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Implications and measurement of herd protection (indirect effects) for enteric vaccine development

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ABSTRACT

Diarrhea remains one of the top five causes of disease and death among young children in developing nations. Fortunately, scientists are making progress developing vaccines against enterotoxigenic *E. coli* (ETEC) and *Shigella*, two of the leading diarrhea pathogens. As vaccine developers start to consider field efficacy trials of these vaccines, they should be aware of the importance of evaluating not only vaccine direct effects on the immunized, but also the herd effects that vaccination can afford to the unimmunized in a community. In a workshop held at the conference titled "Vaccines against Shigella and ETEC (VASE)", we described to participants what herd effects are and we presented on methods used in cholera and rotavirus studies that could be useful for future ETEC and *Shigella* vaccine trials conducted in low and middle-income nations. We also presented evidence on the effects of vaccine herd effects for estimates of vaccine cost-effectiveness.

1. Introduction

Scientists are developing vaccines against ETEC and *Shigella*, which are key diarrheal enteropathogens [1,2]. As vaccine developers advance to field efficacy trials of these vaccines, they should consider study designs that provide the broadest understanding of the protection afforded by their vaccine. As vaccination with ETEC and *Shigella* vaccines should reduce the intensity of direct and/or indirect person-to-person transmission (i.e., fecal-oral) of these pathogens within a community, to have the broadest understanding of vaccine protection, the trial design for an ETEC or *Shigella* vaccine should provide evidence of vaccine effects afforded to the immunized and to the unimmunized as well. This workshop addressed study design for measuring herd effects, experience with measuring herd effects in cholera and rotavirus vaccine studies, and evidence of vaccine herd effects on vaccine cost-effectiveness.

Dr. Wierzba, Senior Scientist, Enteric Vaccines Initiative, PATH opened the workshop by defining herd effects. Herd effects occur when a high proportion of community residents become immune to a pathogen through vaccination thereby decreasing the opportunity for that pathogen to widely circulate and infect the unimmunized. The vaccine therefore affords protection to the immunized and unimmunized as well. He then introduced the topics and speakers as below. Speakers were chosen because of their practical experience in designing and conducting studies of herd effects in trials, observational, and economic studies.

2. Measuring herd effects in clinical studies: a GIS approach

Dr. Mohammad Ali, Senior Scientist, Global Disease Epidemiology and Control, Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA, has published widely on measuring indirect effects. He is also the developer of the GIS approach to vaccine evaluations. His talk was titled "Measuring Herd Effects in Clinical Studies: GIS Approach."

Dr. Ali noted that herd effects are a reduction of infection or disease in the unimmunized segment as a result of immunizing a proportion of the population. Herd effects are demonstrated by the protective impact of a vaccine in a population that exceeds the impact expected on the basis of known protective efficacy of the vaccine and level of vaccine coverage [3]. There are four measures of vaccine protective effectiveness [4]. Direct protection is protection of vaccinated individuals from vaccine-induced immunity. Indirect protection is protection of non-vaccinated individuals living in a vaccinated community. Total protection combines the direct and indirect effects on individual receiving the vaccine. Finally, overall protection is the weighted average of indirect protection of non-vaccinated individuals and total protection of

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vaccinated individuals. Dr. Ali has, as noted, used Geographic Information System (GIS), which is a method designed to work with spatially related data. It describes data as to their position with respect to a known coordinate, their attributes (e.g., demographics and epidemiology data), and spatial interrelations.

Dr. Ali first explored the herd effects in an individually randomized trial exploring the efficacy of an oral whole-cell cholera vaccine. The trial was conducted in 1985 in Matlab, Bangladesh and included children 2–15 years old and women older than 15 years old [5]. Approximately 50,000 residents received vaccine and 25,000 received placebo. Vaccine efficacy was 58% at one year against cholera. GIS data showing the location of each home and vaccine coverage around the home was calculated [6]. In evaluating the herd protection using the GIS approach, the hypothesis is if there is herd protection, then there should be an inverse relationship between risk of cholera in non-vaccinees as well as in vaccinees and the level of vaccine coverage. In the study, the results of the analysis showed a statistically significant, inverse relationship between vaccine coverage and incidence of cholera among both non-vaccinees and vaccinees suggesting indirect effects of the vaccine. These relationships persisted even after controlling for confounding variables such as age and distance to treatment center.

