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An optimization model for reducing typhoid cases in developing countries without increasing public spending

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ABSTRACT

This article considers the investment case for using the Vi polysaccharide vaccine in developing countries from two perspectives: reducing typhoid cases and limiting new health care spending. A case study is presented using data from South and Southeast Asia. The purpose of the paper, however, is to draw broad implications that may apply to developing countries in general. Typical consumer demand functions developed from stated preference household surveys in South and Southeast Asia are used to predict probabilities of adults and children purchasing typhoid vaccinations at different prices. These functions are incorporated in a formal mathematical model. Using data from the recent literature for South and Southeast Asia for typhoid incidence, Vi vaccine effectiveness, public cost of illness, and vaccination program cost, three mass vaccination policy alternatives are evaluated: charging adults and children different (optimal) prices, charging uniform prices, and providing free vaccines. Assuming differential pricing is politically feasible, different vaccine prices for children and adults would maximize the number of typhoid cases avoided from a mass vaccination program if the public sector faces a budget constraint on spending for the vaccination program. However, equal prices for children and adults produce very similar results, and they might be more readily accepted by the community. Alternatively, if vaccines are free, the number of cases is not significantly reduced compared to either pricing policy, but a large external financial contribution from government or donors would be required. A Monte Carlo simulation explores the effects of uncertain parameters on vaccination program outcomes.

1. Introduction

Typhoid is endemic in many developing countries and remains a substantial public health problem despite recent progress in water and sanitation coverage. The new-generation Vi polysaccharide vaccine is a safe and effective public health intervention against typhoid; Acosta et al. [1] report an efficacy of 55–70% for 2–3 years. The Vi polysaccharide vaccine (Vi) is no longer afforded patent protection, has no strict cold chain requirements, and is now manufactured in Vietnam. There are also plans to produce Vi locally in India and Indonesia [2]. Local production will lower prices, and governments must decide whether to use the Vi vaccine and, if so, how that should be done.

Besides the Vi vaccine, several governments are considering proposals for the use of other new vaccines for serious diseases such as Japanese encephalitis and cholera. These new vaccines are outside the standard packages of vaccines recommended by the World Health Organization's Expanded Program on Immunization (EPI). International vaccine donors such as the Global Alliance for Vaccines and Immunization now want national governments to share the costs of vaccine purchases. Because governments' financial resources for new vaccination programs are limited, they face some hard choices.

The investment case for expanded use of the Vi vaccine in developing countries requires a careful examination of the costs and benefits of different program options. There is no consensus as to how best to measure the economic benefits of Vi vaccination programs. From the perspective of public health professionals, the main benefits of vaccination are clearly the reduced morbidity and mortality associated with fewer typhoid cases. National health ministries with fixed budgets view new vaccination initiatives somewhat differently because they may have difficulty persuading finance ministers that a larger health budget is required. Health policymakers thus especially want information on how much money any proposed new vaccination program will save the public sector in terms of reduced costs due to treating fewer active cases in government-subsidized hospitals and health clinics. If the cost savings to the health ministry from treating fewer typhoid patients

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were predicted to exceed the cost of a proposed vaccination program and if the ministry can access financial markets to pay for the initial costs of the program, a new vaccination program would both save money from the public perspective and reduce typhoid morbidity and mortality. But if such cost savings were expected to be less than the costs of the vaccination program, the value of the health outcomes relative to anticipated costs would require a more careful reckoning.

In this article we consider the investment case for wider use of Vi vaccines in developing countries from both of these perspectives simultaneously: the public health objective of reducing the number of typhoid cases, and the financial objective that a new vaccination program should not require substantial new government spending. When donor funding and treatment cost savings are limited, the only way the financial objective can be met is to charge recipients for vaccinations and to use the resulting revenues to offset part of the costs of the vaccination program. But charging user fees for the vaccine conflicts with the public health objective of reducing typhoid cases: some people will be unwilling or unable to pay. Our primary goal here is to quantify the tradeoff between reducing typhoid incidence and meeting financial obligations.

We begin with a brief review of previous attempts to use mathematical optimization models to examine vaccine policy issues. We then present a new optimization model that incorporates vaccine user charges as a way to overcome financial obstacles to expanded use of new vaccines. Then we illustrate our model with (1) deterministic data that represent our best estimates of median results from many typhoid-endemic areas of South and Southeast Asia, and (2) stochastic results based on random parameter draws from probability distributions. Our deterministic and stochastic findings touch in various ways on the model's applicability in developing countries, on optimizing user charges for vaccines, on cost recovery, and on the implications for funding vaccination programs with limited or no financial assistance from international donors. Although we incorporate published data from South and Southeast Asia into our analysis, it is not possible to ascertain universal recommendations for all typhoid endemic locations in Asia. Practitioners would have to input their best, context-specific estimates of parameters to apply this model in a meaningful way.

2. Background

The literature on vaccine policy focuses primarily on the cost effectiveness or cost utility of different vaccines (for example refs. [3–6]). The question of how user charges should be determined to balance competing public health and government financial objectives is not typically broached in economic appraisals of vaccination programs.

Some authors have examined the optimal tax-subsidy scheme for providing vaccines in the presence of herd immunity or herd protection effects (e.g. refs. [7–11]). These models typically assume (1) a homogenous population with regard to risk of infection and willingness to pay for risk reduction, and (2) prospective purchasers understand the relationship between coverage levels and herd protection, and behave strategically. These models solve for the optimal price that equates the marginal social benefit of a vaccine with the marginal cost per fully vaccinated individual.

Several studies have been published that use mathematical optimization techniques for analyzing vaccination policies without including user charges as decision variables. For example, Becker and Starczak [12] describe the use of linear programming to determine the minimum number of vaccinations required to prevent disease epidemics based on strategic allocations among households. They conclude that the optimal allocation of vaccines among households should aim at leaving the same number of susceptible people in every household. Patel et al. [13] report a model to optimally allocate a limited number of flu vaccines in communities whose populations have been subdivided by age, each with a known influenza "attack rate" (analogous to incidence). Embedded in the optimization model is a stochastic epidemiological model developed by the authors that describes the propagation of influenza through the community. No consideration is given to costs, economic benefits, or prices.

Recently a number of studies have appeared that report on the magnitude of private demand for various vaccines. These include applications of the contingent valuation method for estimating private (household) demand for vaccines against diseases such as malaria [14], chickenpox [15], HIV/AIDS [16,17], typhoid [18–20], and cholera [19–23] But these studies have not used the information on private demand to determine appropriate user charges for vaccines, nor has this kind of information been incorporated into either the objective function or the constraint sets of vaccine policy optimization models.

3. Model formulation

This section describes an optimization model that is designed to be used by a government agency (e.g. ministry of health-MOH) for planning a mass vaccination campaign against typhoid fever in a region or city of a developing country. The model presented here addresses the question of pricing in a user-supported, publicly administered mass vaccination program in an area where public (government and donor) financial support is limited. Assume that the government's vaccination policy objective is to maximize the number of typhoid cases avoided subject to the constraint that the program must be funded through (1) user fees, (2) a fixed contribution from the government or an external donor (which could be zero), and (3) the savings realized by avoided (reduced) public costs of treating active cases. Our research question is: What vaccine user fees for adults and for children would maximize the number of typhoid cases avoided while still ensuring that the program does not impose excessive financial obligations on the government? The decision variables in our optimization model are the vaccination prices that should be charged to adults (pa) and children (pc) in the target population.

The incidence of typhoid is typically much higher in children than in adults [24], which has prompted proposals for school-based typhoid vaccination programs that only target children. Pakistan, Vietnam, and Indonesia are all now contemplating the initiation of school-based Vi vaccination [2]. School-based vaccination programs are an important option for consideration, but we prefer to take a broader approach in this analysis that focuses on a mass vaccination program that is open to both children and adults, in part because there is mixed evidence whether the cost per vaccinated individual is very different in school-based versus mass vaccination programs. We examine the possibility of pricing vaccines for adults and children differently, which allows us to consider the option of one group cross-subsidizing vaccines for the other.

We assume that no one in the area has been vaccinated prior to inception of the new vaccination program; thus everyone is initially at risk of typhoid infection. Once the mass vaccination campaign is launched, we assume that all inoculations are completed quickly after which new vaccinations in the area are unavailable for the duration of vaccine effectiveness, about 3 years. When individuals present themselves, they must pay the required fee for their vaccinations in cash.

In the optimization model, the number of cases of typhoid that will be avoided by having a vaccination program is the number of cases that would arise without a program less the number of cases with a program. In the model, the mathematical expressions for adults and children are similar and are distinguished using 'C' for children and 'A' for adults.

