Available online at www.sciencedirect.com

ScienceDirect

Procedia in Vaccinology 2 (2010) 140–146

Procedia in Vaccinology

www.elsevier.com/locate/ procedia

Ninth Global Vaccine Research Forum and Parallel Satellite Symposia,
Bamako, Mali, 6-9 December 2009

Incorporating Cholera Vaccine Herd Protection into Economic Cost-Benefit and Cost-Effectiveness Models

M. Jeuland[a,*], B. Maskery[b], J. Cook[c], C. Poulos[d], J. Clemens[b], D. Lauria[a], J. Stewart[a], M. Lucas[e], D. Whittington[a,f]

[a] *University of North Carolina at Chapel Hill, Chapel Hill, USA*
[b] *International Vaccine Institute, Seoul, Republic of Korea*
[c] *University of Washington, Seattle, USA*
[d] *Research Triangle Institute, Research Triangle Park, USA*
[e] *Ministry of Science and Technology, Maputo, Mozambique*
[f] *Manchester Business School, Manchester, United Kingdom.*

Abstract

Ignoring the indirect effects of vaccination has led to two types of inaccuracies in cholera vaccine policy analysis in endemic settings. First, when herd protection is ignored, the social benefits and cost-effectiveness of vaccination programs are underestimated, such that the programs are rarely considered to be a wise use of scarce public health resources. Once vaccine herd protection is included, use of the vaccine can satisfy both social welfare objectives and benchmark cost effectiveness criteria. Second, design recommendations to implement programs considered most attractive without accounting for the effect of herd protection may not allow the capture of the greatest social benefits. The analysis summarized in this paper demonstrates that it is possible to account for herd protection in both cost-effectiveness and cost-benefit calculations. In the former case, however, it does pose significant interpretation challenges. When herd protection is incorporated into a cost-effectiveness model, cost-effectiveness measures such as costs per DALY avoided become a function of vaccination coverage. When this is the case, there is no obvious decision objective in a cost-effectiveness analysis. Cost-benefit metrics, on the other hand, provide a clear economic argument for when to pursue vaccination efforts and how to design them. More sophisticated measurements of the economic benefits of vaccination should therefore become standard practice when evaluating the potential of vaccination programs.

Keywords: *Cost-benefit analysis; cost-effectiveness analysis; indirect effects; vaccine effectiveness; cholera, externalities*

---

* Corresponding author. *E-mail address: jeuland@email.unc.edu*

1877-282X © 2010 Published by Elsevier Ltd.
doi:10.1016/j.provac.2010.07.006

1. Introduction

Cholera is an infectious disease caused by exposure to the bacterium *Vibrio cholerae* O1 or O139, resulting in acute dehydration and sometimes death. In 2008 the World Health Organization (WHO) reported more than 190 000 cases worldwide and 5 143 deaths, although these estimates are widely regarded as low due to underreporting [1]. Severe cholera is treatable with intravenous rehydration therapy if the patient is diagnosed promptly and has access to basic health care facilities, but mortality risks in epidemic situations can reach 20 percent and higher [2]. Recent upward trends in WHO-reported cholera cases, the reemergence of cholera in parts of West Africa, and the continuing problem of endemic cholera in East Africa and several parts of Asia have prompted increasing concern over vulnerability to infection of poor populations living in unsanitary conditions.

Most public health experts believe that improved sanitation and hygiene is the best method for controlling cholera. However, such improvements have remained elusive in many locations, as evidenced by the persistence of cholera in many developing countries. Another approach is to combine prevention and preparedness activities. Surveys to determine the economic benefits have been shown to produce very plausible measures of the benefits of vaccination [10-13]. This strategy might involve more widespread use of new, safe, and more effective oral cholera vaccines (OCV), of which four have been licensed in some countries. One of these has been licensed in India following a trial in Kolkata and appears particularly promising because it is inexpensive, relatively easy to administer and can be taken out of cold storage for some time during vaccination campaigns, facilitating delivery [3]. Furthermore, there is evidence that cholera vaccination can result in significant herd protection: diminished risk of infection among non-vaccinees and enhanced protection of vaccinees [4, 5]. In 2009, the WHO began recommending vaccination of children in places where incidence exceeds 1 in a thousand (6), and also stated that “the role of OCVs needs to be further assessed in view of their introduction into areas where they can make a difference” [1].

