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The cost-effectiveness of typhoid Vi vaccination programs: Calculations for four urban sites in four Asian countries

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ABSTRACT

The burden of typhoid fever remains high in impoverished settings, and increasing antibiotic resistance is making treatment costly. One strategy for reducing the typhoid morbidity and mortality is vaccination with the Vi polysaccharide vaccine. We use a wealth of new economic and epidemiological data to evaluate the cost-effectiveness of Vi vaccination against typhoid in sites in four Asian cities: Kolkata (India), Karachi (Pakistan), North Jakarta (Indonesia), and Hue (Vietnam). We report results from both a societal as well as a public sector financial perspective.

Baseline disease burden estimates in the four areas are: 750 cases per year in two Kolkata neighborhoods (pop 185,000); 84 cases per year in the city of Hue (pop 280,000); 298 cases per year in two sub-districts in North Jakarta (pop 161,000), and 538 cases per year in three squatter settlements in Karachi (pop 102,000). We estimate that a vaccination program targeting all children (2–14.9) would prevent 456, 158, and 258 typhoid cases (and 4.6, 1.6, and 2.6 deaths), and avert 126, 44, and 72 disability-adjusted life years (DALYs) over 3 years in Kolkata, North Jakarta and Karachi, respectively. The net social costs would be US$160 and US$549, per DALY averted in Kolkata and North Jakarta, respectively. These programs, along with a similar program in Karachi, would be considered "very cost-effective" (e.g. costs per DALY averted less than per capita gross national income (GNI)) under a wide range of assumptions. Community-based vaccination programs that also target adults in Kolkata and Jakarta are less cost-effective because incidence is lower in adults than children, but are also likely to be "very cost-effective". A program targeting school-aged children in Hue, Vietnam would prevent 21 cases, avert 6 DALYs, and not be cost-effective (US$3779 per DALY averted) because of the low typhoid incidence there.

1. Introduction

Typhoid fever, caused by the bacterium *Salmonella enterica* serovar Typhi (hereafter referred to as *S. typhi*), is transmitted through contaminated food or water and characterized by high fever, chills, nausea, headaches and malaise, sometimes with delirium [1]. The global burden of typhoid fever was estimated at 21 million cases and more than 200,000 deaths in 2000, and South and Southeast Asia is believed to have the highest incidence rates [2]. The true burden of disease is thought to be higher because of under-reporting and inadequate surveillance [2]. Resistance to antibiotics is a growing problem [1]. Ochiai et al. [3] reported multi-drug resistance to first line antibiotics (chloramphenicol, ampicillin

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and co-trimoxozole) of up to 67% in *S. typhi* isolates in a surveillance study in Karachi, Pakistan and rates of naladixic acid resistance (indicating reduced effectiveness of ciprofloxacin and other fluoroquinolones) of 44–59% in Hue, Vietnam; Kolkata, India; and Karachi, Pakistan. Griffin [4] reported that 14% of typhoid patients in a Delhi slum in 1998 did not respond to a 10-day course of ciprofloxacin, and Bahl et al. [5] found that the cost of illness for persons with typhoid that did not respond quickly to antibiotics was five times higher than for those who were successfully treated.

Although improvements in water and sanitation infrastructure and food hygiene could reduce the disease burden and lessen the threat of antibiotic resistance, another strategy to reduce typhoid cases in the near term is vaccination with new-generation vaccines in high-risk areas. Vi polysaccharide vaccine is given as an injection and requires only one dose [1]. The best available estimates indicate the Vi vaccine is safe and 65% protective, with protection lasting at least 3 years [6–8]. This vaccine is internationally licensed for children 2 years of age and older [9,10]. The liquid formulation of the live oral vaccine (Ty21a) is also licensed for children 2 years and older. This vaccine requires 3–4 doses at closely spaced intervals and is more expensive than the Vi polysaccharide vaccine [1]. Newer Vi-based vaccines are under development in which Vi polysaccharide is chemically conjugated to a recombinant exotoxin protein (Vi-rEPA, or the “Vi conjugate”) or another carrier protein. Unlike the Vi vaccine, these conjugate vaccines have the potential to protect children under 2 because they induce a T cell-dependent immune response in young children [1,11]. Trials have shown the Vi-rEPA vaccine is safe and effective (almost 90% after 4 years) in children aged 2–5 [1,12], but no studies have yet tested the vaccine in children under 2.

Because health resources are limited in many areas where typhoid is endemic, it is important for local, national, and global health policymakers to evaluate the economic attractiveness of typhoid vaccination programs in relation to other possible health interventions. The goal of this paper is to report on detailed cost-effectiveness analyses of Vi polysaccharide vaccination programs against typhoid fever in four urban settings in four Asian countries using a wealth of new data collected by the Diseases of the Most Impoverished (DOMI) program.

There are relatively few published economic evaluations of typhoid vaccination programs. Papadimitropoulos et al. [13] examined the cost-effectiveness of two types of typhoid vaccines (Ty21a and Vi polysaccharide) for travelers. They found that neither vaccine was cost-effective unless travelers were going to areas with very high incidence rates (200 cases/million travelers) or expected to be in very close personal contact with local inhabitants. Bahl et al. [5] examined incidence (through both active and passive surveillance) and cost of illness in an urban slum in Delhi, India. They found total mean costs of illness (COI) were roughly the same across age groups (~$100 per case in US$1996), though the public share of costs was much higher for preschool children (aged 2–5), largely because these children were more likely to be hospitalized. Mean annual expected costs were on the order of US$0.11–0.22 for adults and US$3.42–5.22 for preschool children (US$1996).

Under a range of vaccine cost estimates, Poulos et al. [14] found that immunizing preschool children against typhoid fever in the same (high-incidence) slum in Delhi would actually be cost saving to the public sector. They also found that immunizing other age groups would likely pass a social cost-benefit test when privately borne costs of illness were counted as benefits of vaccination. Using a contingent valuation approach in Hue, Vietnam, Canh et al. [15] provided a more complete picture of the private economic benefits of a Vi typhoid vaccine. They found that the private benefits that would accrue to the average household in Hue (with 5.6 household members), if all household members received a Vi vaccine, ranged from US$21 to US$27. They found that a vaccination program without user fees would most likely pass a social cost-benefit test, but that there was also significant potential for the program to be self-financing through user fees.

This previous work on the economic attractiveness of typhoid vaccination programs can be greatly enriched using the results of recent research from the Diseases of the Most Impoverished Program. The DOMI program, administered by the International Vaccine Institute and funded by the Bill and Melinda Gates Foundation, involved a number of parallel activities, including epidemiological studies, economic studies, and investigation of the feasibility of vaccine technology transfer. It represents a unique set of site-specific economic and epidemiological data.

2. Methods

2.1. Sites

The sites included in this analysis correspond to the areas with typhoid fever surveillance studies reported in Ochiai et al. [3]: In Kolkata (India), we model the effects of vaccinating two densely populated urban slums – Tiljala (Wards 59 & 60) and Narkeldanga (Wards 29 & 30) – with a combined population of about 185,000 people. We do not analyze programs to vaccinate the entire city. Similarly, we examine programs in two impoverished municipal sub-districts in North Jakarta, Indonesia, with a total population of 161,000 (Tanjung Priok and Koja). Hue is a regional capital in central Vietnam with a population of 280,000 consisting of both urban areas and semi-urban areas at the periphery of the city. The disease surveillance studies included the entire city [3], so we assume vaccinations would occur city-wide in Hue. In Karachi (Pakistan), we examine programs targeting three squatter settlements (Hijrat Colony, Sultanabad, and Bilal Colony), with a combined population of 102,000.

