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Review

Evaluation of vaccines against enteric infections: a clinical and public health research agenda for developing countries

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Enteric infections are a major cause of morbidity and mortality in developing countries. To date, vaccines have played a limited role in public health efforts to control enteric infections. Licensed vaccines exist for cholera and typhoid, but these vaccines are used primarily for travellers; and there are two internationally licensed vaccines for rotavirus, but they are mainly used in affluent countries. The reasons that enteric vaccines are little used in developing countries are multiple, and certainly include financial and political constraints. Also important is the need for more cogent evidence on the performance of enteric vaccines in developing country populations. A partial inventory of research questions would include: (i) does the vaccine perform well in the most relevant settings? (ii) does the vaccine perform well in all epidemiologically relevant age groups? (iii) is there adequate evidence of vaccine safety once the vaccines have been deployed in developing countries? (iv) how effective is the vaccine when given in conjunction with non-vaccine cointerventions? (v) what is the level of vaccine protection against all relevant outcomes? and (vi) what is the expected population level of vaccine protection, including both direct and herd vaccine protective effects? Provision of evidence addressing these questions will help expand the use of enteric vaccines in developing countries.

Keywords: enteric infections; diarrhoea; vaccines; vaccine evaluation; global health

1. INTRODUCTION

Diarrhoeal and other enteric infections are leading causes of death in developing countries. Despite advances in the clinical care of patients with enteric infections, many challenges remain, particularly in disease prevention. Major improvements in water and food quality and sanitation will be the ultimate solutions to reducing the incidence of these infections, but improvements of the scale required to accomplish a major degree of disease prevention remains a distant goal for most developing countries.

Vaccination against enteric infections presents a near-term approach, and great advances in the development of enteric vaccines have been made for several important infectious causes of enteric disease morbidity and mortality, including cholera, enterotoxigenic *Escherichia coli* (ETEC), rotavirus, *Shigella* and typhoid (table 1) [1].

Licensed, new-generation vaccines are now available for cholera, rotavirus and typhoid fever. For cholera, licensed vaccines include a live oral vaccine, CVD 103-HgR (Orochol) and two killed oral vaccines, recombinant cholera toxin B subunit-killed whole cell vaccine (rBS-WC, licensed as Dukoral) and two killed whole cell-only vaccines (licensed as Shanchol in India and as mORC-Vax in Vietnam, respectively) [2–4].

Licensed rotavirus vaccines include a human monovalent vaccine (licensed as Rotarix) and a pentavalent human–bovine reassortant vaccine (licensed as Rotateq) [5,6]. Finally, for typhoid fever, licensed vaccines include Ty21a, a live oral vaccine (licensed as Vivotef) and parenteral Vi polysaccharide vaccine, licensed by many manufacturers under several different product names [7,8].

Despite the availability of multiple licensed products and a robust vaccine pipeline, vaccines against enteric infections are currently used primarily for residents of affluent countries, either as travellers' vaccines, in the case of cholera and typhoid vaccines, or as vaccines for infants, in the case of rotavirus vaccine. The reasons that licensed enteric vaccines are little used for the control of disease for populations in developing countries, who account for a major burden of morbidity and mortality from these diseases, are multiple, and certainly include financial and political constraints. Less emphasized are the gaps in evaluations of these vaccines in developing countries, which have created policy uncertainties about the implementation of the vaccines in public health programmes for the poor in these settings. In this paper, I review several types of question that will need to be addressed in future studies to provide this needed evidence.

2. PERFORMANCE IN THE MOST RELEVANT SETTINGS

It is well-documented that live oral vaccines may fail to confer high-level protection for populations living in

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Table 1. Modern vaccines and vaccine candidates against enteric infections of major public health importance in developing countries (adapted from [1]).

	killed, oral whole cell-based	live, oral genetically attenuated	live, oral vectored	live, oral reassortant	transcutaneous toxin	oral transgenic plant-derived subunit	parental conjugate	parenteral subunit (other)	nasal proteosome	naked DNA	VLP[b]
rotavirus		X[a]		X[a]						X	X
cholera	X[a]	X[a]	X				X			X	
ETEC	X	X	X		X	X					
Shigella	X	X	X				X	X	X		
typhoid		X[a]					X	X[a]			

[a]Includes licensed vaccines.
[b]Virus-like particle.

impoverished settings in developing countries [9]. This problem applies to oral polio vaccine, and has posed a significant challenge for the current global effort to eradicate polio. It is equally problematic for other live oral vaccines. The two currently licensed live oral rotavirus vaccines were originally licensed on the basis of trials done in children who were living in more affluent settings. In order to make a policy recommendation on the use of these vaccines for the world's poorest children, the Global Alliance on Vaccination and Immunization commissioned trials of the vaccines in poor, developing countries in Asia and sub-Saharan Africa. These trials found the expected gradient of protection. For example, for the human–bovine pentavalent vaccine, Rotateq, trials in the US, Finland and Latin America found levels of protection against clinically severe disease of 94–100%, whereas protection in Africa (Ghana, Kenya and Mali) and Asia (Bangladesh and Vietnam) ranged from 39 to 48 per cent (table 2) [10].