A cluster randomized trial was also explored for assessing herd protection using the GIS approach. Cluster randomized trials assume that the disease transmission occurs within cluster with little transmission from outside clusters and limited migration of individuals between clusters. The study of vaccine efficacy of an oral cholera vaccine was conducted in Kolkata City, India [7]. The population under study was ~100,000, and clusters (n = 3933) were residential housing units. The analysis after controlling for the design effect and confounders demonstrated statistically significant total protection (66%) and overall protection (49%), but no indirect effects (0%). Using the GIS approach that explored vaccine coverage of 250 m around each household, a statistically significant inverse relationship was observed between vaccine coverage (0–34%) and risk of cholera (5.54–1.93 case/1000 population). The absence of indirect protection in the cluster randomized design was potentially due to the definition of the cluster whereby minimal transmission across the clusters was not ensured. The GIS approach, in this case, could overcome the distortions introduced by intercluster transmission of cholera by considering vaccine coverage in a relatively wide radius around each individual.

Herd effects can be measured in observational studies. A study of oral cholera vaccine during an outbreak was conducted in Zanzibar [8]. The outbreak occurred in early 2009 and continued through mid 2010. Using the GIS approach, spatial patterns of cholera vaccine coverage were calculated and the incidence of cholera by the level of vaccine coverage around each individual was calculated. A statistically significant inverse relationship was detected by level of vaccine coverage (0–100%) and cholera incidence (2.93–0.73 cases/1000 persons) among unvaccinated individuals.

Case-control design can also be used to assess herd effects [9]. In this design, the vaccine coverage is calculated around each case and control. Indirect, total, overall and enhanced protection can be assessed by evaluating odds of having the case living in a low coverage area versus living in high coverage area. The method was applied using the data from an efficacy trial in Kolkata City, India, described earlier. The results yielded significant indirect protection (PE = 76%, 95% CI: 47–89%) and total protection (PE = 75%, 95% CI: 43–89%). A marginally significant overall protection was observed (PE: 44%, 95% CI: −7% to 70%, p = .08). However, no enhanced protection was observed in the case-control design.

Finally, in Dr. Ali's continued development of methodologies for studying indirect effects, he presented "The fried egg design" in a cluster randomized trial. In this design the interventions are carried out in the entire clusters, but the evaluation samples are taken only form the central area (innermost) of the cluster (i.e., the yolk) in order for controlling contamination from transmission due to contact between clusters.

The speaker noted concern about design costs. The individual randomized trials and observational studies are thought to be of lower cost, while the cluster randomized and fried-egg design are the costliest.

3. Herd effects of rotavirus vaccine in low-income countries

The next workshop speaker was Dr. Aisleen Bennett, MBBS, PhD, Specialty Registrar in Pediatric Infectious Diseases, Great Ormond Street Hospital, London, UK & Institute of Infection & Global Health, University of Liverpool, Liverpool UK. Dr. Bennett spoke on herd effects of rotavirus vaccine in low-income countries. Prior to the widespread introduction of rotavirus vaccine rotavirus was the commonest cause of severe diarrhoeal disease in children under 5 years of age worldwide, responsible for over a third of diarrhoeal deaths and 5% of all deaths in this age group. Rotavirus vaccine trials have shown that efficacy is inversely correlated with under-5 mortality such that protection is lowest in countries with highest child mortality. In the context of low vaccine effectiveness and high disease burden, vaccine herd effects may have an important role in to play in improving vaccine impact and vaccine cost effectiveness. The speaker noted that there is consistent evidence of herd effects from high-income countries but the presence of herd effects is less clear in some middle-income countries (e.g., Ghana and South Africa) and lower income countries. Still, there was some evidence of herd effects recently reported from Rwanda, a low-income country in sub-Saharan Africa.

In Malawi, a low-income country in Southern Africa, prelicensure clinical trial vaccine efficacy for the monovalent rotavirus vaccine was reported as 49.4% [10]. Rotavirus vaccine was introduced into the Malawi national schedule in 2012, and post implementation studies have since been conducted to assess real-world vaccine effectiveness, and the impact of vaccine on rotavirus epidemiology, including evaluating for evidence of rotavirus vaccine herd effects. When the prevalence of rotavirus cases in the unimmunized was evaluated some evidence of reduction in rotavirus episodes in unvaccinated infants <12 months olds was identified, but not in children 12–59 months of age [11]. In hospitalized infants with rotavirus disease the observed effect of the vaccine was 9% greater than expected according to vaccine coverage and efficacy estimates, with the observed additional effect being attributed to herd effects (10). Due to ongoing high vaccine uptake, it is increasingly challenging to evaluate rotavirus vaccine herd effects using standard epidemiological techniques. Mathematical models fit to 12 years of Malawi data are therefore being used in ongoing work to evaluate for evidence of herd effects.