Our results pertain only to the cost-effectiveness of vaccination in these specific locations and cannot be extrapolated to the country-level. Nonetheless, the cost-effectiveness model that we use could be readily modified to include other locations, or nationwide programs.

2.2. Modeling approach

Our analysis generally employs standard cost-effectiveness methods used by the Disease Control Priorities Project (or DCP, [16]) and WHO’s CHOICE project [17]. We first assess the baseline burden of disease in terms of cases, deaths and disability-adjusted life years (DALYs) for each of the four urban sites. Like the DCP [18], we use uniform age-weights that apply the same value to an extra year of life regardless of the age of its recipient (we explore the effects of non-uniform age-weights in the sensitivity analysis).

Because we use DALYs for our health outcome measure, we incorporate reductions in morbidity from vaccination (years of life lost to disability or YLD) as well as reductions in typhoid mortality (years of life lost or YLL). To calculate the number of life years saved from mortality reductions, we use country-specific life expectancies (LE) from WHO life tables, and discount life years using a 3% real (i.e. net of inflation) discount rate [16,17]. Eqs. (1)–(4) below show the calculation of DALYs avoided:

$$\text{DALYs avoided per year in age group } i = \text{YLL avoided per year} + \text{YLD avoided per year} \quad (1)$$

Table 1
Site-specific model parameters

Parameters	Kolkata, India	Hue, Vietnam	North Jakarta, Indonesia	Karachi, Pakistan
Population	185,000	282,000	161,000	102,000
Description	2 urban "slums"	City-wide, urban and semi-urban	2 poor urban districts	3 urban squatter settlements
Mean observed Incidence (cases per 1000)[a]				
2–4.9 years	3.4 (1.9–6.3)	n/a	1.5 (0.89–2.5)	5.7 (4.4–7.4)
5–14.9 years	4.9 (4.0–6.7)	0.24 (0.16–0.43)	1.8 (1.5–2.5)	4.1 (3.7–5.2)
15+ years	1.2 (0.9–1.6)	n/a	0.51 (0.40–0.66)	n/a
Private cost of illness (2007$)				
Children (<15 years)	$11.7 (6–18)	$40 (20–60)	$56 (28–84)	n/a
Adults (15+ years)	$11.7 (6–18)	n/a	$210 (105–315)	n/a
Public cost of illness (2007$)				
Children (<15 years)	$4.3 (2–6)	$35 (18–53)	$23 (12–35)	$2.1 (1.1–3.2)
Adults (15+ years)	$4.3 (2–6)	n/a	$27 (13–40)	n/a
Delivery cost per dose (2007$)	$0.5 (0.3–2.5)	$0.5 (0.3–2.5)	$1.0 (0.6–5.0)	$0.5 (0.3–2.5)
Acquisition cost per dose (2007$)	$0.57 (0.4–0.8)	$0.57 (0.4–0.8)	$0.57 (0.4–0.8)	$0.57 (0.4–0.8)
Median hourly wage (2007$), ($\bar{X}$, SD)	$0.18 (0.23, 0.21)	$0.22 (0.31, 0.33)	$0.51 (0.63, 0.53)	$0.29 (0.42, 0.34)
Primary school enrollment (%)	89%	95%	96%	66%
Secondary school enrollment (%)	48%	59%	59%	30%
Percent of age group covered if vaccine is free[b]				
< 5 years	73% (58–88)	26% (21–31)	59% (47–71)	58% (46–70)
5–14 years	69% (55–83)	63% (50–76)	50% (40–60)	48% (38–58)
15+ years	62% (50–74)	54% (43–65)	29% (23–35)	n/a

Notes: Base case value shown, with uncertainty range in brackets. All currency values are in US$, translated from local currency using market exchange rates (not adjusted for purchasing parity).

[a] Based on blood-culture tests, which are known to produce false negatives. True incidence is assumed to be double the observed incidence. Bounds in brackets represent 95% Wilson (binomial) confidence intervals.

[b] This is the percent of people who hear about the program and would take if free. These predicted coverage rates are adjusted for time-to-think, lowering them by ~10–15%. We assume only 80% of the population learns about the program; these percentages are multiplied by 0.8 in the model.

$$\text{YLD}_i \text{ avoided per year} = ((1-\text{CFR}_i)\times \text{Eff}\times \text{Cover}_i \times N_i I_i) \times \text{Length} \times \text{DALY weight} \quad (2)$$

$$\text{YLL}_i \text{ avoided per year} = \left(\frac{\text{CFR}_i \times \text{Eff}\times \text{Cover}_i \times N_i I_i}{0.03}\right) \times (1-\exp(-0.03\text{LE}_i)) \quad (3)$$

$$\text{Total DALYs avoided in age group } i = \sum_{t=0}^{\text{Dur}} \frac{\text{DALYs avoided per year}_i}{(1+0.03)^t} \quad (4)$$

where i indexes the age group targeted, Eff is the effectiveness of the vaccine, Cover is the percentage of the age group who would be vaccinated if the vaccine were provided free, CFR is the case fatality rate, Length is the disease's average duration (i.e. number of days sick with typhoid), N is the number of people in age group i, Dur is the vaccine's duration, and I is the group's typhoid incidence. For all programs, we assume a one-period model, i.e. we estimate the costs of immunizing the target population in year 1, and compare these costs with the effects on disease burden (cases, deaths, DALYs) over the duration of the vaccine's effectiveness (3 years).

We examine three types of typhoid Vi vaccination programs. All three options involve campaigns rather than routine immunizations because the Vi vaccine is not effective in children younger than two and cannot be included in the infant EPI schedule. The first two options involve school-based vaccination since typhoid incidence is typically highest in this age group. The first school-based option (Option 1) would target only children 5–14 years old actually enrolled in school. The second school-based option (Option 2) would target all children who are old enough to receive the vaccine safely (2 years) but younger than 15 years, including school-aged children who do not attend school. We assume that mothers could bring younger children (2–4 years old) and unenrolled children to the school for vaccination. The third type of program (Option 3) would target adults as well as eligible children and would require a community-based vaccination campaign. Because the Karachi disease surveillance studies did not include adults, we only evaluate the school-based options (Options 1 and 2) in this site. Similarly, disease surveillance in Hue included only 5–18-year-olds so we evaluate only a school-based option for children 5–14 years old (Option 1).

We consider the costs of the vaccine program options from a both a public sector financial and a societal perspective. Vaccine manufacturing/acquisition costs and delivery costs (discussed below) are assumed to be borne by the government (public) sector, and we assume there are no user fees collected from vaccine recipients. We reduce vaccination program costs by the cost of illness that would have been borne by the public sector ("public COI") if the vaccination program had not been implemented, again using a financial discount rate of 3% [17] for public COI avoided in years 2 and 3. We call the result after this subtraction "net public cost". For a societal perspective, we further reduce program costs by the discounted value of avoided cost of illness borne by patients ("private COI"), but add the opportunity cost of time traveling to the clinic and waiting to be seen. We call this result "net social cost".

