high and cost-effective in other high-incidence situations, when compared to WHO norms. Targeting vaccination to the highest incidence age-groups is likely to improve cost-effectiveness substantially. Economic perspective and vaccine costs substantially affect estimates, with disease incidence, case-fatality rates, and vaccine efficacy over time also important determinants of cost-effectiveness and sources of uncertainty. Static economic models may under-estimate benefits of typhoid vaccination by omitting indirect protection.

Typhoid fever transmission models currently require per-setting epidemiological parameterisation to inform their use in economic evaluation, which may limit their generalisability. We found no economic evaluation based on transmission dynamic modelling, and no economic evaluation of typhoid vaccination against interventions such as improvements in sanitation or hygiene.

1. Introduction

Typhoid fever is an exclusively human enterically transmitted systemic disease caused by infection with the bacterium *Salmonella enterica enterica* serovar Typhi. Although largely controlled in Europe and North America, typhoid remains endemic in many parts of the world, notably Asia, where it is an important cause of febrile illness in crowded, low-income settings [1]. A notable feature of typhoid is the carrier state – asymptomatically infected individuals who continue to shed *S.* Typhi in their stool or urine for many years, thereby sustaining transmission [2].

Despite a recommendation by the World Health Organization in 2008 that typhoid vaccination be considered for the control of endemic disease and outbreaks, programmatic use remains limited [3].

In the early twentieth-century, public health officials were debating the best methods of evaluating typhoid vaccine effectiveness, and whether vaccination was a distraction from improvements in sanitation and hygiene [4]. These remain contemporary policy issues for ministries of health and other health partners who may be considering programmatic anti-typhoid vaccination as a counterpart to other anti-typhoid measures such as improvements to income distributions, sanitation, water supplies and hand washing with soap (post-defecation and before the preparation of food in the home or sold in the street) as well as identification and management of carriage [5–8]. Transmission dynamic

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modelling and economic evaluation are two informative tools to support such decisions [9,10].

Where health budgets are limited, allocation of resources to activities which generate the best value for money maximises the population's health (not withstanding other health programme criteria such as equity). To compare between and across health states, cost utility analysis (CUA) can be employed using a common metric of health, such as disability-adjusted life-year (DALY). The World Health Organization's Choosing Interventions that are Cost-Effective project (WHO-CHOICE) describes interventions as "cost-effective" if they add a DALY at a cost of less than three times Gross Domestic Product (GDP) per capita, and "highly cost-effective" if each DALY costs less than GDP per capita. These are arbitrary thresholds and meeting them does not necessarily lead to the intervention being adopted, as health decision-makers are often required to make choices between multiple interventions that fall below these thresholds. Furthermore, even highly cost-effective activities may be too expensive overall for a health service to provide within budget: a hypothetical drug adding a year of life and costing GDP per capita for each person treated would require the entire national economy to be spent giving the drug to every member of the population [11].

By building on the germ theory of disease, and mass-action principles from the physical sciences [12], mechanistic mathematical modelling enables extrapolation beyond observed data, and can be used to project the expected trends of disease in a population or the potential impact of control strategies such as vaccination. Through capturing indirect effects of immunisation – the reduced incidence of disease in members of a population not themselves immunised, commonly described as "herd immunity" – these transmission dynamic models capture the impact of such interventions more completely than static economic models measuring only the direct effects in vaccinees [13].

In this review, typhoid transmission dynamic models and typhoid vaccine economic evaluations are examined for their potential contributions to informing disease control, identification of gaps in knowledge and indication of directions for further research.

2. Methods

PubMed was searched on 23 October 2014 without date restriction using the following terms: ("Typhoid Fever"[Mesh]) AND ("Nonlinear Dynamics"[Mesh] OR "Models, Theoretical"[Mesh] OR "Models, Statistical"[Mesh] OR "Computer Simulation"[Mesh] OR "Models, Economic"[Mesh] OR "Least-Squares Analysis"[Mesh] OR "Likelihood Functions"[Mesh] OR "Resource Allocation"[Mesh] OR "Cost-Benefit Analysis"[Mesh]) AND (Humans[Mesh]) NOT "Mice"[Mesh].

Personal libraries were reviewed and reference lists in papers searched for modelling and economic studies that may not have been identified by the above search strategy. Results were restricted to those available in English. We obtained information about unpublished studies through the Coalition against Typhoid and International Vaccine Institute.

Studies were included if they modelled typhoid transmission and/or analysed the cost-effectiveness of vaccination in endemic settings. Endemic settings were identified using recent high-quality reviews [14,15]. We included cost of illness (COI) studies if they were linked to an analytical study, and willingness-to pay (WTP) studies if they included an economic evaluation or were linked to an analytical study. Studies were excluded if they used geographical or statistical modelling, including time-series analysis, without transmission dynamics, or if they addressed transmission or cost-effectiveness in non-endemic populations, such as international travellers.

Transmission models were assessed for their model structure, data sources, parameter estimates, use of fitting methods, sensitivity analysis and the contribution of their approach to epidemiological understanding of typhoid. Economic studies were evaluated by data sources, economic evaluation approach, perspective, comparator programmes, use of sensitivity analysis and capture of indirect effects of vaccination.

3. Results

Seventy-nine titles were retrieved. Ten modelling papers were selected for review based on title or abstract. One was discarded as a non-mechanistic time series study [16], one as it modelled outbreaks in a non-endemic setting [17], while two papers were of the same model and considered together [18,19]. These are summarised in Tables 1 and 2. A further, as yet unpublished, transmission model has been developed by the International Vaccine Institute (personal communication, Jin Kyung Park) and is not reviewed here.

Seven titles were identified as economic evaluation and obtained for full-text review (Tables 3 and 4) alongside two underpinning COI studies and one underpinning WTP study (Table 5). A further COI study was identified but excluded as not linked to a published economic evaluation [40].

There was minimal overlap found between transmission modelling and economic evaluation. Of the transmission dynamic models, only those by the Cvjetanović group also had cost-effectiveness components [18–20]. One economic study included quantitative consideration of indirect protection [27].

3.1. Transmission dynamic models

The seven typhoid models identified range from two-state analytical tools to complex individual-based simulation or multi-state compartmental models (see Table 1). Only two models were formally fitted to data [24,25].

The structures of models (Tables 2a and 2b) are based on different assessments or representations of the natural history of typhoid fever, particularly in how immunity to *S.* Typhi is considered.

Table 1
Summary of typhoid transmission model types.

Characteristic	Number of models ($n = 7$)	References
Type of model		
Compartmental		
Deterministic	6	[18–24]
Stochastic	0	
Individual-based stochastic	1	[25]
Scope of model		
Analytical/mathematical		
Without data	1	[22]
Uses data without fitting	1	[23]
Exploratory/epidemiological		
Uses data without fitting	1	[21]
Fitted to data	1	[25]
Policy-oriented/public health		
Uses data without fitting	2	[18–20]
Fitted to data	1	[24]
Parameter-fitting method		
Maximum likelihood estimation	2 of 2	[24,25]
Bayesian	0	
Investigates vaccination	4	[18–21,24]
Compares with improved sanitation, hygiene or water supply	4 of 4	[18–21,24]
Include economic evaluation of vaccination	2 of 4	[18–20]