Arguments over the merit of such programs have typically focused on their low cost-effectiveness. The Disease Control Priorities (DCP) Project ranked cholera immunization for infants with WC/rBS (Dukoral) vaccine, which costs about $6-8 per dose, among the least cost-effective interventions targeting diarrheal disease, with cost effectiveness ratios of US$1 402 to US$8 357 per DALY (disability-adjusted life year) averted [7]. Murray et al. [8] found that vaccination was less cost effective (about $3 000/DALY averted) than several other control strategies, including cholera disease treatment ($10-160/DALY averted) and certain types of water and sanitation improvements ($430/DALY averted). However, recent analyses for the new, low-cost vaccine (which only costs about $1 per dose), show that cost-effectiveness can be much higher, especially when herd protection effects are included [9].

Herd protection however raises new difficulties for policy-makers who would base cholera vaccination program design on cost-effectiveness outcomes. In the presence of herd effects, measures such as average costs per DALY avoided become a function of vaccination coverage, such that there is no obvious decision objective in a cost-effectiveness analysis. For example, choosing a coverage level that minimizes the costs per DALY avoided could result in a very low coverage level; expanding coverage might still save DALYs at low cost. Maximizing the number of DALYs avoided may result in very high marginal costs per DALY avoided if herd protection can reduce disease burden significantly at lower coverage rates.

Cost-benefit metrics, on the other hand, provide a clear economic argument for when to pursue vaccination efforts and how to design them. These measures require careful nonmarket valuation studies of the demand for vaccines within a target population, which can be difficult because the vaccines are not usually available in private markets. Such studies are nonetheless possible and of vaccination should therefore become part of the standard toolkit for evaluating the potential of vaccination programs.

This paper summarizes the cost-effectiveness (Section 2) and cost-benefit models (Section 3) for vaccination programs, and discusses how herd protection can be included in each of them. These sections also briefly review the results obtained from using such models to evaluate potential cholera vaccination programs in Beira, Mozambique, where the disease is endemic. Section 4 concludes.

2. Model of vaccine cost-effectiveness including herd protection

Cost-effectiveness studies of vaccine programs typically report outcomes in terms of metrics such as the cost per case avoided or, in order to more fully account for the morbidity and mortality burden caused by the disease being targeted, the cost per DALY avoided [9, 14]. A crucial parameter in this calculation is the effectiveness of the vaccine over time Eff_t:

$$\frac{Total\ Cost}{DALYs\ avoided} = \frac{\sum_i N_i \cdot Cov_i \cdot c - COI^{pub,avoided}}{\sum_{t=1}^{Dur} \sum_i \left(YLL\ avoided_{i,t} + YLD\ avoided_{i,t}\right)/(1+d)^{t-1}} =$$

$$\frac{\sum_i N_i \cdot Cov_i \cdot c - COI^{pub,avoided}}{\sum_{t=1}^{Dur} \sum_i \mathrm{Eff}_t \cdot Cov_i \cdot N_i \cdot I_i \cdot [CFR_i \cdot (1 - e^{-0.03 \cdot LE_i})/d + (1 - CFR_i) \cdot (l \cdot w^{DALY})]/(1+d)^{t-1}}, \qquad (1)$$

where $YLD\ avoided_{i,t}$ and $YLL\ avoided_{i,t}$ are the years of life in disability avoided and the years of life lost avoided in age group i and year t due to vaccination. Eff_t is the effectiveness of the vaccine in year t, Cov_i is the percentage of age group i that is vaccinated in the program, LE_i, CFR_i, I_i and N_i are the life expectancy, case fatality rate, cholera incidence and number of people in age group i, l is the average duration of the disease, Dur is the vaccine duration, w^{DALY} is the DALY weight ascribed to cholera, and d is the discount rate. The parameter c is the cost of the vaccine per fully-immunized person, and $COI^{pub,\ avoided}$ is the public cost of illness avoided, which is equal to:

$$COI^{pub,avoided} = \sum_{t=1}^{Dur} \sum_i Eff_t \cdot Cov_i \cdot N_i \cdot I_i \cdot COI_i^{pub}/(1+d)^{t-1}, \qquad (2)$$

where COI_i^{pub} is the public cost of illness per case of cholera in age group i.