We report the commonly used thresholds for "cost-effective" and "very cost-effective" that compare the cost-effectiveness ratio to per capita income [17,19]. A "very cost-effective" intervention is assumed to be one with a cost-effectiveness ratio less than per capita gross national income (GNI), and a "cost-effective" intervention is one with a ratio less than three times per capita GNI [20]. Satisfying these thresholds is probably a necessary but not a sufficient condition for a vaccination program option to be attractive from an economic perspective. Financial resources for health are limited in these settings, and other interventions which also qualify as "very cost-effective" may have even more attractive cost-effectiveness ratios. Furthermore, our cost-effectiveness analysis should not be confused with a full accounting of all the social benefits and costs of the program options. We return to this limitation of cost-effectiveness analyses in the concluding section of the paper.

2.3. Construction of base case and sensitivity analysis

The first step in our cost-effectiveness analysis is to calculate the cost-effectiveness ratios of the three program options (from a societal and public sector financial perspective) for the "base case" set of parameter values presented in Table 1. We then explore the effect of using non-uniform age-weights on our cost-effectiveness calculations. We next investigate the impact of uncertainty in the parameters with two types of sensitivity analysis. The first examines the impact of varying a few of the most important parameters (cost per fully vaccinated individual, incidence, and case fatality rates) individually while keeping all other parameters at their base case values. The second sensitivity analysis uses a probabilistic Monte Carlo framework that allows all uncertain parameters to vary simultaneously. We used Crystal Ball, a Microsoft Excel plug-in, to run the simulations. The results presented used 10,000 draws from triangular parameter probability functions for all but three variables, with low and high ends of the distribution set to the assumed lower and upper bounds (shown in brackets in Table 1), and the peak of the triangle (the most likely value) set to the base case value. Hourly wage, incidence and duration are modeled as log-normal, normal and discrete distributions (see below for further detail). We explore the effect of other distributional assumptions on our Monte Carlo results in Appendix A.

2.4. Model parameters

2.4.1. Epidemiological parameters

Data on baseline typhoid incidence come from a recent compilation of multi-year surveillance in each of the four DOMI sites [3]. The observed typhoid incidence is generally highest in school-aged children (5–14), ranging from 0.24 cases per 1000 in Hue to 4.9 cases per 1000 in Kolkata (Table 1). With the exception of Karachi, observed incidence in young children is lower than incidence in school-aged children, and adult incidence is still lower (in the two sites with adult surveillance data). Overall, Kolkata and Karachi represent the sites with highest incidence; Hue has the lowest incidence, and North Jakarta falls in between. Although blood-culture tests for identification of *S. typhi* isolates are still considered the gold standard due to their high specificity, they are known to produce false negatives in 32–70% of samples [3]. For our base case models, we follow Ochiai et al. [3] and double the incidence rates in Table 1 to account for this. For uncertainty analysis, we fit a normal distribution to the Wilson score 95% confidence intervals from Ochiai et al. [3] (shown in brackets in Table 1).

We use 65% as the base case for vaccine efficacy, ranging from 55% to 75% in the uncertainty analysis [9,10]. Although indirect (herd) protection may reduce cases even further, we include only direct protection in our analysis because reliable empirical evidence of herd protection from typhoid vaccination is not available. We assume the duration of the vaccine's protection ranges from 2 years to 4 years, with a base case value of 3 years [9,10]. We use a discrete probability function for duration where the probability of the vaccine having the base case duration (3 years) is 0.5, and the probability of the vaccine protecting one year less or one year more is 0.25 each.

According to the WHO [21], the case fatality rate for typhoid cases treated with antibiotics is about 1%. CFR without treatment can range from 4% to 10% [21]. The CFR in a January 2005 outbreak in Congo was 0.5% (214 deaths in 42,564 cases) [22]. Crump et al. [2] use 1% based on "conservative estimates from hospital-based typhoid fever studies, mortality data from countries with reliable

Table 2
Parameters used in all five sites

	All sites
Case fatality rate	1% (0.5–3%)
Effectiveness of vaccine	65% (55–75%)
Duration of vaccine	3 years (2–4 years)
DALY weight	0.27 (0.075–0.471)
Length of illness	7 days (4–21)
Discount rate	3%
Time spent traveling and waiting to be vaccinated	40 min

national typhoid fever surveillance systems that employ blood-culture confirmation of cases, and expert opinion." Parry et al. [1] also list 1% as a good estimate. For our analysis a mean case fatality rate for typhoid of 1% is assumed for all four study sites, with lower and upper bounds of 0.5–3% for the uncertainty analysis (Table 2).

Parry et al. [1] reported a range of "mean fever clearance times" with different antibiotics from 4 to 7 days, increasing to a mean of 9 days in "clinical failures" or cases where antimicrobials were not initially successful. Treatment times can increase to 21 days if third-line antibiotics (e.g. cephalosporins) are necessary [1]. We assume the average typhoid case lasts 1 week, with lower and upper bounds of 4 days and 3 weeks, respectively.

We use a mean DALY weight of 0.27, which lies within a range of weights for somewhat similar diseases (malaria, Japanese encephalitis, dengue, upper respiratory infections) [17]. The lower bound and upper bounds are those for dengue fever (0.08), and neurological sequelae of malaria (0.47).

2.4.2. School enrollment

For program Option 1, we use the most recent data from UNESCO [23] on the net enrollment rate (Table 1), or the percentage of school-aged children who are actually attending school, to calculate the total number of school-aged children who might be vaccinated. We use national-level data because we are unaware of data specific to our study sites. Because the age group (5–15-year-olds) spans both primary and secondary school, we use the average of the primary and secondary school enrollment rates in the model. We do not vary the enrollment rates in the sensitivity analysis because they affect only the absolute number of cases and deaths avoided, not the cost-effectiveness ratios (in the absence of herd protection).

2.4.3. Cost of illness

The DOMI project's economic studies in these sites provide data on the costs of illness from contracting typhoid fever, both to the public sector and to families [24]. All cost-of-illness estimates were converted to US$2007 using current market exchange rates rather than terms adjusted for purchasing power parity (following the approach in the DCP [18]).

To measure private costs of illness, families with culture-proven cases were visited at home 7, 14, and 90 days after onset of illness. For adult cases, the patient was interviewed. For cases in children, an adult familiar with both the episode and the household finances was interviewed. The single protocol and standard questionnaires were developed to ensure that comparable data were collected in each study site.

The questionnaires measured direct costs and indirect costs. Direct costs include the costs of medical treatment, medicines, laboratory tests, transportation, food, lodging, and the costs of special items such as foods or herbs. The indirect costs included the lost wages due to lost work time by the patients, their caregivers, and their substitutes. The indirect costs also include estimates of the productivity losses due to forgone nonmarket activities including school, housework, and childcare (Table 3). The estimated mone-

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Table 3
Components of private and public costs

Component	Private costs	Public costs
Direct costs	• Treatment—including: • diagnostic tests • medicine • examination • bed charges[b] • Transportation • Nonmedical items—including foods and beverages used to aid treatment • Lodging and meals for other persons[a] • Other payments	Publicly borne costs of: • an outpatient visit in a public clinic • a day of hospitalization in a public hospital • the medicines received by the patient in the treatment of the disease • the diagnostic tests used for patients with the disease
Indirect costs	• Patient's lost income/production[d] • Substitute laborers' net lost income/production[c] • Caretakers' lost income/production • Other persons' lost income/production	n/a

From Poulos et al. [24].
[a] These were most often persons who accompanied the patient when they sought treatment.
[b] If there is an overnight stay.
[c] A substitute is someone who did the patient's or caregiver's work for them while they were either sick or giving care. This is "net" because substitute laborers result in a net increase or decrease in lost productivity. On the one hand, they can increase losses if they are not able to perform their own work. On the other hand, they reduce losses when they replace patients lost labor. This item is equal to (substitute laborers' own lost income/production) + (substitute laborers' contributions to income/production by doing patients' work).
[d] These productivity losses also reflect time spent waiting and traveling to receive health care.

tary value of nonmarket activities depends on the subject's age and the activity [24].