Dr. Bennett concluded that there was some evidence of herd effects in infants and following routine rotavirus vaccine introduction in Malawi, but ongoing evaluations of herd effects using conventional epidemiological techniques will be challenging in view of on-going high vaccine coverage. Post implementation evaluations of rotavirus vaccine herd effects in low-income countries are challenging. Going forward consideration should be given to evaluation of vaccine herd effects in low-income countries as part of prelicensure studies.

4. Impact of herd protection on cost-effectiveness of enteric and other vaccines

Ann Levin, MPH, PhD, Health Economist, Levin & Morgan, LLC, Bethesda, Maryland. USA spoke on herd protection and its impact on cost-effectiveness of enteric vaccines. An ACER is the average

cost-effectiveness ratio of the cost to benefit of intervention without reference to a comparator. An ICER is incremental cost associated with one additional unit of the measure of effect. If herd effects increase vaccine effectiveness, then there is an increase in an ACER or ICER. If herd effects have no impact or reduce vaccine effectiveness, then there is no change or there is a decrease in ACER and in ICER.

Two models can be employed to explore herd effects. The static model assumes constant rates of infection and only accounts for direct vaccine effects. Dynamic models consider direct and herd effects of vaccination by modeling mixing patterns between vaccinated and unvaccinated individuals. Dynamic models often result in more favorable ICERs. For example, a 20% increase in impact for herd effects was suggested for Haemophilus influenza Type B (Hib) vaccination in India [12] and 5% to 35% for pertussis vaccination in the United States [13]. Rotavirus has also shown herd effects including 15% increase in protection [14] and 45% reduction in unvaccinated individuals at 80% coverage [15].

Some studies have explored the impact of herd effects on cost-effectiveness. A study of rotavirus vaccination in England and Wales found the vaccine not to be cost-effective with using a static model, but cost effective when using a dynamic model. In that study, cost per QALY (Quality-adjusted Life Year) averted ranged from US$27,000 with herd effects to US$35,000 given a cost of $60 per vaccination and assuming immunity begins to decline as soon as the vaccine is given (i.e., immediate waning). Due to herd effects, the threshold price of cost-effectiveness was reduced by 4–13% [15]. A study of GAVI-eligible countries assumed unvaccinated children would have half the protection as rotavirus vaccinated children times the proportion of children vaccinated [14]. In this model, the cost-effectiveness ratio was $50 with herd effects and $63 without herd effects in the WHO region of the Americas. This is a 25% increase in cost-effectiveness due to herd effects.

Using data from four countries (i.e., Bangladesh, India, Indonesia, and Mozambique), the cost-effectiveness of an oral cholera vaccine with and without herd effects was measured [16]. Herd protection ranged from 0% to 33% assuming vaccine effectiveness of 60% in the first two years and 50% in the third year after introduction. The cost per DALY (Disability-adjusted Life Year) averted was one-third with herd effects compared to cost per DALY without herd effects. In Bangladesh, the cost effectiveness was US $1886 and US$497 without and with herd effects, respectively.

Researchers conducted a cost-effectiveness analysis of an oral cholera vaccine administered to high risk groups in Dhaka, Bangladesh [17,18]. The cost of a campaign in residents aged one years and above using single dose vials was $15.3 million, treatment savings was $1.5 million for a net cost of $12.7 million. The cost-effectiveness was improved when herd effects were considered.

In conclusion, Dr. Levin found that when herd effects are positive and included in a model, cost-effectiveness can increase by 20–50%. Thus, it is important to present cost-effectiveness models with herd effects to not underestimate vaccine benefits. However, it should be noted that incremental cost effectiveness ratios may be less favorable when herd effects induce a shift upward in age of first infection (e.g., increased rubella infections in first trimester of pregnancy) or lead to serotype replacement as with pneumococcal vaccines [19].

5. Final thoughts and discussion

While post-licensure studies have been employed to explore indirect effects, it was generally agreed that pre-licensure field efficacy trials rather than post-licensure observational studies are the best approach to measuring indirect effects. The absence of knowledge on the protection afforded by vaccine indirect effects is inappropriate. Cluster-randomized trials offer a trial design to measure indirect effects as well as total and overall protection, but can be costly. The use of GIS methods presented here can also be employed, and are less expensive relative to cluster-randomized trials. As presented during the workshop, when indirect effects are present, the cost-effectiveness of vaccines is increased, that is, it improves ICERs and ACERs and make vaccines more attractive to donors and policy makers.