If vaccination provides indirect protection to non-vaccinated members of the population, or provides additional protection to the vaccinated, equation 1 will underestimate the true cost-effectiveness [9]. In the presence of herd protection by vaccination the disease burden reduction will increase, which affects the $COI^{pub,\ avoided}$ and Eff_t terms in equation 1. Equations 1 and 2 must be modified to account for the fact that overall vaccine effectiveness is a function of the coverage in the N age groups in the population, or:

$$Eff_t = Eff(N_1, \ldots N_N; Cov_1, \ldots, Cov_N), \qquad (3)$$

It is certainly possible to use the correct measure of overall effectiveness from equation 3 rather than the one from equation 1. All that is needed is to carry out vaccine effectiveness studies capable of discerning the extent and nature of the herd effects from vaccinating different age groups, of which there are an increasing number [4, 15]. Then, overall effectiveness can be expressed as a function of coverage levels in those different age groups. Unfortunately, there is a larger problem with basing decisions on cost-effectiveness in this case: the cost per DALY avoided becomes a function of the level of vaccine coverage in the target population. This result is also obtained if there are economies or diseconomies of scale in a vaccination program, i.e. if the cost of vaccination is also a function of coverage, which seems plausible. On the one hand, choosing a coverage level that minimizes the cost per DALY avoided could result in a very low coverage level; expanding coverage might still save DALYs at very little cost [16]. On the other, simply maximizing the number of DALYs avoided will result in very high marginal costs per DALY avoided.

Results from calculations for cholera programs in Beira demonstrate that when we account for cholera herd protection, larger programs tend to have higher cost per DALY avoided than smaller programs (Table 1, data from ref [9]). For example, going from Program Option 1 targeting only school children, to Option 2 for all children, raises the cost per DALY avoided from \$128 to \$139. Further adding adults in a community-based program yields a cost per DALY avoided of \$331. Results in other sites have shown similar trends [9]. This is because the marginal increases in vaccine effectiveness are decreasing with program size, and because incidence is lower in adults. Still, it is difficult to determine which level of cost-effectiveness is too high or too low.

3. Cost-benefit model of vaccination including herd protection

In contrast to cost-effectiveness analysis, cost-benefit analysis offers a simple framework for choosing the level of vaccination coverage (via selection of the vaccine price *p*) that is most beneficial to society [17]. In this case, when there is no herd protection, a social planner's objective is to maximize the net benefits of vaccination, where:

$$Net\ benefits = \sum_i (N_i^v \cdot WTP_i^v(p) + COI^{pub,avoided} - N_i \cdot Cov_i \cdot c), \qquad (4)$$

where WTP_i^v is the average willingness-to-pay (total benefits) for a vaccinated individual in age group i for vaccines purchased at price p. WTP_i^v is increasing in p, because higher vaccine prices result in exclusion of individuals with willingness to pay less than the price that is charged. Individuals do not take account of the public cost of illness savings $COI^{pub,\ avoided}$ when choosing whether or not to obtain vaccines, so this must be added to the overall benefits of the program. The costs of vaccination are then debited from these two types of benefits to obtain the overall benefits of a program.

When the vaccine provides significant herd protection, the planner's objective must be modified to account for the benefits to unvaccinated persons.

$$Net\ benefits = \sum_i (N_i^v \cdot WTP_i^v(p, Eff^v) + N_i^u \cdot WTP_i^u(p, Eff^u) + COI^{pub,avoided} - N_i \cdot Cov_i \cdot c) \qquad (5)$$

where WTP_i^u is the average willingness-to-pay (total benefits) for a unvaccinated individual in age group i for vaccines purchased at price p. WTP_i^v and WTP_i^u are each now a function of effectiveness Eff^v and Eff^u, which are themselves dependent on coverage levels. Like WTP_i^v, WTP_i^u is increasing in p because the marginal individual excluded by increasing price p has higher demand for vaccines than the rest of the unvaccinated pool of individuals. Because $WTP_i^v > WTP_i^u$ at all prices, though, the average private benefit (net of payments for vaccines) may be increasing or decreasing in p, depending on 1) the number of individuals who switch from the purchasing to non-purchasing group, and 2) the extent of herd protection to the unvaccinated. $COI^{pub,\ avoided}$ now includes public cost-of-illness savings to both the vaccinated and unvaccinated.

One common objection to use of cost-benefit analysis for evaluation of vaccination programs is that the demand for vaccines – the terms WTP_i^v and WTP_i^u in equation 4 – are typically not known, because vaccines are not traded in markets. There are, however, a growing number of demand studies for cholera vaccines in developing countries, which have yielded plausible estimates of willingness-to-pay. These studies use both stated and revealed preference methodologies commonly used in the field of environmental economics [10-13]. The information from such studies has been used to conduct cost-benefit analysis of cholera vaccination programs in Beira, Mozambique and Kolkata, India [16, 17]. As with the cost-effectiveness results, these studies show that the net benefits of vaccination programs in Beira increase dramatically when herd protection is included in the calculations (**Table 1**, data from ref [16]).

Table 1. Outcomes of cost-effectiveness and cost-benefit analyses for cholera vaccination programs without user fees, in Beira, Mozambique (Results from (9) and (16)).