Private costs of illness were $11.7 per case in Kolkata (both adults and children), $40 per child case in Hue, and $56 and $210 per case in children and adults in North Jakarta (Table 1). Data on private cost of illness were not available for Karachi.

Public costs of treatment were measured at local health facilities using a micro-costing (bottom-up) methodology. First, data from public and private health facilities providing treatment were used to produce estimates of the cost of a day's hospitalization, the cost of a clinic visit, and the average cost of medicines and diagnostic tests. This information was combined with data from a sample of patients who were treated to estimate the provider's treatment cost per case of disease. The portion of the total cost of treatment that was borne by the public sector was then calculated as the provider cost of treatment minus the fees received from patients for their treatment (the fees received from patients were measured in private COI interviews as direct costs paid to public health facilities for medicine, treatment, and laboratory tests).

Provider cost was drawn from facilities serving the disease burden study [3] because they allowed for good access to facility records, they had data on culture confirmed typhoid infections, and this minimized travel and logistical costs. In Karachi, expert local information was used to generate a set of assumptions about health care, and available data sources were used to construct costs for typical treatment regimes.

Though public treatment cost studies in each country were not identical because of differences in the health care systems, availability of data, and the design of the DOMI projects in each country, similar components were measured to maximize comparability of findings. Table 4 summarizes the public health care system in each country and the facility sample that was used to estimate provider treatment cost.

The public treatment costs (provider treatment costs minus patients' payments) for hospitalized and non-hospitalized cases were, respectively, US$116 and US$ 1 in Hue, US$90 and US$10 in North Jakarta, US$100 and US$2 in Kolkata, and US$17 and US$0.1 in Karachi. Hospitalization rates for adult cases were 2%

Table 4
Description of study sites and facilities included in cost-of-illness studies

Study site	Facilities included in the public cost studies	Notes
Hue, Vietnam	Public health facilities serving the study area: • Hue City Hospital • 3 polyclinics • 3 midwife clinics • 25 commune health centers • Private providers were not included	DOMI patients receive care in the same environment as the general population, with the exception of additional diagnostic procedures to confirm cases.
North Jakarta, Indonesia	Public health facilities serving the study area: • 2 hospitals • 8 health centers	DOMI patients receive care in the same environment as the general population, with the exception of additional lab tests to confirm cases.
Karachi, Pakistan	Since special clinics were set up to treat DOMI patients, public costs were not observed. Local expert opinion was used in analysis	Observed care environment not representative of typical health services sought by the general public.
Kolkata, India	DOMI patients were identified in screening clinics specifically set up for the project. Patients were then directed to private health care providers and reimbursed for treatment expenses. Public cost data collected from: • BC Roy Pediatric Hospital • Infectious Disease/Beliaghata General Hospital	Though there are public health services, many residents in poor urban areas rely on private health care.

From Poulos et al. [24].

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in Kolkata and 32% in North Jakarta. Hospitalization rates for cases in children were 1% in Kolkata, 28% in Hue, 10% in North Jakarta, and 10% in Karachi. In Kolkata and Hue, resistance to seven antibiotics (including ampicilin, cotrimoxizole (also known as TMP-SMZ), and chloramphenocol) was measured. Although public costs were higher in Kolkata for drug-resistant cases compared to drug-sensitive cases, the difference was not statistically significant in either site [24]. This paper uses the average public COI for all ages weighted by hospitalization rate, given in Table 1.

2.4.4. Demand for typhoid vaccines

DOMI also conducted studies of private vaccine demand that estimated the quantity of typhoid vaccines demanded by households as a function of price [15,25–27]. These provide an estimate of anticipated coverage levels for different ages given the provision of a free vaccine. The quantity of typhoid vaccines demanded at a price (user charge) of zero was estimated from responses to questions posed to respondents in contingent valuation surveys. These estimates of vaccine demand at a zero price were adjusted to account for the effect of giving respondents time to think about their answers. Several studies of private demand for cholera and typhoid vaccines have found that respondents who were given the opportunity to consider the vaccine scenario overnight expressed more certainty about their responses and lower willingness to pay [25,26,28,29]. We adjust coverage levels in the four sites to reflect the average effect of time to think from these studies (without this adjustment, coverage levels would be 10–15% higher). For sensitivity analysis we further vary these time-to-think-adjusted estimates by ±20% of their base value. Furthermore, we assume that 80% of people would be informed of the vaccination campaign through a social marketing campaign. We do not vary the percentage of people informed of the program in the sensitivity analysis because it has little effect on the ratio of costs to disease-reduction benefits. We assume that even the program targeting only school-aged children would not vaccinate 100% of enrolled children because parents may not permit their children to receive the vaccine; we assume the same demand intercept (the percentage who would take a free vaccine).

2.4.5. Vaccine costs

The social cost of a typhoid vaccination program is composed of three main components: (1) the cost of acquiring vaccines from the manufacturer, (2) the cost of delivering and administering the vaccine to the target population, and (3) the time and pecuniary costs incurred by household members to travel to the vaccination outpost and to wait to receive the vaccine. None of the three cost components is known with certainty. They depend on a number of factors for which there is little information in the published vaccine cost literature. For the cost estimates used in this paper we rely on data collected on vaccination costs during the Vi demonstration projects in the DOMI study sites and a recent review and analysis of this literature by Lauria and Stewart [30] (for further detail on vaccination cost assumptions, see Appendix A).

We use a total base case acquisition cost, including the cost of wastage, customs, freight and insurance, of US$0.57 per dose. We use the same base case acquisition cost for all sites, including Vietnam and India (which already has local production), because the cost of customs, freight and insurance are within the overall margin of error. We vary this acquisition cost in the sensitivity analysis from US$0.4 to US$0.8 per dose [30].

We follow a commonly used convention in the cost-effectiveness literature (see Sinha et al. [31] for a recent example) and assume that delivery costs are captured in a constant marginal cost per vaccinated individual rather than including fixed (i.e. set up) costs. This implies constant returns to scale in vaccination. We assume that the marginal delivery cost per dose is the same for a school-based program (Options 1 and 2) as for a community-based vaccination program (Option 3).

For India, Pakistan and Vietnam, low-income countries with gross national incomes per capita on the order of US$800–900, we use Lauria and Stewart's estimate of US$0.5 per dose for delivery costs. For the sensitivity analyses, we base the uncertainty ranges on the 16 studies for low-income countries reviewed by Lauria and Stewart. The 12.5–87.5% confidence interval (obtained by dropping the two highest and two lowest delivery cost estimates) is US$0.3–2.5 per dose, which we use as the lower and upper bounds in the sensitivity analysis. For Indonesia, a middle-income country with a GNI per capita of US$1800, we use Lauria and Stewart's estimate of delivery costs for middle-income countries of US$1.0 per dose. Because their study only included six middle-income countries and because costs are assumed to be twice as high in middle-income countries, we derive the uncertainty range by doubling the range described above for low-income countries, or US$0.6–5.0 per dose.