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Let *POPC* and *POPA* be the number of children and adults, respectively, in the area where the vaccination program is launched, whose sum is total population *POP*. A mass vaccination program will not be able to reach the entire population for various reasons (e.g., some families may not learn about the vaccination program, may be traveling away from home, or may be physically unable to travel to a vaccination outpost). The group of candidates for vaccination is the product $\theta \cdot POP$ where θ is the fraction of the population that can participate in a vaccination program, which is the same for adults and children ($\theta \cdot POP = \theta \cdot POPC + \theta \cdot POPA$). The adjustment using θ should not be confused with the portion of the population that could participate in the program but chooses not to do so (e.g., because of user fees, skepticism about vaccine efficacy, or a perception that they are not at risk of infection).

Let $PC(pc)$ be the probability that a child candidate will be inoculated if the vaccination fee is *pc,* and $PA(pa)$ is the probability that an adult candidate will be inoculated if the vaccination fee is *pa;* the mathematical forms of *PC* and *PA*, the coverage-price functions, are discussed in Section 4; note that the decision variables *pc* and *pa* are embedded in *PC* and *PA*, respectively, and that the two functions are similar but not identical. The number of children in the area who are vaccinated is therefore $PC \cdot \theta \cdot POPC$, and the number of adults is $PA \cdot \theta \cdot POPA$. There is empirical evidence that the Vi vaccine reduces typhoid incidence by about 55–85% in the vaccinated population. The best estimate of vaccine efficacy, EFF, is thus 0.7, where *EFF* is the probability that an inoculated person is completely protected by the vaccine for the duration of its effectiveness. Protection starts immediately after vaccination and lasts for 3 years, during which we assume that effectiveness is unchanged each year and is identical for children and adults.[1] Thus, the number of children protected against disease due to vaccination is $EFF \cdot PC \cdot \theta \cdot POPC$, and the number of protected adults is $EFF \cdot PA \cdot \theta \cdot POPA$. To simplify the notation, we make the substitutions in Eqs. (1) and (2), which lead to the expression in Eq. (3) for the total number of persons in the area protected by vaccination. Following on Eqs. (1) and (2), we define the fraction of unprotected children *FUPC* and adults *FUPA* as $(1 - FPC)$ and $(1 - FPA)$, respectively. Note that these fractions of protected and unprotected children and adults contain the decision variables *pc* and *pa*.

$$\text{Fraction of protected children due to vaccination} = FPC = EFF \cdot PC \cdot \theta \tag{1}$$

$$\text{Fraction of protected adults due to vaccination} = FPA = EFF \cdot PA \cdot \theta \tag{2}$$

$$\text{Total persons protected by vaccination} = (FPC \cdot POPC) + (FPA \cdot POPA) \tag{3}$$

It follows that the number of persons not protected by the vaccination campaign is

$$\text{Total persons not protected} = FUPC \cdot POPC + FUPA \cdot POPA, \tag{4}$$

which consists of persons who are unvaccinated (non candidates plus candidates who decide not to be vaccinated) and others who are vaccinated but for whom the vaccine is ineffective.

Some of the persons not directly protected by vaccination may be protected by herd immunity. However, the technical literature on herd protection from Vi vaccinations is sketchy, and the phenomenon is not well understood. Thus, the model in this section assumes no protection from herd immunity. A modified model to consider herd protection is presented in Appendix A.

The annual number of child cases of typhoid in the absence of the vaccination program is $IC \cdot POPC$, where IC = child incidence of typhoid (child cases per year per child in the area) prior to launching the campaign; similarly, $IA \cdot POPA$ = annual adult cases, and IA = adult incidence. Thus, the total cases without a campaign over the 3-year period of vaccine effectiveness to which this model applies is

$$\text{Total cases without program} = 3 \cdot IC \cdot POPC + 3 \cdot IA \cdot POPA \tag{5}$$

The number of typhoid cases that occur in each year of vaccine effectiveness *with* a vaccination program is the product of the number of unprotected children and adults in Eq. (4) and their respective incidences of typhoid in the area, *IC* and *IA*, prior to launch of the program. Multiplying these incidences by the terms in Eq. (4) for unprotected children and adults results in the expression for the number of typhoid cases with the vaccination program over the 3-year period of vaccine effectiveness shown in Eq. (6). Subtracting Eq. (6) from Eq. (5) and substituting *FPC* for $(1 - FUPC)$ and *FPA* for $(1 - FUPA)$ results in the expression in Eq. (7) for total cases of illness avoided by having the vaccination program.

$$\text{Cases with program} = 3 \cdot IC \cdot POPC \cdot FUPC + 3 \cdot IA \cdot POPA \cdot FUPA \tag{6}$$

$$\text{Cases avoided} = 3 \cdot IC \cdot POPC \cdot FPC + 3 \cdot IA \cdot POPA \cdot FPA \tag{7}$$

We assume that the user of this model (the ministry of health or other vaccination planning agency) requires that the sum of (i) a fixed contribution from the government or external donor, (ii) revenue from vaccinations, and (iii) the present value savings on the public cost of illness avoided during the next three years must equal the program cost. We consider the fixed contribution, *S*, to be an exogenous variable that would be specified prior to model solution. Revenue from selling vaccines is the product of the number of persons vaccinated and the user fees they pay: $pc \cdot PC \cdot \theta \cdot POPC$ for children and $pa \cdot PA \cdot \theta \cdot POPA$ for adults.

The annual public sector cost of illness avoided assuming all cases of illness are treated at public expense and that all savings on cases avoided accrue to the health ministry is the number of cases avoided each year that the vaccine is effective (i.e. in years 1, 2, and 3), which is Eq. (7) divided by 3, multiplied by the average public cost of treating a typhoid patient (*COI*), which is assumed to be the same for children and adults. However, it is possible that some cases of illness are not treated at public expense, and that the entire savings for those that are treated might not accrue to the health ministry in charge of the vaccination campaign. Hence, we introduce σ to indicate the fraction of cases that are treated at public expense and μ to indicate the fraction of public savings that accrues to the vaccination planning agency; $\sigma = 1$ if all cases of illness are treated at public expense, and $\mu = 1$ if all public savings accrue to the health ministry; σ and μ are assumed to be the same for children and adults. The annual savings need to be discounted from the end of years 1, 2 and 3 to the beginning of year 1 by multiplying by the present worth factor (*PWF*) for an equal annual series, where $PWF = [1 - (1 + r)^{-3}]/r$ and r = annual interest rate for financial transactions. Thus the income side of the financial ledger is

$$S + pc \cdot PC \cdot \theta \cdot POPC + pa \cdot PA \cdot \theta \cdot POPA + \sigma \cdot \mu \cdot PWF \cdot COI \cdot IC \cdot POPC \cdot FPC + \sigma \cdot \mu \cdot PWF \cdot COI \cdot IA \cdot POPA \cdot FPA \tag{8}$$

The cost of the vaccination program is assumed to be the sum of a fixed cost that is mainly incurred for launching the program

[1] There is some evidence that efficacy declines somewhat in the third year. This effect could be approximated in our model by slightly reducing average efficacy over the duration of protection.

Table 1
Model parameters.

Parameter [lit. reference]	Symbol	Best	Lower bound	Upper bound
Typical parameter values for South and Southeast Asia				
Intercept child demand function [18,20]	αc	0.8	0.50	0.95
Slope child demand function [18,20]	βc	−0.1	−0.05	−0.30
Intercept adult demand function [18,20]	αa	0.5	0.35	0.65
Slope adult demand function [18,20]	βa	−0.2	−0.10	−0.60
Child typhoid incidence, cases/year per 1000 children [26]	*IC*	3.5	0.3	10
Adult typhoid incidence, cases/year per 1000 adults [26]	*IA*	1.0	0.1	2.5
Cost of treating a sick child (US$) [27,28]	*COIC*	30	0	100
Cost of treating a sick adult (US$) [27,28]	*COIA*	30	0	100
Cost of a vaccination (US$) [29–31]	*C*	1.0	0.5	2.0
Fixed cost of the program (US$) [29–31]	*F*	100,000	50,000	200,000
Vaccine efficacy [1]	*EFF*	0.70	0.55	0.85
Assumed parameter values				
Fraction of children and adults participating in program	θ	0.9	0.8	1.0
Interest rate (% per annum)	*r*	8.0	6.0	10.0
Donor contribution to vaccination program (US$)	*S*	0	–	–
Fraction of typhoid cases treated at public expense	σ	1.0	–	–
Fraction of treatment cost avoided that accrues to MOH	μ	1.0	–	–
Total number of children in case study	*POPC*	300,000	–	–
Total number of adults in case study	*POPA*	700,000	NA	NA

plus variable costs for operating the program. Assuming the variable cost per delivered vaccination is constant, this function reflects economies of scale.[2] The fixed cost, *F*, covers expenses for basic program administration, social marketing, and publicity. The variable costs include the cost of supplies plus the labor, travel and administrative costs for delivering the doses of vaccine. Some fixed cost components, however, may sometimes be categorized as variable costs, and vice versa. Assuming the variable cost of vaccination delivery C is constant and independent of the number of vaccinations delivered, the variable cost is the product of the number of persons vaccinated and variable delivery cost per vaccinated person, which results in the cost side of the ledger shown in Eq. (9).

$$F + C \cdot PC \cdot \theta \cdot POPC + C \cdot PA \cdot \theta \cdot POPA \qquad (9)$$

The revenue neutrality constraint that equates income and costs is thus obtained by setting Eq. (8) equal to Eq. (9). This completes the optimization model. The policy problem is to find the optimal vaccination user fees to be charged for adults and children, pa^* and pc^*, that maximize the number of typhoid cases avoided, Eq. (7), subject to the revenue neutrality constraint, Eq. (8) equal to Eq. (9). The optimal results for this model can be obtained using a variety of methods including Lagrangian analysis, non-linear programming, and others.[3] The model can be used for making simulations under a wide variety of different conditions, which can provide important insights into the planning of vaccination campaigns.