Outcomes	Not including herd protection	Including herd protection
Option 1: School-based program targeting school children (5-14 yrs)		
Number of vaccinations	65,900	65,900
Overall coverage (%)	12	12
Cases avoided over 3 yrs	323	2,615
Net public cost per DALY averted ($)	1,748	128
Net benefits of program (thousands of US$)	-16	454
Option 2: School-based program targeting all 1-14 yrs		
Number of vaccinations	89,300	89,300
Overall coverage (%)	16	16
Cases avoided over 3 yrs	672	3,393
Net public cost per DALY averted ($)	1,081	139
Net benefits of program (thousands of US$)	22	489
Option 3: Community-based program (all persons 1 yr and older)		
Number of vaccinations	257,600	257,600
Overall coverage (%)	47	47
Cases avoided over 3 yrs	1,772	5,692
Net public cost per DALY averted ($)	1,353	331
Net benefits of program (thousands of US$)	-101	-28
“Very cost effective” threshold (per capita GDP)	$382	$382
“Cost effective” threshold (3 x per capita GDP)	$1,146	$1,146

Note: Costs per fully-vaccinated individual (2 doses) were assumed to be the same for community and school-based programs.

The calculations also demonstrate some of the problems with cost-effectiveness metrics. First, programs that appear “very cost effective” may in fact be expensive from a social perspective, for example Option 3, which has a cost-effectiveness ratio of $331/DALY averted (less than the $382 threshold for “very cost effective” programs) but results in negative net benefits. Second, programs which appear less cost-effective may in fact deliver higher net benefits (comparing Options 1 and 2, for example). In that case, expansion of the program to include all children results in higher cost per DALY averted ($139 versus $128), but that expansion is still worthwhile from a social perspective, since it provides an additional net benefit of about $35 000.

4. Conclusions

This paper presented basic models for conducting cost-benefit and cost-effectiveness analyses that include herd protection. Such models have been applied in previously published research to analyze cholera vaccination program options in Beira, Mozambique, using site-specific data on disease incidence, willingness-to-pay for vaccines, and cost-of-illness [9, 16]. Here we compared the cost-effectiveness and cost-benefit outcomes obtained in those papers, for programs in Beira without user fees. The results showed that ignoring herd protection effects leads to major underestimates of both the net benefits and cost-effectiveness of cholera vaccination. Thus, at some point in the process of testing the field effectiveness of vaccines, studies should also be carried out that would allow detection of herd effects if they exist.

While it is possible to include herd protection in cost-effectiveness models, doing so raises significant interpretation challenges. When herd protection is incorporated into a cost-effectiveness model, cost-effectiveness measures such as costs per DALY avoided become a function of vaccination coverage, and that there is no straightforward way to determine how many people should be targeted. Plus, the same result follows if vaccination program costs are subject to economies or diseconomies of scale, which is likely to occur in most real world programs, depending on the characteristics of the sites and the preferences of individuals with regards to acquiring vaccines.

Cost-benefit metrics, on the other hand, provide a clear economic argument for when it is socially-beneficial to pursue vaccination efforts, and how these can be designed to maximize net benefits. While this paper only presented results for programs without user fees, cost-benefit analysis can also be used to compare the outcomes of programs that charge different prices to vaccines [16]. Cost-benefit calculations do however require information that is not always collected in field research on the potential of vaccination programs, most notably on the demand (or willingness-to-pay) for vaccines. Even in Beira, where such information was obtained, there are questions about how much willingness-to-pay varies as a function of vaccine effectiveness, which is important to assess when conducting thorough cost-benefit analysis in the presence of herd effects [16]. More sophisticated measurements of the economic benefits of vaccination should therefore become standard practice when evaluating the potential of vaccination programs.

5. Acknowledgements

This work was supported by the Diseases of the Most Impoverished (DOMI) program, administered by the International Vaccine Institute (IVI) with support from the Bill and Melinda Gates Foundation. The DOMI program works to accelerate the development and introduction of new-generation vaccines against cholera, typhoid fever, and shigellosis. The results of the program support public decision making regarding immunization programs for cholera and typhoid fever.

Many individuals contributed to the research efforts in Beira and to the development of the policy models described here. Associated with data collection efforts in Mozambique were local counterparts Francisco Songane, Alberto Baptista, Fauzia Ismael, Avertino Barreto, Juvenaldo Amos, and Arminda Macuamule; members of the Médecins Sans Frontières and World Health Organization teams Philippe Cavailler, Valerie Perroud, Margaret McChesney, Sonia Ampuero, Philippe Guérin, Dominique Legros, Thomas Nierle, Claude Mahoudeau, Bruno Lab, Pierre Kahozi-Sangwa, and Claire-Lise Chaignat; and IVI team members Jacqueline Deen, Lorenz von Seidlein, Xuan-Yi Wang, Mahesh Puri, Mohammed Ali, and Andrew Nyamete. Finally, thanks are also due to those attending the 3rd Vaccine Global Congress in Bamako, who provided helpful comments on this work.