We assume the costs of traveling and waiting to be vaccinated are zero for Option 1 targeting only enrolled school children. For Options 2 and 3, we assume that young children and unenrolled school-aged children are accompanied by an adult (the travel/time cost for enrolled children remains zero). We assume recipients spend 10 min walking (each way) to a nearby vaccination outpost; there are no financial transportation costs (e.g. bus fare). We assume recipients then spend 20 min waiting to be vaccinated. We value this 40 min at one-half the median hourly wage observed among working adults in the four sites (using data from the private demand studies described above and converted to US$2007 using market exchange rates). We allow this assumption to vary in the sensitivity analysis by allowing the median hourly wage to vary as a lognormal distribution (the mean and standard deviation from the demand studies is provided in Table 1).

3. Results

3.1. Base case

3.1.1. Baseline epidemiology

Baseline disease burden estimates in the four areas are: 750 cases per year in two Kolkata neighborhoods (pop 185,000); 84 cases per year in the city of Hue (pop 280,000); 298 cases per year in two sub-districts in North Jakarta (pop 161,000), and 538 cases per year in three squatter settlements in Karachi (pop 102,000) (Table 5). With a baseline case fatality rate of 1%, this translates to 7.5, 0.8, 3.0, and 5.4 deaths from typhoid fever in Kolkata, Hue, North Jakarta and Karachi. Expected annual hospitalizations, DALYs private costs, and public costs are provided in Table 5.

3.1.2. Option 1 – School-based vaccination targeting only school-age children

Program Option 1, targeting only children 5–14 years old who attend school, would be considered "very cost-effective" in Kolkata, Karachi and North Jakarta. In the two urban slums in Kolkata, for example, we estimate that program would vaccinate 13,781 school children at a total financial cost of US$14,745, preventing 263 typhoid cases over 3 years (Table 5). Preventing these 263 cases would reduce public expenditures on treating typhoid by US$1086 (with savings in years 2 and 3 discounted at 3%). In fact, none of the three program options examined in any of the four sites would be cost saving to the public sector; expected public sector treatment cost savings are less than vaccination program costs for the base case and for the entire range of plausible vaccine cost estimates. The net public cost per DALY avoided for Option 1 in Kolkata is

Table 5
Vaccination program outcomes – base case analysis

Parameters	Kolkata, India	Hue, Vietnam	North Jakarta, Indonesia	Karachi, Pakistan
Baseline disease burden (no vaccination)[a]				
Expected cases per year	750	84	298	538
Expected deaths per year	7.5	0.8	3.0	5.4
Expected DALYs per year	199	23	81	149
Expected hospitalizations per year	11	24	52	54
Publicly borne cost of illness per year	$3,185	$1,441	$7,275	$1,142
Privately borne cost of illness per year	$8,759	$3,401	$16,761	n/a
Option 1 – School-based program targeting only enrolled children				
Number vaccinations	13,781	22,965	14,705	5,394
Cases avoided over duration	263	21	103	87
Deaths avoided over duration	2.6	0.2	1.0	0.9
Hospitalizations avoided over duration	6	6	6	6
Cases avoided per 1000 vaccinated	19.1	0.9	7.0	16.1
Deaths avoided per 1000 vaccinated	0.19	0.01	0.07	0.16
YLL avoided over duration	71	6	28	24
YLD avoided over duration	1	0	1	0
DALYs avoided over duration	73	6	29	24
Public COI avoided over duration	$1,086	$732	$2,342	$179
Private COI avoided over duration	$2,988	$842	$5,643	n/a
Total program costs	$14,745	$24,572	$23,087	$5,772
Average cost per immunized person	$1.07	$1.07	$1.57	$1.07
Total travel/time costs	$0	$0	$0	$0
Net public costs	$13,659	$23,841	$20,745	$5,593
Net public cost per case avoided	$188	$3,917	$721	$231
Net social costs	$10,671	$22,998	$15,102	n/a
Net social cost per DALY avoided	$147	$3,779	$525	n/a
Option 2 – School-based program targeting both school-aged and younger children				
Number vaccinations	25,520		23,306	14,717
Cases avoided over duration	456		158	258
Deaths avoided over duration	4.6		1.6	2.6
Hospitalizations avoided	5		16	26
Cases avoided per 1000 vaccinated	17.9		6.8	17.6
Deaths avoided per 1000 vaccinated	0.18		0.07	0.18
YLL avoided over duration	124		44	71
YLD avoided over duration	2		1	1
DALYs avoided over duration	126		44	72
Public COI avoided over duration	$1,882	n/a	$3,593	$533
Private COI avoided over duration	$5,174		$8,657	n/a
Total program costs	$27,306		$36,590	$15,747
Average cost per immunized person	$1.07		$1.57	$1.07
Total travel/time costs	$708		$1,455	$901
Net public costs	$25,424		$32,997	$15,214
Net public cost per case avoided	$201		$745	$210
Net social costs	$20,958		$25,795	n/a
Net social cost per DALY avoided	$160		$549	n/a
Option 3 – Community-based program (all ages)				
Number vaccinations	90,945		45,975	
Cases avoided over duration	762		203	
Deaths avoided over duration	7.6		2.0	
Hospitalizations avoided	21		61	
Cases avoided per 1000 vaccinated	8.4		4.4	
Deaths avoided per 1000 vaccinated	0.08		0.04	
YLL avoided over duration	194		54	
YLD avoided over duration	4		1	
DALYs avoided over duration	198		55	
Public COI avoided over duration	$3,145	n/a	$4,756	n/a
Private COI avoided over duration	$8,648		$11,122	
Total program costs	$97,311		$72,181	
Average cost per immunized person	$1.07		$1.57	
Total travel/time costs	$4,653		$5,289	
Net public costs	$94,166		$67,425	
Net public cost per case avoided	$476		$1,228	
Net social costs	$90,171		$61,593	
Net social cost per DALY avoided	$433		$1,025	
GNI thresholds (for reference)				
"Cost-effective"	$2,613	$2,394	$5,436	$2,679
"Very cost-effective"	$871	$798	$1,812	$893

Notes: YLLs, YLDs, and DALYs calculated using uniform age-weights and discounted at 3%. Results presented in US Dollars converted from local currency with market exchange rates.

[a] In Hue, baseline incidence rates were not measured in Ochiai et al. [3] for children under 5 or adults over 18; we assume adult incidence is the same as incidence in children 16–18, incidence in children under 5 is the same as incidence in children 5–14, and the adult hospitalization rate is the same as for children. Similarly, in Karachi we assume incidence among children under 2 is the same as children 2–5 for lack of data. We assume adult incidence is 1.28 per 1000 based on data for 16–18-year-olds (unpublished data from the study reported in ref. [3]), and assume child and adult hospitalization rates are the same.

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US$188. From a societal perspective, the program in Kolkata would reduce private costs of illness by $2988, yielding a net social cost of $10,671, or US$147 per DALY avoided.