4. Data

The data for applying the model are summarized in Table 1, which indicates the best estimate of each parameter used in the deterministic application of Section 5 and the ranges of parameter values used in the stochastic analysis that follows it. We assume that the illustrative case study has a population of one million, with 300,000 children (*POPC*) and 700,000 adults (*POPA*).

Typhoid fever can affect any age group, but incidence is generally believed to peak between the ages of 5 and 12 years [25]. A recent five-country study provides typhoid incidence estimates from Hue, Vietnam; Karachi, Pakistan; Kolkata, India; North Jakarta, Indonesia; and Hechi, China [26]. The ranges of incidence at these sites are 0.1–2.5 cases per year per 1000 adults and 0.3–10.0 cases per year per 1000 children; incidence among children is typically 2–4 times higher than among adults.[4]

These sites represent a range of typhoid incidences. The Karachi, Kolkata, and N. Jakarta samples were all taken from urban slums where incidence was 10–20 times greater than for Hue or Hechi. In a separate 1996 study in an urban slum in Delhi, India, typhoid incidences were estimated to be considerably higher [27].

For the deterministic model in Section 5, annual incidence of typhoid fever in children (*IC*) is 3.5 cases per 1000 children, and annual incidence in adults (*IA*) is 1.0 case per 1000 adults, both of which are within the ranges cited above. Multiplying populations by incidences, the number of new child cases of typhoid each year in the absence of a vaccination program in the case study would be 1050, and the number of new adult cases would be 700. This amounts to a total of 1750 new cases per year or 5250 cases for the 3-year period of vaccine effectiveness (model planning period), assuming child and adult populations and incidences remain constant.

Public cost-of-illness (*COI*) estimates include expenditures on physician time, laboratory tests, medicines, overnight treatment stays, and other expenses. Public *COI* per case estimates are available from each of the five sites where incidence was estimated [28]; they vary by site and by the level of health care provided. The average public *COI* per case varies from zero in China, where individuals pay the full cost of treatment, to US$ 100 in Delhi; it was US$ 2 in Karachi.[5] Hospitalized typhoid cases are about 10–50 times more

[2] If the variable cost were to increase as the number of vaccinations increased, there would be economies of scale with increasing vaccination sales up to the point where average vaccination cost started to increase. Beyond that point, there would be diseconomies of scale for any additional vaccinations.

[3] The Lagrangian expression L is: $3 \cdot IC \cdot POPC \cdot FPC + 3 \cdot IA \cdot POPA \cdot FPA - \pi\{S + pc \cdot PC \cdot \theta \cdot POPC + pa \cdot PA \cdot \theta \cdot POPA + \sigma \cdot \mu \cdot PWFCOI \cdot IC \cdot POPC \cdot FPC + \sigma \cdot \mu \cdot PWFCOI \cdot IA \cdot POPA \cdot FPA - [F + C \cdot PC \cdot \theta \cdot POPC + C \cdot PA \cdot \theta \cdot POPA]\}$, where π, the undetermined Lagrangian multiplier, denotes the marginal change in the cases of illness avoided per unit change in present value net revenue. The optimal prices pc^* and pa^* can be found using the calculus by solving $\partial L/\partial(pc) = \partial L/\partial(pa) = \partial L/\partial(\pi) = 0$. In order to do so, the functional forms of *PA* and *PC* in terms of *pa* and *pc* must be specified.

[4] These incidence rates are for blood-culture confirmed typhoid, but this test has low specificity and epidemiologists commonly assume that the actual typhoid incidence is twice the blood culture confirmed rate.

[5] The cost of living varies considerably across the sites after accounting for differences in exchange rates; purchasing power parity (PPP) calculations attempt to provide a comparison of currency purchasing power based on the average costs of common household items and dietary staples. For example, the Delhi public *COI* per case estimate of US$ 100 corresponds to about PPP$450 after accounting for the purchasing power of the Indian rupee to the US dollar.

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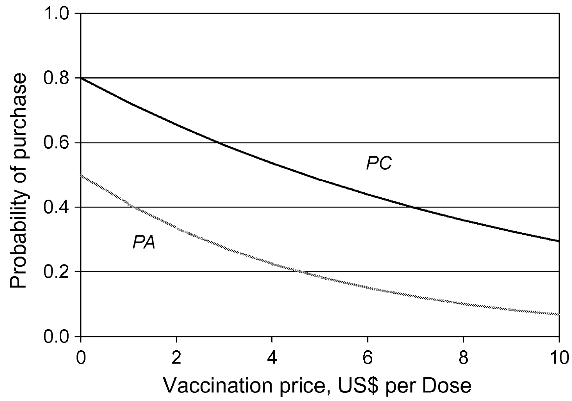

Fig. 1. Probability that the average adult, PA, or child, PC, purchases a vaccination.

expensive than non-hospitalized cases [27,28]. Public *COI* per case was about five times higher for children than for adults in Delhi, but *COI* per case was slightly higher for adults than for children in Jakarta. Across the study sites, the median public *COI* per case is about US$ 30. Using this estimate for the deterministic case study, the annual public expenditure for treating typhoid would be US$ 52,500 if all 1750 cases per year were treated. We are not aware of any published estimates of the fraction of cases treated at public expense (σ) nor the disposition of savings (μ) on cases of illness avoided resulting from mass vaccination campaigns; both parameters are assumed to be 1.0 for both the deterministic and stochastic analyses.

All costs in the examples of Section 5 are based on several studies conducted under the aegis of the International Vaccine Institute (IVI) [29–31], and they are 2007 values. The average variable cost of vaccinating an individual (child or adult) with the Vi vaccine is estimated to be US$ 1.0 via a mass vaccination program that is offered through neighborhood-level medical clinics. These costs are similar to the actual costs for vaccination trials conducted by the IVI in Hue, Vietnam, in 2003 [30]. The fixed cost for the deterministic case study (F) is US$ 100,000, or about US$ 0.1 per person in the area. In a recent cholera mass vaccination campaign that immunized about 50,000 persons, the fixed costs for the awareness campaign was about US$ 0.20 per person [29], and in a similar cholera campaign in Vietnam that immunized about 300,000 persons, the fixed cost was US$ 0.14 per person [31].

Two studies of private demand for the Vi vaccine conducted for the IVI in Hue, Vietnam, and Kolkata, India, constitute the basis for the price-coverage (willingness-to-pay) functions *PC* and *PA* in the model of Section 3 [18–20]. The demand equations in the model that support Fig. 1 fall between the estimates for the Kolkata and Hue sites. The extent to which these demands are typical of South and Southeast Asia is unknown since these studies were among the first of their kind. Heads of households were asked in an in-person interview to indicate the number of vaccines they would purchase for their households at proffered prices and which members would receive them. Poisson models[6] [Eq. (10)] were fitted to the responses based on which household members would be vaccinated, resulting in separate Poisson equations for adults and children.

$$P(n) = \frac{\exp(\lambda) \cdot \lambda^n}{n!} \quad n = 0, 1, 2, \ldots \tag{10}$$

$P(n)$ is the probability that a household would purchase n vaccinations, and λ, the Poisson parameter, indicates the average number of vaccines households would purchase, which is a function of such variables as household size, the price of a vaccination, household income, and concern about contracting typhoid. The child demand function *PC*, which is based on the Poisson parameter λ for children, is shown in Eq. (11), and the demand function for adults is in Eq. (12).

PC is the probability that a child will be vaccinated if the price is *pc*, which can be derived from the Poisson parameter for children λc. The average number of vaccinations a typical household will purchase for its children at price *pc* is obtained from λc by inserting average values from the household survey for all of its variables except price. Dividing the resulting expression by the average number of children in sample households yields the fraction of children that will be vaccinated, which is *PC*; *PA* is similarly obtained by dividing λa by the average number of adults in households. The resulting demand functions are shown in Eqs. (11) and (12) for children and adults, respectively.

$$PC = \alpha c \cdot \exp(\beta c \cdot pc) \tag{11}$$

$$PA = \alpha a \cdot \exp(\beta a \cdot pa) \tag{12}$$

In Eq. (11), αc, the intercept of the demand function, is the probability that a child in a typical household will be vaccinated if the price is zero, and βc is the price coefficient (<0) that indicates how the number of vaccinations purchased changes as price changes; the interpretation for adult parameters in Eq. (12) is similar.[7] If vaccinations are free, 80% of the children and 50% of the adults will be vaccinated, as shown in Fig. 1. The low intercept for adults is probably because respondents believed the disease is more serious and more prevalent for children than for adults.