Declaration of interests

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Bourgeois AL, Wierzba TF, Walker RI. Status of vaccine research and development for enterotoxigenic Escherichia coli. Vaccine 2016;34:2880–6.
[2] Mani S, Wierzba T, Walker RI. Status of vaccine research and development for Shigella. Vaccine 2016;34:2887–94.
[3] Clemens J. Evaluation of vaccines against enteric infections: a clinical and public health research agenda for developing countries. Philos Trans R Soc Lond B Biol Sci 2011;366:2799–805.
[4] Halloran ME, Longini IM, Struchiener CJ. Design and analysis of vaccine studies. New York, NY: Springer; 2010.
[5] Clemens JD, Stanton B, Stoll B, Shahid NS, Banu H, Chowdhury AK. Breast feeding as a determinant of severity in shigellosis. Evidence for protection throughout the first three years of life in Bangladeshi children. Am J Epidemiol 1986;123:710–20.
[6] Ali M, Emch M, von Seidlein L, Yunus M, Sack DA, Rao M, et al. Herd immunity conferred by killed oral cholera vaccines in Bangladesh: a reanalysis. Lancet 2005;366:44–9.
[7] Ali M, Sur D, You YA, Kanungo S, Sah B, Manna B, et al. Herd protection by a bivalent killed whole-cell oral cholera vaccine in the slums of Kolkata, India. Clin Infect Dis 2013;56:1123–31.
[8] Khatib AM, Ali M, von Seidlein L, Kim DR, Hashim R, Reyburn R, et al. Effectiveness of an oral cholera vaccine in Zanzibar: findings from a mass vaccination campaign and observational cohort study. Lancet Infect Dis 2012;12:837–44.
[9] Ali M, Nelson AR, Lopez AL, Sack DA. Updated global burden of cholera in endemic countries. PLoS Negl Trop Dis 2015;9:e0003832.
[10] Madhi SA, Cunliffe NA, Steele D, Witte D, Kirsten M, Louw C, et al. Effect of human rotavirus vaccine on severe diarrhea in African infants. N Engl J Med 2010;362:289–98.
[11] Bennett A, Pollock L, Jere KC, Pitzer VE, Parashar U, Tate JE, et al. Direct and possible indirect effects of vaccination on rotavirus hospitalisations among children in Malawi four years after programmatic introduction. Vaccine 2018;36:7142–8.
[12] Clark AD, Griffiths UK, Abbas SS, Rao KD, Privor-Dumm L, Hajjeh R, et al. Impact and cost-effectiveness of Haemophilus influenzae type b conjugate vaccination in India. J Pediatr 2013;163:S60–72.
[13] Caro JJ, Getsios D, El-Hadi W, Payne K, O'Brien JA. Pertussis immunization of adolescents in the United States: an economic evaluation. Pediatr Infect Dis J 2005;24:S75–82.
[14] Atherly DE, Lewis KD, Tate J, Parashar UD, Rheingans RD. Projected health and economic impact of rotavirus vaccination in GAVI-eligible countries: 2011–2030. Vaccine 2012;30(Suppl 1):A7–A14.
[15] Atkins KE, Shim E, Carroll S, Quilici S, Galvani AP. The cost-effectiveness of pentavalent rotavirus vaccination in England and Wales. Vaccine 2012;30:6766–76.
[16] Jeuland M, Cook J, Poulos C, Clemens J, Whittington D, Group DCES. Cost-effectiveness of new-generation oral cholera vaccines: a multisite analysis. Value Health 2009;12:899–908.
[17] Khan AI, Khan IA, Siddique SA, Rahman A, Islam MT, Bhuiya MAI, et al. Feasibility, coverage and cost of oral cholera vaccination conducted by icddr, b using the existing national immunization service delivery mechanism in rural setting Keraniganj. Bangladesh: Hum Vaccin Immunother; 2018.
[18] Khan AI, Levin A, Chao DL, DeRoeck D, Dimitrov DT, Khan JAM, et al. The impact and cost-effectiveness of controlling cholera through the use of oral cholera vaccines in urban Bangladesh: a disease modeling and economic analysis. PLoS Negl Trop Dis 2018;12:e0006652.
[19] Nymark LS, Sharma T, Miller A, Enemark U, Griffiths UK. Inclusion of the value of herd immunity in economic evaluations of vaccines. A systematic review of methods used. Vaccine 2017;35:6828–41.