Compared to the Kolkata slums, the three settlements in Karachi have a somewhat lower baseline incidence among school-aged children and a lower public COI per case. As such, the net public costs per DALY avoided are higher for program Option 1 in Karachi (US$231 per DALY vs. US$188 in Kolkata). (We do not report cost-effectiveness in Karachi from a societal perspective because data on private cost of illness is unavailable.) The two sub-districts in North Jakarta have lower incidences than either the Kolkata or Karachi sites and higher delivery costs per dose, yielding cost-effectiveness ratios of $721 (public sector perspective) and $525 (social perspective) per DALY averted for program Option 1. Because these ratios are all less than per capita GNI (provided for reference at the bottom of Table 5), program Option 1 would be considered "very cost-effective" in our sites in Kolkata, Karachi and North Jakarta.

The incidence is an order of magnitude lower in Hue than the other three sites, so the ratio for program Option 1 is an order of magnitude higher (US$3917 and US$3779 per DALY avoided for public sector and social perspectives). This program would not be considered "cost-effective".

3.1.3. Option 2 – School-based vaccination targeting school-age and younger children

Program Option 2 is a school-based program that would make vaccines available to all children (aged 2–14) in the study sites. Because children must still be old enough to be safely vaccinated (≥2years), the difference between Options 1 and 2 is (a) adding school-aged children who are not enrolled in school, (b) adding young children (aged 2–4.9 years old), and (c) incorporating the travel/time costs of bringing these children to be vaccinated. The main effect of adding these children is to increase the number of vaccinations, the number of cases avoided and the total costs. For example, program Option 2 for the two Kolkata slums would vaccinate 11,739 more children than Option 1, avoiding 193 more typhoid cases but costing $12,561 more in total program costs (and $708 in travel/time costs). Because these effects move in parallel, the difference in cost-effectiveness ratios is small. In Kolkata, program Option 2 has a net social cost of US$160 per DALY avoided vs. US$147 for Option 1. Option 2 is slightly less cost-effective than Option 1 primarily because young children have a lower baseline incidence than school children in Kolkata (3.4 per 1000 vs. 4.9 per 1000 in school children, see Table 1). This is also true in North Jakarta, where program Option 2 is slightly less cost-effective than Option 1 (net social costs of US$549 per DALY vs. US$525). The opposite is true in Karachi, where young children have higher incidence than school children, so Option 2 is slightly more cost-effective than Option 1 (net public costs of US$210 per DALY vs. US$231 in Option 1).

3.1.4. Option 3 – Community-based vaccination targeting adults and children

Community-based vaccination programs which target adults as well as children have less favorable cost-effectiveness ratios in the two sites with adult incidence data (Kolkata and North Jakarta) because incidence is lower in adults than in children. A community-based vaccination program targeting the two Kolkata slums would vaccinate many more people (90,945 people) than either of the first two options at a higher total cost of US$97,311, or US$476 and US$433 per DALY avoided (public and social perspectives). These ratios, however, would still meet the "very cost-effective" criterion. A community-based vaccination program in the two North Jakarta districts would vaccinate 45,975 people at a total cost of US$72,181. At US$1228 and US$1025 per DALY averted, these ratio are also "very cost-effective".

Table 6
Net social costs per DALY averted with non-uniform age-weights

Parameters	Kolkata, India	Hue, Vietnam	North Jakarta, Indonesia
Program Option 1	$81	$2,356	$330
Program Option 2	$155	n/a	$546
Program Option 3	$322	n/a	$898

Notes: Program Option 1 targets only school-aged children (5–14.9), Option 2 also includes young children (2–4.9); Option 3 is a community-based program targeting all ages. Age-weighting parameter values used are $\beta = 0.04$ and $C = 0.1658$, the values used in the original 1990 Global Burden of Disease study [32]. These parameter values give the highest weight to DALYs avoided among those aged 25 and weights less than 1 to DALYs avoided in children under age 9 and adults over age 55. See also Chapter 5 of the DCPP [16].

3.2. Sensitivity analyses

3.2.1. Effect of non-uniform age-weights

We explore the effects of using non-uniform age-weights in Table 6. For brevity, this analysis and the other sensitivity analyses below refer only to cost-effectiveness from a social perspective; a similar analysis for public sector financial cost-effectiveness is available in the online appendix. We use the parameters for the weighting function used in the original Global Burden of Disease study [32] and, as before, we discount life years at 3%. These parameter values (namely $\beta = 0.04$) imply weights greater than 1 for DALYs avoided among those aged 9–55 (peaking at age 25) and weights less than 1 for the old and the young. Because typhoid incidence is highest in school-aged children in all sites except Karachi, and because we do not model typhoid vaccination in children under 2, cost-effectiveness ratios all improve from the baseline case with non-uniform age-weights.

3.2.2. Which model parameters have the largest effect on cost-effectiveness?

The five parameters that have the largest effect on the ratio of net social cost per DALY are vaccine cost, the case fatality rate, the vaccine's duration, the baseline incidence, and the vaccine's efficacy. In almost all cases, the ratio is most sensitive to vaccine cost. Figs. 1–3 show the one-way sensitivity analysis for cost, or the effect of varying only the cost parameter within the uncertainty range in Table 1 and leaving all other parameters at their base case value. For program Option 1 (targeting school-aged children only) in Kolkata, for example, the ratio varies from US$77 per DALY avoided if the total cost per vaccinated person is US$0.7 to 569 per DALY if the cost is US$3.3 per person. Within the entire range of assumptions about vaccine cost, however, the program would be "very cost-effective" (shown as a dashed line in Fig. 1). This is true for both program Options 1 and 2 in Kolkata (and similarly for public sector cost-effectiveness in Karachi; see online appendix). Program Option 3 would be "very cost-effective" in Kolkata if the total cost per vaccinated person were less than US$2.03 (Fig. 3). Program Options 1, 2 and 3 would be "very cost-effective" in North Jakarta if total vaccine costs were less than US$4.08, US$3.97, and US$2.51, respectively. The program in Hue would not be "cost-effective" within the entire range of plausible vaccine cost estimates.

Table 7 shows the one-sensitivity analysis for the other parameters which have the largest effect on cost-effectiveness. For program Options 1 or 2 in Kolkata and North Jakarta, the choice of individual parameter estimates does not change the overall assessment of whether the program is "very cost-effective": the CE ratios for these programs in these locations are nearly always lower than GNI per capita. Similarly, within the entire assumed range of parameter estimates for Hue, the CE ratio is always larger than US$800 per DALY, and "cost-effective" (<US$2394 per DALY) only for values of the case fatality rate or the incidence rate at the highest end of plausible values.