For exponential demand functions like Eqs. (11) and (12), revenues from vaccinations ($pc{\cdot}PC{\cdot}\theta{\cdot}POPC$ and $pa{\cdot}PA{\cdot}\theta{\cdot}POPA$) increase as price increases up to a maximum when the price ($\hat{p}$) is $-1/\beta$; for prices higher than $\hat{p}$, revenues decrease. Hence, for the parameters βc and βa, the revenue-maximizing user fee for children $\hat{p}c$ is US$ 10 per dose, and for adults $\hat{p}a$ is US$ 5.

5. Results

This section presents results from applying the optimization model to an illustrative case using the data in Section 4. Results from the deterministic application are presented first based on the parameter values labeled "Best" in Table 1 followed by results from a sensitivity analysis. All results assume that vaccinations are provided in existing health outposts. Neither the government nor external donors contribute to the program ($S = 0$). The fraction of the total population that participates in the vaccination program is 90% ($\theta = 0.9$). All cases of typhoid are treated at government expense ($\sigma = 1.0$), and all savings on public treatment costs avoided accrue to the Ministry of Health ($\mu = 1.0$).

5.1. Basic model

Solving the optimization model with the parameter values from Table 1 produces the optimal price for children (pc^*) of zero and for adults (pa^*) of US$ 2.30. The results for this example are in the third column of Table 2 labeled "Basic Model;" data in Table 2 are rounded for ease of exposition. Without a vaccination program, there would be a total of 5250 cases of typhoid fever over a 3-year period (row 3), and 2000 (row 6) of them (40%) could be avoided by charging the optimal prices. Because vaccinations are free for children, about 70% of them would be vaccinated, which avoids 1590 child cases, reduc-

[6] The negative binomial was used in cases where mean and variance were unequal. The two models are similar, and both employ the Poisson parameter λ.

[7] β is the percentage change (as a decimal) in the probability of buying a vaccination per unit change in price.

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Table 2
Model results.

		Basic Model	Equal Price Model	Free Vaccines
1	Optimal child price, pc^* (US$)	0.00	1.10	0.00
2	Optimal adult price, pa^* (US$)	2.30	1.10	0.00
3	Total cases without program	5250	5250	5250
4	Child cases without program	3150	3150	3150
5	Adult cases without program	2100	2100	2100
6	Total cases avoided	2000	1950	2250
7	Child cases avoided	1590	1420	1590
8	Adult cases avoided	410	530	660
9	Total persons vaccinated	420,000	440,000	540,000
10	Children vaccinated	220,000	190,000	220,000
11	Adults vaccinated	200,000	250,000	320,000
12	Net cost of program (US$)	0	0	582,000
13	Total project cost	520,000	540,000	640,000
14	Revenue from vaccinations (US$)	468,000	490,000	0
15	Income from COI avoided (US$)	52,000	50,000	58,000

ing from 3150 the number of cases without a program, as shown in rows 7 and 4. However, only about 410 of the 2100 adult cases (20%) are avoided (rows 8 and 5), which is due to the relatively low vaccine demand by adults (row 11). The vaccination program costs US$ 520,000 (row 13), US$ 52,000 of which (10%) would be covered by public treatment costs avoided (row 15) and 90% of which would be covered by vaccination sales. Every vaccinated adult would pay not only for her own vaccination but for a child as well. To avoid 2000 typhoid cases in the target population over a 3-year period, it would be necessary to vaccinate about 420,000 persons (row 9), which is about 200 vaccinations per case avoided.

How can it be 'optimal' to impose most of the financial burden on vaccinating adults who have only modest risk and many of whom are not inclined to be vaccinated even if vaccines are free? To address this question, we begin by considering the optimality conditions for the model in Section 3, which can be derived from Lagrangian analysis. The Lagrangian expression L is Eq. (7) less the Lagrangian multiplier (a new decision variable, π) multiplied by the difference between Eqs. (8) and (9), as shown in footnote 3. The optimality conditions for user fees are obtained by simultaneously solving the partial derivatives of L and setting them equal to zero. Let us denote $\partial L/\partial(pa)$ as L_a, $\partial L/\partial(pc)$ as L_c, and $\partial L/\partial\pi$ as L_π. Substituting Eqs. (11) and (12) into the Lagrangian expression for PC and PA respectively, solving $L_a = L_c = 0$, and setting the two resulting equations equal to each other yields the expression in Eq. (13) for optimal child and adult vaccination fees after substituting the revenue maximizing prices ($\hat{p}c$ and $\hat{p}a$) for $(-1/\beta c)$ and $(-1/\beta a)$, respectively

$$\frac{IC}{[pc - \hat{p}c - C]} = \frac{IA}{[pa - \hat{p}a - C]} \tag{13}$$

$L_\pi = 0$ yields Eq. (8) less Eq. (9) equal to zero. These two optimality conditions, Eq. (13) and Eq. (8) less Eq. (9) equal to zero, can be solved simultaneously for determining optimal user fees pa^* and pc^*. These equations contain all the parameters used to develop the model and thus they all affect optimal user fees. However, only a few of them appear in Eq. (13), which is a necessary condition but not sufficient for optimality.

The optimality condition in Eq. (13) indicates the relative magnitudes of optimal child and adult prices. It shows that it is optimal to make the adult and child vaccination fees equal only if the left hand side equals the right hand side. But the incidences for children (IC) and adults (IA) are different in the illustrative example, and the revenue maximizing prices are different for adults ($\hat{p}a$) and children ($\hat{p}c$). Thus the optimal vaccination fees for adults (pa^*) and children (pc^*) should be different.

Suppose we set the fee for vaccinating children in Eq. (13) to zero ($pc = 0$), which is the optimal result from solving the Basic Model,

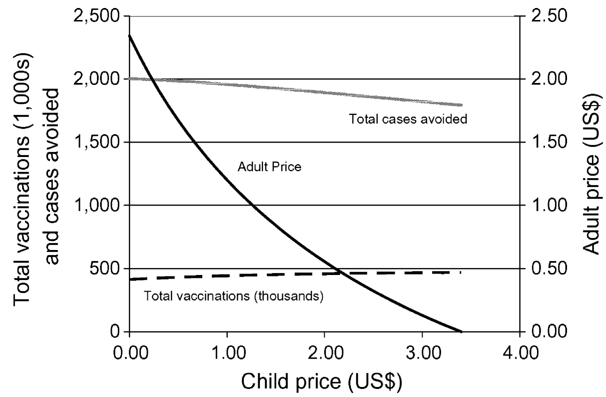

Fig. 2. Program outcomes for all revenue neutral price combinations.

and then solve the equation for the adult vaccination price (pa)

$$pa = (\hat{p}a + C) - (\hat{p}c + C) \cdot \left(\frac{IA}{IC}\right) \tag{14}$$

But the fee charged to adults must be greater than zero because if $pc = 0$, child vaccinations produce no revenue and the model requires financial self-sufficiency. Hence the right side of Eq. (14) must exceed zero, yielding

$$\frac{IC}{IA} > \left(\frac{\hat{p}c + C}{\hat{p}a + C}\right). \tag{15}$$

Eq. (15) is a necessary condition for providing free vaccinations for children. If this condition holds, the fee charged to children should be small or zero, and the burden of financing the vaccination program should largely fall upon the adults who are vaccinated. Conversely, if the inequality in Eq. (15) is reversed with the left side smaller than the right, then the price for adults should be less than that for children. Using the parameter values for the illustrative example ($\hat{p}a = 5$, $\hat{p}c = 10$, $C = 1$), the numerator of the term on the right side of Eq. (15) is 11 and the denominator is 6. Thus, the optimal price for children is less than that for adults if the ratio of child to adult typhoid incidence is greater than about 1.8; in our case, the ratio of child-to-adult incidence is 3.5. Given this high incidence ratio, the only way the child price would not be less than adult price is if the demand for vaccinating children were much more inelastic than for adults, i.e., if the number of children for whom their households were willing to buy vaccinations decreased very little as the price they were charged increased, which would happen if $\hat{p}c$ were greater than US$ 20.

Fig. 2 shows the adult and child price combinations that satisfy the revenue neutrality constraint of the Basic Model, e.g. (US$ 2.3 and 0), or (US$ 1.2 and 1.0), or (US$ 0.5 and 2.0). Note that the curve for "Total cases avoided" is maximized when child price is zero, and it decreases monotonically as child price increases. Conversely, "Total vaccinations" are minimized when child vaccinations are free, and they increase monotonically as child price increases. The first implication from Fig. 2 is that a non-optimal combination of child and adult prices has a relatively small effect on the number of cases avoided if the revenue neutrality constraint is satisfied, and the second is that had the objective been to maximize vaccination sales instead of cases avoided, the optimal price combination would have been strikingly different, with children paying a much higher price than adults.