REFERENCES

1. **WHO**. Cholera, 2008. Weekly Epidemiological Record 2009;84(31):309-324.
2. **Naidoo A. and Patric K.** Cholera: a continuous epidemic in Africa. J R Soc Promo Health 2002;122(2):89.
3. **Sur D.; Lopez A. L.; Kanungo S.; Paisley A.; Manna B.; Ali M. et al.** Efficacy and safety of a modifi ed killed-whole-cell oral cholera vaccine in India: an interim analysis of a cluster-randomised, double-blind, placebo-controlled trial. Lancet 2009;374:1694-702.
4. **Ali M.; Emch M.; von Seidlein L.; Yunus M.; Sack D. A.; Rao M. et al.** Herd immunity conferred by killed oral cholera vaccines in Bangladesh: a reanalysis. Lancet 2005 Jul 2;366(9479):44-49.
5. **Longini I. M.; Nizam A.; Ali M.; Yunus M.; Shenvi N. and Clemens J. D.** Controlling Endemic Cholera with Oral Vaccines. PLOS Med 2007 November 2007;4(11):1776-83.
6. **WHO**. Meeting of the Strategic Advisory Group of Experts on immunization, October 2009 – conclusions and recommendations. Weekly Epidemiological Record 2009;84(50):517-532.
7. **Jamison D.; Breman J.; Measham A.; Alleyne G.; Claeson M.; Evans D. et al.** Disease Control Priorities in Developing Countries. 2 ed. New York, NY: Oxford University Press, 2006.
8. **Murray J.; McFarland D. A. and Waldman R. J.** Cost-effectiveness of oral cholera vaccine in a stable refugee population at risk for epidemic cholera and in a population with endemic cholera. Bull World Health Organ 1998;76(4):343-352.
9. **Jeuland M.; Cook J.; Poulos C.; Clemens J.; Whittington D. and DOMI Cholera Economics Study Group**. Cost-Effectiveness of New-Generation Oral Cholera Vaccines: A Multisite Analysis. Value Health 2009;12(6):899-908.
10. **Jeuland M.; Lucas M.; Clemens J. and Whittington D.** Estimating the private benefits of vaccination against cholera in Beira, Mozambique: A travel cost approach. J Dev Econ 2010;91:310–322.
11. **Lucas M.; Jeuland M.; Deen J.; Lazaro N.; MacMahon M.; Nyamete A. et al.** Private Demand for Cholera Vaccines in Beira, Mozambique. Vaccine 2006 2007;25(14):2599-2609.
12. **Whittington D.; Sur D.; Cook J.; Chatterjee S.; Maskery B.; Lahiri M. et al.** Rethinking cholera and typhoid vaccination policies for the poor: Private demand in Kolkata, India. World Dev 2009;37(2):399-409.
13. **Cook J.; Whittington D.; Canh D. G.; Johnson F. R. and Nyamete A.** Reliability of stated preferences for cholera and typhoid vaccines with time to think in Hue, Vietnam. Econ Inq 2007 2006;45(1):100-114.

14. **Cook J.; Jeuland M.; Whittington D.; Poulos C.; Clemens J.; Sur D. et al.** The cost-effectiveness of typhoid Vi vaccination programs: Calculations for four urban sites in four Asian countries. Vaccine 2008;26(50):6305-6316.
15. **Ali M.; Emch M.; Yunus M.; Sack D.; L.Lopez A.; Holmgren J. et al.** Vaccine Herd Protection of Bangladeshi Infants and Young Children against Cholera: Implications for Vaccine Deployment and Person-to-Person Transmission. International Vaccine Institute. Seoul, Korea, 2008.
16. **Jeuland M.; Lucas M.; Clemens J. and Whittington D.** A Cost–Benefit Analysis of Cholera Vaccination Programs in Beira, Mozambique. World Bank Econ Rev 2009;23(2):235-267.
17. **Cook J.; Jeuland M.; Maskery B.; Lauria D.; Sur D.; Clemens J. et al.** Using Private Demand Studies to Calculate Socially Optimal Vaccine Subsidies in Developing Countries. J Policy Anal Manag 2009;28(1):6–28.