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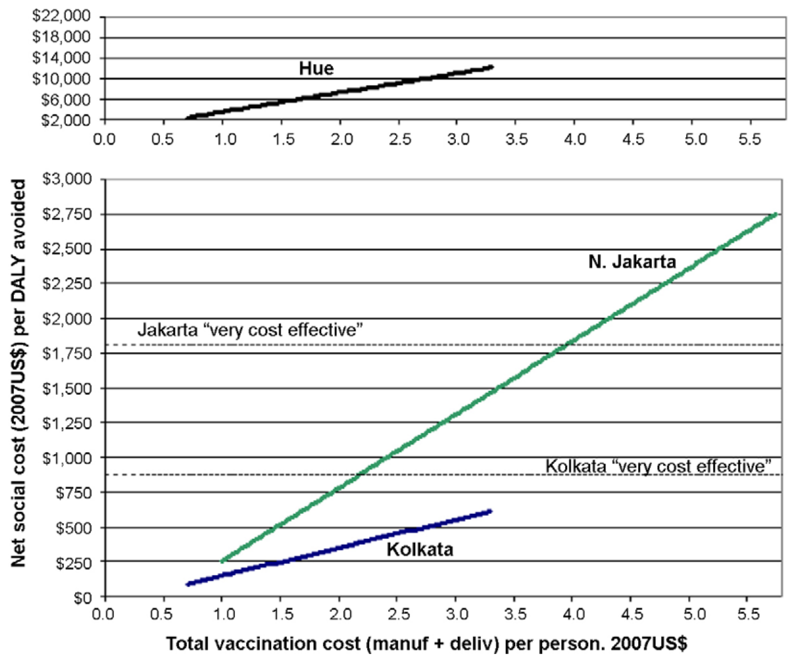

Fig. 1. Effect of variation in total vaccination cost per dose on net social cost per DALY avoided for program that targets only children attending school (Option 1). *Notes*: Dashed lines indicate costs at which program becomes "very cost-effective" (see Table 5). Programs in Kolkata and Jakarta are "cost-effective" across the range of vaccine costs considered. Programs in Hue are not cost-effective across the range of vaccine costs considered.

3.2.3. *Monte Carlo simulations*

Finally, we allow all parameters to vary simultaneously in a Monte Carlo framework. Table 8 presents the median costs per DALY avoided, 95% confidence intervals, and the probability that the net social costs per DALY will be less than per capita GNI for all three program options. Again, programs targeting school-aged children only (Option 1), or targeting younger children as well (Option 2) in Kolkata and Jakarta (Option 2) are the most attractive, and will certainly pass the GNI cost-effectiveness threshold (Table 8). Programs in Hue will not pass this threshold due to the low typhoid incidence in this site. Monte Carlo simulations for net public costs and for other distributional assumptions are provided in the online appendix.

4. Discussion

Our results indicate that typhoid vaccination programs targeting children (Options 1 or 2) have "very cost-effective" ratios (from either a public sector or societal perspective) in the high-incidence areas of Kolkata, Karachi, and North Jakarta. Although the ratios are sensitive to our estimated cost per vaccinated person, our conclusions hold across a range of plausible assumptions about vaccine cost, case fatality rate, incidence and vaccine effectiveness. Comparing Options 1 and 2, the program targeting only school children (Option 1) has a slightly lower ratio in Kolkata and Karachi, but slightly higher ratio in Jakarta. On balance, we think the economic differences between Options 1 and 2 are minimal, and that

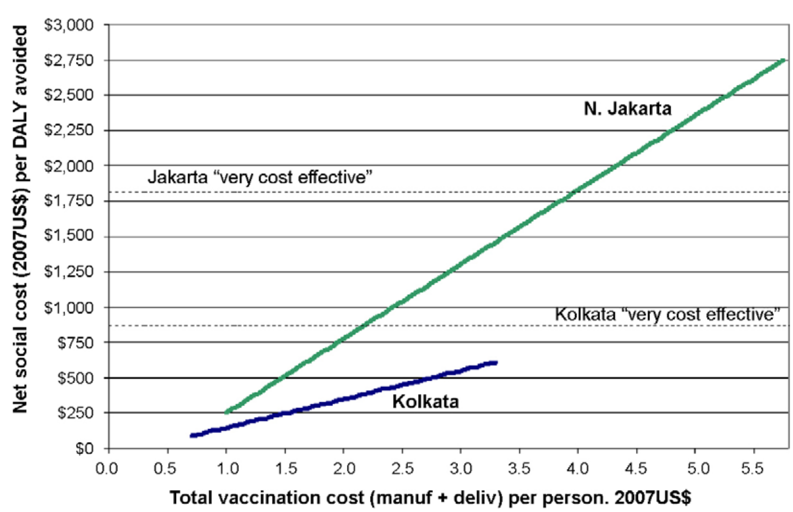

Fig. 2. Effect of variation in total vaccination cost per dose on net social cost per DALY avoided for program that targets school-aged and younger children (Option 2). *Notes*: Dashed lines indicate costs at which program becomes "very cost-effective" (see Table 5). Programs in Kolkata and Jakarta are "cost-effective" across the range of vaccine costs considered.

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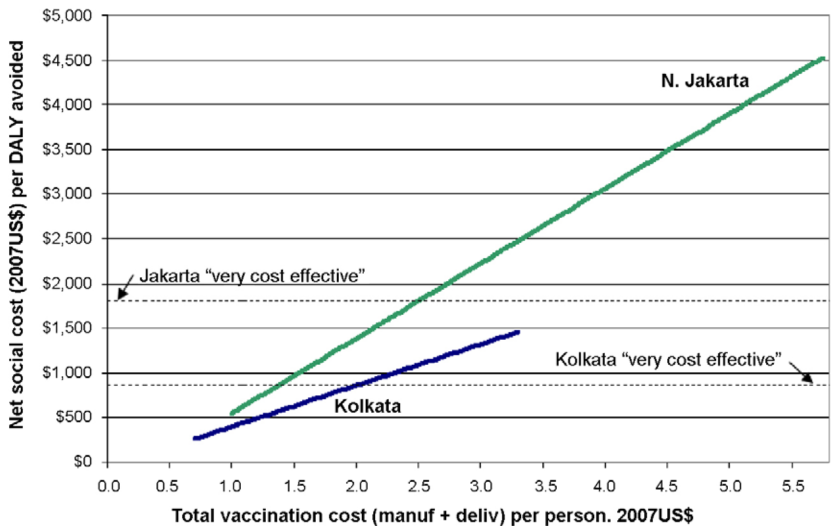

Fig. 3. Effect of variation in total vaccination cost per dose on net social cost per DALY avoided for community-based vaccination program that targets both adults and children (Option 3). *Notes*: Dashed lines indicate costs at which program becomes "very cost-effective" (see Table 5). Programs in Kolkata and Jakarta are "cost-effective" across the range of vaccine costs considered.

there is a strong moral argument for including young children in a vaccination program. Community-based vaccination programs which include adults as well as children have less favorable cost-effectiveness ratios because child incidence is greater than adult incidence in all sites. Still, community-based programs in Kolkata and North Jakarta would be "very cost-effective".

No program in Hue is likely to be cost-effective for any of the three program options. This conclusion is driven by the low typhoid incidence in Hue and holds across a range of plausible parameter values. Typhoid vaccination may, of course, be more attractive in other sites in Vietnam where incidence is higher. Lin et al. [33], for example, reported a blood-culture-confirmed incidence level (5.3

Table 7
Effect of individual parameter uncertainty on social cost-effectiveness ratios

	Vaccine cost	CFR	Duration	Incidence	Efficacy
Value	(See below)	3–0.5%	2–4 years	(See Table 1)	55–75%
Kolkata, India	$0.7–3.3				
Program Option 1	77–569	49–288	98–244	93–190	120–184
Program Option 2	85–610	54–315	109–263	94–221	131–199
Program Option 3	262–1,459	146–849	315–668	290–571	367–522
North Jakarta, Indonesia	$1.0–5.8				
Program Option 1	234–2,688	177–1,032	333–909	301–698	418–671
Program Option 2	249–2,774	185–1,079	352–944	300–774	439–699
Program Option 3	548–4,567	346–2,013	711–1,654	646–1,382	850–1,264
Hue, Vietnam	$0.7–3.3				
Program Option 1	2,383–12,193	1,275–7,426	2,814–5,710	2,005–5,715	3,240–4,513

Notes: Net social costs are in US$2007 adjusted at market exchange rates. Results not reported for Karachi because data on private COI is unavailable. Program Option 1 targets only school-aged children (5–14.9), Option 2 also includes young children (2–4.9); Option 3 is a community-based program targeting all ages.