5.2. A uniform pricing policy

High child incidence of typhoid relative to adults can make it optimal to charge adults more, even to provide free vaccines for children, which could pose difficulties for implementing a policy of

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differential prices. It may seem unfair to households without children to charge adults higher prices when the cost of vaccinating adults and children is the same. Moreover, the practical difficulties could be formidable when vaccines against other diseases are introduced into a community.

To address these concerns, the Basic Model was changed to require adults and children to pay the same price. The results are shown in the column of Table 2 labeled "Equal Price Model." Rows 1 and 2 show that the optimal price for children and adults is US$ 1.10, which is slightly more than the variable cost of a vaccination (C = 1.0). This departure from optimal differential pricing has only a small effect on the number of typhoid cases avoided: only 50 fewer out of 2000 (row 6). Reducing the adult price from US$ 2.30 and increasing the child price from zero would result (row 11) in 50,000 more adult vaccinations and 30,000 (row 10) fewer child vaccinations. Income from the cost of illness avoided (row 15) is only 4% less than the optimal result from the Basic Model, and the total program cost (row 13) is only US$ 20,000 (4%) more. Although US$ 468,000 in revenue from vaccination sales was needed for the optimal result in the Basic Model, the required revenue from sales with uniform pricing is only US$ 22,000 more (row 14). This is because more people are vaccinated and fewer cases are avoided, as shown in Fig. 2. Given that children do not pay for their vaccinations (their parents or adult caregivers do), this premium for charging equal instead of optimal prices is modest, and it may mitigate concerns about fairness in launching a vaccination program.

5.3. A policy of free vaccinations

Our third model addresses the possibility of supplying vaccines free of charge to both adults and children (see column labeled "Free Vaccines" in Table 2). Recall that the objective is to maximize the number of typhoid cases avoided, which is 2250 if vaccines were free (row 6). Compared to the optimal solution for the Basic Model, only 250 (10%) more cases would be avoided in 3 years by making vaccines free. However, row 9 shows that 540,000 persons would be vaccinated if vaccines were free, compared to 420,000 in the Basic Model, which means that 120,000 additional vaccinations would be needed to avoid the additional cases of typhoid, which is twice the average number of vaccinations per case avoided as in the Basic Model. The financial consequences of providing free vaccines are shown in rows 14 and 12. No revenue would be generated from sales, so the only receipts would be savings from cases avoided. Thus, in order to finance a free vaccination program, an external contribution of about US$ 580,000 would be required.

5.4. Sensitivity analysis

The wide variety of conditions in South and Southeast Asia and the inherent uncertainty in the parameter values even for a specific location cannot be adequately captured in the deterministic model. In this section, we conduct sensitivity analyses using Monte Carlo simulation (MCS), treating most of the model parameters as random variables. We consider three alternatives: (1) the Basic Model that treats adult and child prices as separate decision variables, (2) the Equal Price Model that constrains adult and child prices to be the same, and (3) the Free Vaccines Model that sets prices equal to zero.

The basic features of the deterministic case apply to the MCS without change, e.g. the child and adult populations, the absence of contributions from donors, the fraction of typhoid cases treated at public expense, and the fraction of public treatment costs avoided that offsets the vaccination campaign cost. Two parameters from the deterministic case are varied slightly for the MCS: the interest rate r and the fraction of the population θ that participates in the campaign. Ten additional parameters are varied based on values from the technical literature. For each of them, the probability

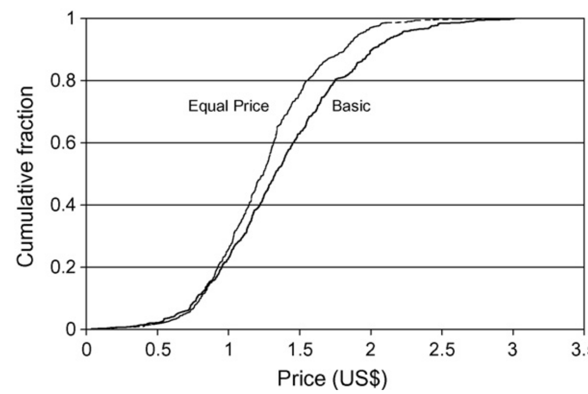

Fig. 3. Distributions of average optimal prices from Basic and Equal Price Models.

density function (pdf) is assumed to be triangular, with the lower and upper bounds and most-likely ("Best") values shown in Table 1, which also lists literature citations.

There are two different ways to make a MCS. The first would be to hold the child and adult prices at their optimal values from the deterministic models and then ask: if the state of nature deviates from the deterministic parameter values, how would outcomes of the vaccination campaign be affected? We use an alternative, second approach, which is to produce an optimal solution for each of the 500 MCS trials.

Typhoid incidence is almost always assumed to be higher in children than in adults, which was ensured in the MCS by using correlations that resulted in child incidence exceeding adult incidence for more than 99% of the trials. The ratio of child to adult typhoid incidence in the deterministic case was 3.5, and in the MCS it ranged from 1 to 20 with a median of 4. Correlations were also used for the parameters of the demand functions, α and β, to ensure that child coverage would exceed adult coverage for identical prices; the median ratio of α-values for children and adults in the MCS was about 1.5, and the median ratio of $\hat{p}$ values for children and adults was about 2.0, both of which closely match the ratios in the deterministic model. The same pdf for the public cost of treating typhoid cases was used for both adults and children, but allowance was made for different costs of treating adults and children in the same region because adults (or children) are sometimes treated as out-patients while the others are in-patients.

The MCS found that the adult price pa^* exceeded the child price pc^* in 86% of the trials. The probability that vaccinations should be free for children was 33%, and for adults it was only 1%. In about two-thirds of the trials, it was optimal to charge both adults and children, and when both are charged, the probability is 80% that the adult price will be higher. The cumulative distribution function (cdf) of optimal prices from the Equal Price Model (Fig. 3) is not much different than the one for average prices from the Basic Model, where average price is the sum of adult and child prices divided by 2. The probability is 70% that the average price will be between US$ 1 and 2 (Fig. 3).

The MCS showed why the optimal adult price from the Basic Model sometimes exceeds the child price and vice versa. When $((IC/IA) - (\hat{p}c/\hat{p}a))$ is positive $(pa^* - pc^*)$ is positive, and when $((IC/IA) - (\hat{p}c/\hat{p}a))$ is negative $(pa^* - pc^*)$ is negative. As $((IC/IA) - (\hat{p}c/\hat{p}a))$ approaches zero, the adult and child prices approach the same value. Thus IC, IA, $\hat{p}c$, and $\hat{p}a$ are the main determinants of whether optimal prices should be higher for adults or children.

Fig. 4 shows the cdf of cases avoided for the three models. The distributions are remarkably similar, with median values of about 2200, 2000, and 2600 for the Basic Model, the Equal Price Model, and the Free Vaccines Model, respectively. In 90% of the simulations, the difference in cases avoided between the Basic and Equal Price

Table 3
Cumulative distribution functions for Basic Model.

Cumulative % (a)	Vaccinations/case avoided (b)	Total cost US$/case avoided (c)	Total cost US$/vaccination (d)	COI savings/total cost (%) (e)	Net cost US$/vaccination (f)
5	90	123	0.97	4	0.68
10	102	134	1.07	5	0.79
15	109	146	1.12	6	0.85
20	116	161	1.17	7	0.92
25	123	173	1.21	8	0.98
30	130	184	1.25	9	1.03
35	138	198	1.30	10	1.08
40	145	209	1.35	12	1.14
45	153	219	1.40	13	1.18
50	163	232	1.44	14	1.23
55	172	250	1.49	15	1.27
60	186	260	1.54	17	1.31
65	198	281	1.59	18	1.35
70	211	306	1.63	20	1.42
75	225	327	1.70	21	1.49
80	237	366	1.76	25	1.55
85	268	432	1.89	28	1.65
90	310	522	2.02	31	1.82
95	410	669	2.13	37	1.93
100	791	1577	2.97	94	2.91

Models was less than 250. Although the differences from one model to another are small, the range of cases avoided for any single model is substantial, roughly an order of magnitude from 500 to 5000, which is mainly due to variation in child incidence.

The number of vaccinations required to avoid a single case of illness is shown in col. (b) of Table 3. All of the data are for the Basic Model, but results are about the same for the other two models across all columns. The median is about 160 vaccinations per case avoided. Col. (c) shows that the median cost per case avoided is about US$ 230.

Table 3 shows the distributions of three cost indicators in cols. (d)–(f). The median value of total cost per vaccination in col. (d) for the Basic Model is a little less than US$ 1.50. The probability is 85% that the cost per vaccination is between US$ 1.00 and 2.00. The results for the Equal Price Model are similar.