Table 8
Results of Monte Carlo analysis on net social cost per DALY avoided (US$2007)

	Kolkata, India	Hue, Vietnam	North Jakarta, Indonesia
Option 1 – School-based Program targeting only school-aged children			
Mean (median)	200 (163)	4,367 (3,499)	860 (681)
95% confidence interval	41–578	1,002–13,148	133–2,617
%Chance "very cost-effective"	>99%	<1%	92%
Option 2 – School-based program targeting both school-aged and younger children			
Mean (median)	211 (173)		880 (703)
95% confidence interval	44–604	n/a	144–2,649
%Chance "very cost-effective"	>99%		91%
Option 3 – Community-based program (all ages)			
Mean (median)	536 (445)		1,526 (1,242)
95% confidence interval	140–1,453	n/a	319–4,396
%Chance "very cost-effective"	86%		71%

Notes: Results from 10,000 model runs, triangular distributions for parameters with lower and upper values set to ranges shown in brackets in Table 1 (except for incidence, duration, and hourly wage).

per 1000) among 5–9-year-olds in Dong Thap province similar to that observed in Kolkata and Karachi.

The principal usefulness of cost-effectiveness analysis is not in comparing ratios with an absolute threshold such as per capita GNI, however, but in the ability to compare various policy interventions using a common metric. A donor or health policymaker interested in investing in typhoid vaccination programs in any of these four sites should carefully consider the burden of other diseases in each site and other health interventions that could improve health status. Information on the cost-effectiveness of these other programs would ideally be site-specific, but the Disease Control Priorities project [16] provides a useful compendium of the cost-effectiveness of a range of health interventions. Laxminarayan et al. [34] list several "neglected low-cost opportunities" for South Asia based on the DCP, including: HIV/AIDS interventions ($9–126 per DALY); tuberculosis vaccination and control ($8–263 per DALY); and expansion of existing EPI coverage ($8 per DALY averted). (The 2005–2006 Indian National Family Health Survey [35] reported that 77% of children in Kolkata, for example, have received three doses of DTP (diphtheria, tetanus and pertussis), 83% have received three polio doses, and 81% have received a measles vaccine.) Although the cost-effectiveness of typhoid programs targeting children in Kolkata, Karachi and North Jakarta are at the upper end of these ranges, our results indicate that typhoid vaccination deserves careful consideration in high-incidence endemic settings similar to our study sites (with the exception of low-incidence Hue). Financing free vaccination, however, remains an important challenge; we return to this topic in the concluding paragraph.

There are several important limitations of the analysis. First, we assume pre-schoolers can be vaccinated through a local school, which might be logistically challenging in practice. Because we assume the same delivery costs for school- and community-based vaccination programs, however, this assumption does not alter the cost-effectiveness ratios.

Second, our approach does not account for the possibility that the 80% of slum dwellers who we assumed heard about the vaccination program may have lower incidence than the 20% who did not because of differences in access-to-care. If this were true, and if the passive surveillance method used in the baseline incidence study [3] captured all cases in the catchment area, this would mean our cost-effectiveness results are too optimistic. In other words, our approach may overestimate the program's ability to reach those most at risk.

Third, because of extensive training and public awareness campaigns that accompanied the surveillance studies, there was an increased awareness of the disease among providers and patients. Along with the establishment of community-based clinics in the Kolkata and Karachi study sites, this meant that febrile patients most likely sought treatment more often and earlier than they would likely do normally. This resulted in fewer severe complications like splenic rupture: there were in fact no splenic ruptures reported in any of the four surveillance sites. This would make the public and private costs of illness observed too low and make the cost-effectiveness ratios too pessimistic. The availability of over-the-counter antibiotics also raises the possibility that some patients may have self-medicated before seeking treatment, again lowering public treatment costs though not privately borne costs [3]. Although no typhoid deaths occurred in any of the study sites, this may have also been due to the better than average quality of care in the DOMI clinics. Because we use a baseline case fatality rate of 1% in our analysis rather than the observed rate of 0%, however, our results should not be biased unless treatment regimes in the absence of DOMI clinics would result in case fatality rates higher than 1%.

Fourth, we had no data to inform our assumption about the amount of time spent traveling and waiting to be vaccinated and the opportunity costs of this time. Although we model fairly short travel and queueing times because all four sites are densely populated urban areas, these times and costs may in fact be substantial for adults. Although free vaccination is one strategy for helping the poor, where queues are long and vaccination clinics are inconveniently located, the poor may not be able to afford time away from their work to bring their children to be vaccinated.

Fifth, we assume that the marginal delivery cost per dose is the same for a school-based program (Options 1 and 2) as for a community-based vaccination program (Option 3). It is possible that average delivery costs for school-based programs may be lower than for community-based programs because there may be other school-based programs which a vaccination program can share costs with, because health staff time might be used more efficiently, and because less social marketing might be needed. We feel, however, that the body of evidence is not strong enough to warrant the use of different delivery costs for our program options (see online appendix for more discussion of delivery cost assumptions).

In addition to asking the question of whether typhoid vaccination is cost-effective, a donor or policy maker might take a social cost-benefit perspective and ask whether the economic benefits of a vaccination program that provides vaccines for free exceed its economic costs. The cost-effectiveness approach presented in this paper avoids placing an economic value on preventing a case of typhoid, subsuming all economic benefits within the DALY metric and simply comparing the costs of preventing one more DALY across policy interventions. Although a DALY measure reflects both the (non-monetized) morbidity and mortality outcomes of the vaccination intervention, it may be undesirable to assume that the value of the risk reduction obtained from vaccination applies equally for heterogeneous populations in four different countries. A program with a favorable ratio of net social cost per DALY avoided may still fail a social cost-benefit test, and vice versa.

Finally, the paper does not address the very real challenge of financing free vaccinations. Government health resources are extremely limited in the countries in question, and there may not be sufficient funds for the health ministries to pay for a typhoid vaccination program without large increases in per capita spending on health. In India, for example, public sector per capita spending on health was ∼US$4.5 in 2001–2002 according to the Indian Ministry of Health's National Health Accounts data [36]. On a per capita basis, a typhoid vaccination program in the two slums that cost US$1.1 per vaccinated individual would consume nearly a quarter of public sector health care spending. Donors may fund these programs, though donors may also view their role as catalysts for health improvements in the short-run while expecting that local governments will eventually take over financial responsibility for the vaccination program in the medium term [37]. This is particularly important for typhoid vaccines because re-vaccination must occur every 3 years to ensure continued protection and because financial savings from the avoided public treatment costs are relatively small (and may be difficult to convert to cash to pay for vaccination programs in practice). Our analysis ignores the potential to recover some or all of vaccination costs by asking users to share the costs through user fees; it may be possible to charge adults user fees that cross-subsidize vaccines for children [38].

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.vaccine.2008.09.040.

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