Col. (e) in Table 3 indicates the percentage of total cost that is covered by savings on the public cost of treating typhoid cases that have been avoided by the vaccination program. The median value indicates that COI savings cover only about 15% of total cost. The probability is 90% that COI savings cover less than 30% of the total cost of a program. Col. (f) indicates the net cost per vaccination, which is the difference between total cost and COI savings. The median net cost is about US$ 1.20 per vaccination, and the probability is 95% that it is in the range US$ 0.50–2.00.

Table 4 shows the effects of the parameters in col. (a) on the variance of selected outcomes for the three models. None (0%) of the variation in "Adult price" [col. (b)] is due to the fraction of adults or children θ that participate in the vaccination campaign nor to the efficacy of the vaccine. However, 38% of the variation is due to the variable cost of a vaccination. Four other parameters also have large effects on adult prices: child and adult incidence, and child and adult price coefficients in the demand functions. On the other hand, the public cost of treating illness, the intercepts of the demand functions, and the fixed costs of the program have little effect on adult prices.

Some parameters have only small effects on the program outcomes and decision variables shown in each column of Table 4, e.g., the interest rate, the efficacy of the vaccine, the fixed cost of the vaccination program, and the public costs of treating illness. Alternatively, some variables have large effects on some, but not all of the columns of Table 4. For example, the percentage of the population that participates in a vaccination campaign θ has no effect on outcomes for the Basic and Equal Price Models, but it has a large effect on the number of vaccinations if they are free.

The same five parameters that affect adult prices account for most of the variation in child prices, as shown in col. (c) of Table 4. The variable cost of a vaccination has the largest effect on variation in adult prices, but child incidence and the price coefficient in the adult demand function have the largest effects on child prices.

We conclude this section with a few observations. Col. (d) of Table 4 shows that child incidence has the greatest effect by far on the cases of illness avoided in all three models. The variable cost of a vaccination is also an important parameter. It accounts for 60% of the variation in total cost (col. e) for the Basic and Equal Price Models, 85% of the variation in the price that should be charged (col. g) for the Equal Price Model, and 87% of the total cost of a campaign if vaccinations are free (col. h).

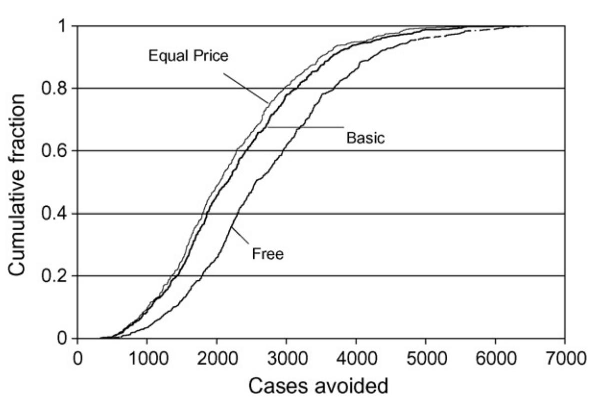

Fig. 4. Distributions of cases avoided from MCS simulations.

6. Discussion

The three pricing scenarios presented in this paper yield about the same maximum number of typhoid cases avoided from a vaccination campaign. For 90% of the MCS trials, the difference between the Basic and Equal Price Models is less than 250 cases. The Basic Model, which treats both adult and child prices as decision variables, shows in its deterministic application that adults should pay more than US$ 2.00 for vaccinations and that children should get them free. In the Equal Price Model, the optimal price for both children and adults is US$ 1.10, only slightly more than the variable cost of a vaccination, and in the Free Vaccine Model, the price is zero. Thus, variation in the best prices to charge users is wide, which

Table 4
Analysis of variance of results from Monte Carlo simulations.

(a)	Adult price (b)	Child price (c)	Cases avoided (d)	Total cost (e)	Total vaccines (f)	Price (g)	Total cost (h)	Total vaccines (j)
Basic Model[a]	Yes	Yes	Yes	Yes	Yes	No	No	No
Equal Price Model[a]	No	No	Yes	Yes	Yes	Yes	No	No
Free Vaccines Model[a]	No	No	Yes	No	No	No	Yes	Yes
Common parameters								
θ = fraction of child/adult pop participating	0%	0%	2%	3%	7%	0%	2%	23%
Eff = efficacy of vaccine	0%	0%	8%	0%	0%	0%	0%	0%
F = fixed cost of vaccination program	1%	4%	0%	5%	1%	6%	3%	0%
r = interest rate	0%	0%	0%	0%	0%	0%	0%	0%
C = variable cost of a vaccination	38%	12%	3%	60%	30%	85%	87%	0%
Child parameters								
IC = child incidence	12%	30%	73%	1%	2%	3%	0%	0%
αc = child demand intercept	0%	0%	7%	6%	13%	1%	3%	25%
βc = child price coefficient	14%	13%	0%	5%	9%	0%	0%	0%
COIc = public cost of treating a child	2%	1%	0%	1%	2%	4%	0%	0%
Adult parameters								
IA = adult incidence	17%	11%	4%	4%	6%	0%	0%	0%
αa = adult demand intercept	1%	0%	1%	9%	16%	0%	5%	52%
βa = adult price coefficient	15%	29%	2%	7%	14%	0%	0%	0%
COIa = public cost of treating an adult	0%	0%	0%	0%	0%	0%	0%	0%

[a] "Yes" and "No" indicate the models to which table values apply.

poses a problem for designers of vaccination campaigns. Moreover, in the stochastic application of the Basic Model, sometimes it is optimal to charge only children and not adults, but usually it is optimal to charge both. It is also usually best to charge adults more than children, but not always.

Examination of the optimality conditions reveals the underlying rationale for these results. Eq. (13) shows the relative magnitudes of the two prices, which depend on adult and child incidences, the adult and child demand functions, and the variable cost of a vaccination. However, the revenue neutrality constraint must also be considered in making final price selections, which means that all the parameters in the Basic Model have roles to play in optimal pricing. The conclusion for when both adult and child prices are treated as decision variables is that policy makers need accurate information that is not easy to obtain.

The Equal Price Model is at the opposite extreme. Since both adults and children are charged the same price, it is easy to show from the revenue neutrality constraint that the optimal price to charge the users should be equal to the average net cost of the vaccination campaign. From Table 2, total project cost in the optimal solution of the Equal Price Model is US$ 540,000, and the total number of vaccinations is 440,000, which results in average cost of US$ 1.20 per vaccination. However, the savings on the public cost of treating cases of illness is US$ 0.10 per vaccinated person, which when subtracted from the total cost per vaccination results in the optimal price of US$ 1.10. It follows that no optimization model is needed to determine optimal price when it is the same for adults and children; policy makers need accurate information on the vaccination demands of adults and children and on costs and incidences, but beyond that, simple calculations yield the optimal price to charge and indicators of program performance.

Given that both the Basic Model and the Equal Price Model produce very similar outcomes in terms of cases of illness avoided, setting equal prices is generally the preferred approach if users need to be charged. Not only is it easy to apply, but also the price is very robust, as shown by the MCS in which 85% of the variation in optimal price is due to one parameter, the variable cost of a vaccination.

The choice between charging prices and offering free vaccines is straightforward. For the illustrative deterministic case, charging equal prices would have net program cost of zero, and it would avoid nearly 2000 cases of illness over the 3-year period of vaccine effectiveness. Providing free vaccines, however, would have net program cost of nearly US$ 600,000 that would have to be covered by government or donors. It would avoid only 300 more cases (15%) than by charging the users. Moreover, the incremental cost of moving from a vaccination program with user fees to a program without user fees is US$ 100,000 and results in only 300 additional cases avoided. Thus, this paper reveals striking differences among the three different pricing strategies for vaccination campaigns, which can provide a sound basis for selection by policy makers.

Appendix A. Typhoid optimization model including herd protection

This appendix examines how the indirect protection of vaccination might affect the design of typhoid vaccination programs. Indirect vaccination effects are generally categorized as either herd *protection* or herd *immunity*. Herd immunity only results from vaccines that use live but pathogenically inactive bacteria or viruses. Vaccine recipients shed the live bacteria or viruses, which are then available to protect others. Herd protection indirectly reduces exposure to typhoid by reducing the number of persons that would contract and spread disease if they had not been vaccinated. Since the Vi vaccine does not incorporate live bacteria, there can be no herd immunity effect, but a herd protection effect is possible and perhaps even likely. We have no published empirical evidence to quantify a herd protection effect for the Vi vaccine. In this appendix we develop a simple herd protection model and apply assumed herd protection relationships to explore some of its implications.[8]

We begin by postulating a relationship between typhoid vaccination coverage rates and indirect protection effects. Because typhoid vaccines are less than 100% effective, both vaccinated and unvaccinated persons would benefit from herd protection. The introduction of a vaccination program decreases disease prevalence by preventing transmission of typhoid to a fraction of vaccinated individuals. The Vi vaccine has a 70% average efficacy rate for 3 years. As the vaccination coverage rate increases, the number of protected persons increases, which causes a reduction in the number of susceptible individuals in the community. As a result, the rate of infection decreases, disease prevalence declines, and expo-

[8] This section draws from ref. [32–35].

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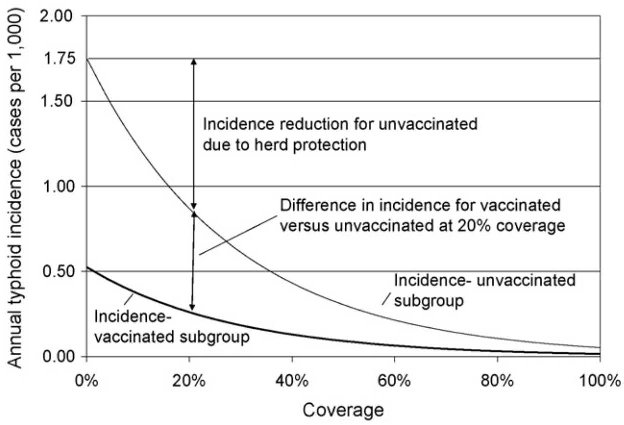

Fig. A.1. Vaccinated and unvaccinated incidences as a function of coverage.

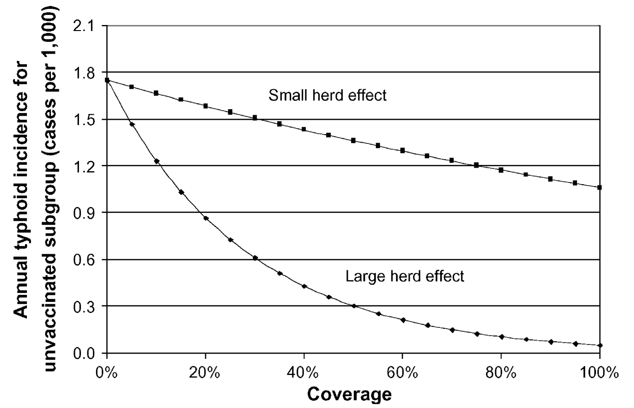

Fig. A.2. Large and small herd protection effects for unvaccinated persons as a function of coverage.

sure for susceptible individuals (both unvaccinated and vaccinated) is reduced.

A graph of an assumed herd protection relationship between vaccination coverage and disease incidence for vaccinated and unvaccinated subgroups is shown in Fig. A.1. We assume Fig. A.1 characterizes herd protection for the model presented in this appendix. Typhoid incidence before launching a vaccination program is 1.75 cases per year per 1000 persons,[9] which is the population-weighted average of adult and child incidence rates identified in Table 1. The direct protection of vaccination reduces incidence for vaccinated persons by 70% relative to unvaccinated persons at any coverage level. For example, suppose the coverage rate is 15% and one wants to know the effect of vaccinating one more person. At 15% coverage, let us assume that indirect protection effects have reduced incidence for unvaccinated persons from the baseline risk of 1.75 cases per 1000 to 1.0 case per thousand via a reduction in exposure. The risk for the marginal vaccinated person is 70% less, which thus reduces her risk from 1.0 to 0.3 case per 1000.[10]

In summary, incidences for the vaccinated and unvaccinated subgroups decrease monotonically with coverage due to herd protection. The change in incidence for unvaccinated persons results from reduced exposure while the change in incidence for vaccinated persons results from the combination of direct vaccine protection and reduced exposure.

Since empirical evidence for Vi-induced herd protection effects is lacking, this appendix assumes two different relationships, one in which the herd effect is "large" and the other in which it is "small." The purpose of the appendix is to compare the impact of both large and small herd effects on optimal pricing and other vaccination program outcomes with those in Section 5 where herd protection is ignored. Fig. A.2 shows the assumed graphs of large and small herd effects for unvaccinated persons in the illustrative example, using the child and adult populations and incidences from Table 1. For the large herd protection effect, unvaccinated incidence decreases rapidly as a function of coverage. At 20% coverage, the risk of infection (incidence) for unvaccinated persons decreases by about half relative to baseline incidence. At 90% coverage, the unvaccinated incidence is only about 5% of the baseline risk. In contrast, unvaccinated incidence decreases much less with the small herd protection effect; even at 90% coverage, the incidence for unvaccinated persons only declines by about 35% relative to the baseline incidence.

The number of cases avoided is the difference in the number of cases with and without the vaccination program. The number of cases without the vaccination program is the same as for the Basic Model in Section 3, which is shown in Eq. (A.1). The number of typhoid cases depends on the adult and child populations (*POPA* and *POPC*), baseline incidence rates for adults and children (IA^0 and IC^0), and the duration of vaccine protection (3 years).

$$\text{Typhoid cases without program} = 3 \cdot IA^0 \cdot POPA + 3 \cdot IC^0 \cdot POPC. \tag{A.1}$$

The incidence rates after launching the vaccination program are shown in equations (A.2) and (A.3) for unvaccinated adults (*IUA*) and children (*IUC*), respectively

$$IUC = IC^0 \cdot \exp\{\gamma C \cdot [\theta \cdot POPC \cdot PC(pc)] + \gamma A \cdot [\theta \cdot POPA \cdot PA(pa)]\} \tag{A.2}$$

$$IUA = IA^0 \cdot \exp\{\gamma C \cdot [\theta \cdot POPC \cdot PC(pc)] + \gamma A \cdot [\theta \cdot POPA \cdot PA(pa)]\}. \tag{A.3}$$

The terms in square brackets in equations (A.2) and (A.3) are the numbers of vaccinated children and adults, which include the decision variables *pa* and *pc* for pricing vaccinations; γC is a coefficient that represents the herd protection effect of child coverage on the incidences of both unvaccinated adults and children, and γA represents the herd effect of adult coverage on the incidences of both unvaccinated adults and children. Both coefficients are less than zero causing increases in coverage to reduce incidences. Large coefficients (i.e. more negative coefficients) indicate large herd protection effects. The exponential form, just one of many functional relationships that could be used, is shown in Figs. A.1 and A.2. The coefficient γC represents the magnitude of the herd protection effect per vaccinated child, and γA is the effect per vaccinated adult. Direct vaccine protection reduces incidence by 70% for vaccinated persons relative to the unvaccinated at any coverage rate. The incidences for vaccinated adults (*IVA*) and vaccinated children (*IVC*) are shown in Eqs. (A.4) and (A.5), respectively

$$IVC = (1 - EFF) \cdot IUC \tag{A.4}$$

$$IVA = (1 - EFF) \cdot IUA \tag{A.5}$$

The total number of typhoid cases after launching the vaccination program is the sum of the cases among vaccinated adults and

[9] Baseline incidence is the average of child and adult incidences weighted by their populations, viz. (0.7·1.0 + 0.3·3.5)/1.0 = 1.75 cases/year/1000 persons.

[10] A related article examines empirical herd protection for a cholera vaccination program. Unlike for typhoid, there is empirical evidence of herd protection via cholera vaccination. That article does not subdivide the population into adult and child subgroups [9].

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Table A.1
Comparison of optimal outcomes for programs with and without herd protection.

Scenario	Basic Model	1	2	3	4
	No herd protection	Large herd effect for adults and children	Small herd effect for adults and children	Large herd effect for children, small for adults	Large herd effect for adults, small for children
Optimal child price, US$	0	2.8	0.5	0	2.9
Child cases avoided	1600	2800	1800	2500	2500
Optimal adult price, US$	2.3	0	1.6	2.0	0
Adult cases avoided	410	1800	790	1400	1760
Total cases avoided	2000	4600	2600	3900	4200
Total vaccinations	410,000	480,000	430,000	430,000	480,000
Total program cost, US$	510,000	580,000	530,000	530,000	580,000
Total public COI savings, US$	50,000	120,000	70,000	100,000	110,000

children plus the cases among unvaccinated adults and children. The number of cases for each of these 4 categories is the product of the number of persons in the category and its incidence. For example, the annual number of cases of illness among vaccinated children is [No. vaccinated children] × [Incidence among vaccinated children]. The incidences for the 4 categories are in Eqs. (A.2)–(A.5), the numbers of vaccinated children and adults are $PC{\cdot}\theta{\cdot}POPC$ and $PA{\cdot}\theta{\cdot}POPA$, respectively, and the numbers of unvaccinated children and adults are $(1-PC{\cdot}\theta){\cdot}POPC$ and $(1-PA{\cdot}\theta){\cdot}POPA$, respectively. The expression for the total number of typhoid cases with the vaccination program that occur over the 3-year period of vaccine protection is shown in Eq. (A.6). The model assumes that potential vaccine purchasers are unaware of herd protection effects and do not consider how the vaccination program would reduce risk for unvaccinated persons or how their purchase decision impacts demand among neighbors. Thus, vaccine demand depends on the user fees assessed to adults and children just as in the Basic Model of Section 3. Similar to the Basic Model, vaccine demand is represented by the relationships PA for adults and PC for children which are each functions of their respective vaccination prices.

$$3 \cdot \{POPC \cdot \theta \cdot PC \cdot IVC + POPC \cdot (1-\theta \cdot PC) \cdot IUC + POPA \cdot \theta \cdot PA \cdot IVA + POPA \cdot (1-\theta \cdot PA) \cdot IUA\} \quad (A.6)$$

The total expected number of cases avoided by the vaccination program over the 3-year period of vaccine effectiveness is the difference between Eqs. (A.1) and (A.6), which is shown in Eq. (A.7). For ease of notation, let us call the term in braces ACA, the *Annual Cases Avoided*.

$$3 \cdot \{[IA^0 \cdot POPA + IC^0 \cdot POPC] - [POPC \cdot \theta \cdot PC \cdot IVC + POPC \cdot (1-\theta \cdot PC) \cdot IUC + POPA \cdot \theta \cdot PA \cdot IVA + POPA \cdot (1-\theta \cdot PA) \cdot IUA]\} = 3 \cdot \{ACA\} \quad (A.7)$$

The revenue neutrality constraint is similar to the Basic Model. Vaccine revenues are equal to the number of adult and child vaccines purchased multiplied by their respective prices

$$\theta \cdot POPA \cdot PA \cdot pa + \theta \cdot POPC \cdot PC \cdot pc. \quad (A.8)$$

In addition to revenue from sales, the income side of the ledger includes the present value savings over the 3-year period of vaccine effectiveness from reduced public costs of treating the cases of illness avoided by having the mass vaccination campaign. Similar to the Basic Model in Section 3, we use σ to indicate the fraction of illness cases that are treated at public expense and μ to indicate the fraction of public savings that accrues to the vaccination planning agency; $\sigma = 1$ if all cases of illness are treated at public expense, and $\mu = 1$ if all public savings accrue to the health ministry; σ and μ are assumed to be the same for children and adults as is COI, the public cost of treating a patient. The present worth factor $PWF = [1-(1+r)^{-3}]/r$ is identical to that in the Basic Model, where r is the annual interest rate. Extracting from Eq. (A.7) the expression for annual cases of illness avoided, ACA, we obtain the expression in Eq. (A.9) for the present value of savings on cases of illness avoided, which together with Eq. (A.8) represents total income from the vaccination campaign

$$\sigma \cdot \mu \cdot PWF \cdot COI \cdot \{ACA\} \quad (A.9)$$

The cost side of the ledger includes only vaccination costs, which are equal to the sum of fixed and variable costs as in the model of Section 3 and as shown in Eq. (A.10).

$$F + \theta \cdot POPC \cdot PC \cdot C + \theta \cdot POPA \cdot PA \cdot C \quad (A.10)$$

The policy question for this model that includes herd protection is identical to the one in Section 3 for the Basic Model: What are the optimal vaccination prices for adults and children (pa^* and pc^*) that maximize the cases of illness avoided in Eq. (A.7) subject to the requirement that vaccination program income (Eq. (A.8) plus Eq. (A.9)) exactly equals program cost (Eq. (A.10)). Methods of solution are identical to those described in Section 3. In principle, Lagrangian analysis can be used to develop the optimality conditions for this model, but there is no simple analytical solution, and thus we present some numerical results from solving the model using the same parameter values employed for solving the Basic Model reported in Table 1.

Equations (A.2) and (A.3) are the heart of the herd protection model of this appendix; they contain two parameters, γC and γA, that give rise to the following four different scenarios.

1. *Herd protection is large*. For this case, we let $\gamma A = \gamma C = 3.5 \times 10^{-6}$ to obtain the large percentage risk reduction shown in Fig. A.2.
2. *Herd protection is small*. For this case, we let $\gamma A = \gamma C = 5.0 \times 10^{-7}$ to obtain the small percentage risk reduction shown in Fig. A.2.
3. *Herd protection is large from vaccinating children, but small from vaccinating adults*. For this case, $\gamma C = 3.5 \times 10^{-6}$ and $\gamma A = 5.0 \times 10^{-7}$, which suggests that children are primarily responsible for spreading typhoid in the community.
4. *Herd protection is large from vaccinating adults, but small from vaccinating children*. For this case, $\gamma C = 5.0 \times 10^{-7}$ and $\gamma A = 3.5 \times 10^{-6}$, which suggests that adults are primarily responsible for spreading typhoid.

In Table A.1, we present the optimal prices and vaccination program outcomes for each of the four different scenarios along with the original solution to the Basic Model. Before examining the table in detail, we can make the following general observations:

- The range of optimal prices for the four herd scenarios is similar to the range for the Basic Model, from zero to about US$ 2.9. The existence of herd protection makes it optimal to vaccinate more people than if herd protection did not exist. Thus, optimal prices with herd are somewhat lower than prices without herd, and program cost is higher.

- The number of cases of illness avoided, however, is quite different between the two models. Obviously, herd protection results in fewer cases of illness (more cases avoided). Where the herd protection effect is large for at least one subgroup of the population (which is the solution for 3 of the 4 herd scenarios), the number of cases avoided is at least double that of the Basic Model. As expected, a small herd effect (scenario 2) has a small marginal payoff in terms of additional cases avoided above those due to the direct vaccination effect.
- With more cases avoided due to the herd effect, the public savings on treating illness is much larger than in the Basic Model. However, the results of simulations presented in Table A.1 assumed (i) all cases of illness are treated at public expense and (ii) all savings accrue to the ministry of health (MOH) to offset program cost. It is possible that the entire savings do not accrue to the MOH. If the accrual to MOH is partial or small, then vaccination programs with herd protection need to recover more costs from users than programs without herd protection.

With these general observations, we can now be more specific about the results in Table A.1. In 4 of the 5 scenarios reported in Table A.1, the optimal prices are for a "corner solution," i.e. either pc^* or pa^* is equal to zero. Fig. 2 shows all the adult and child price combinations that satisfy the revenue neutrality constraint for the Basic Model. In the absence of herd protection, the number of cases avoided is maximized by providing free vaccines to children. This strategy also minimizes the total number of vaccines delivered because adult demand is much more elastic than child demand. The number of vaccinations is maximized by providing free vaccines to adults. In general, it is expected that low incidence groups would have more elastic demand. Thus, the importance of the relative coverage-incidence relationships needs to be re-examined in light of herd protection effects, especially if herd effect are larger for one of the subgroups.

- If the herd protection effect is large and equivalent for adults and children (scenario 1), it is optimal to maximize the number of vaccinations. This can be accomplished by providing free vaccines for adults and charging households for vaccines for children. The number of vaccines provided to children would be less than the result for the Basic Model *without* herd protection, but this is more than offset by the increase in adult vaccination. Since herd protection impacts are large, maximizing vaccination coverage is more important than targeting vaccines for children with high incidence. Assuming that it is politically feasible to provide free vaccines for adults in scenario 1, about 88% of all typhoid cases would be avoided, which is much greater than the 38% reduction in cases for the Basic Model in Section 3. Because of the large increase in cases avoided, the public COI savings are significantly larger and thus reduce the total amount of user revenue required.
- In scenario 2, the herd protection effects are small, and the optimal prices, although not a corner solution, are similar to those for the Basic Model without herd protection. Because herd effects are small, it is less important to maximize total vaccination coverage (i.e. adult + children coverage). Instead, it is optimal to subsidize vaccination for the high incidence subgroup, children, who experience 3.5 times greater incidence than adults.
- In scenario 3, the herd protection effects are large for child vaccinations, but small for adult vaccinations. The implications are that children are primarily responsible for spreading disease, and that an increase in child coverage has a much larger herd protection effect relative to an increase in adult coverage. It is optimal to provide free vaccines for children. Despite the prioritization of vaccines for children, the program still reduces the number of adult cases by 67%, most via indirect protection.
- In Scenario 4, the herd protection effects are large for adults but small for children. Thus, an increase in adult coverage has a much greater herd protection effect than an increase in child coverage. It is optimal to provide free vaccinations for adults. Program outcomes are similar to those for scenario 1 in which the optimal adult price is also zero. The number of vaccines delivered is almost the same, but about 400 fewer cases (5%) are avoided due to the reduced herd protection effect for child vaccinations. The case for free adult vaccination is stronger than in Scenario 1 because adult vaccination has a much stronger impact on child incidence.

In summary, the optimal prices are influenced by both the magnitude of herd protection effects and the propensity for each subgroup to spread disease within the community. In the Basic Model, differences in demand elasticity, population size, and incidence between adults and children are the primary determinants of optimal prices. Given our best parameter estimates for the Basic Model, the greater child incidence is more important than the greater adult population and demand elasticity; thus, it is optimal to maximize the coverage rate for children by providing them with free vaccines. If children are primarily responsible for spreading typhoid throughout the community (γC is more negative than γA), it remains optimal to maximize their coverage rate by providing free vaccines. If herd protection effects are sufficiently large and the adult herd protection coefficient is the same or more negative than the child coefficient, it is optimal to maximize the total number of vaccinations by reducing adult price. Thus, maximization of vaccination sales can become more important than the difference in baseline adult and child incidence rates. The magnitude of herd protection effects greatly influences the total number of cases avoided and the value of public treatment cost savings.

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