As another example, the live oral cholera vaccine CVD 103-HgR provided robust protection to North American adult volunteers challenged with cholera experimentally, but failed to protect when tested in a poor urban setting Indonesia [11,12]. These experiences underscore the need to evaluate enteric vaccines in the most impoverished populations who experience the highest burdens of enteric diseases.

It is also important to consider the epidemiological setting for vaccine application. For example, cholera is known to occur in a stable, predictable endemic form, as well as in unpredictable epidemics. To date, evaluations of the protection by oral cholera vaccines have been undertaken in endemic settings, as it is in these settings that the incidence of cholera can be predicted. Yet many of the world's cholera crises, such as the one currently occurring in Haiti, have been epidemics, and controversy surrounds whether the use of cholera vaccines in such settings would be helpful [13]. There is a clear need for evaluations of oral cholera vaccines during cholera epidemics.

Randomized trials such as these can provide crucial information on vaccine performance in developing country settings, but randomized trials may not be a feasible, affordable or ethical approach to addressing the diversity of questions about vaccine performance in the geographical and epidemiological settings in which the vaccines will be deployed. Observational studies of already deployed enteric vaccines will be critical to evaluate their practical impact, which may be lesser or greater than predicted on the basis of conventional randomized trials [14]. Such studies will depend on development of high-quality surveillance for enteric diseases in these settings.

3. PERFORMANCE IN THE MOST RELEVANT AGE GROUPS

The age groups for which an enteric vaccine is licensed must match the epidemiology of the targeted disease in developing countries. The two modern licensed vaccines for typhoid fever—Ty21a, which is indicated only for persons more than 6 years of age, and Vi polysaccharide, which is indicated only for persons more than 2 years of age—are suitable for use in travellers,

Table 2. Results of randomized, placebo-controlled trials of oral pentavalent human-bovine (WC3) reassortant rotavirus vaccine in middle-upper versus lower income countries (adapted from [10]).

location	age of vaccinees	no. doses	titre (pfu)[a]	follow-up	PE[b] (95% CI)* (%)	severity classification
mid-upper						
US	2–6 months	3	10^7	1 year	100 (44,100)	Clark $\geq$17
US, Finland	2–6 months	3	10^7	2 years	98 (88,100)	Vesikari $\geq$11
US, Finland, Latin America	2–8 months	3	$10^{7.3}$	1 year	94 (91,97)	hospitalization ED visits
lower						
Ghana, Kenya, Mali	4–21weeks	3	2×10^7	2 years	39 (19,55)	Vesikari $\geq$11
Bangladesh, Vietnam	4–26 weeks	3	2×10^7	2 years	48 (22,66)	Vesikari $\geq$11

*$p < 0.001$for interaction of PE between middle-upper versus lower income countries.
[a]Plaque-forming units.
[b]Protective efficacy.

Table 3. Annual incidence (per 1000) of blood culture-confirmed typhoid fever in five Asian sites (adapted from [15]).

age group	Karachi, Pakistan ($n = 41\,845$)	Kolkata, India ($n = 56\,946$)	N. Jakarta, Indonesia ($n = 160\,261$)	Hue, Vietnam ($n = 84\,455$)	Hechi, China ($n = 97\,928$)
0–1 years	n.a.[a]	0.9	0	n.a.	n.a.
2–4 years	5.7	3.4	1.5	n.a.	n.a.
5–15 years	4.1	4.9	1.8	0.2	0.3
16– years	n.a.	1.2	0.5	0.1	0.1

[a]n.a.: surveillance not conducted for this age group.

and also for school-based immunization programmes. However, an appreciable fraction of the burden of typhoid fever occurs in children under 5 years of age, especially in settings in which the burden of disease is very high, such as urban areas of South Asia. This is well illustrated by population-based studies of the incidence of typhoid fever, conducted in five Asian countries by the Diseases of the Most Impoverished (DOMI) Programme (table 3) [15]. In order to address this burden in a programmatically feasible fashion in developing country settings, it is necessary that a typhoid vaccine be appropriate for use in the routine schedule of immunizations for infants. Fortunately, great progress is being made in the development of a Vi-protein typhoid conjugate and improved genetically attenuated, live oral vaccines, which have the potential for being deployed in routine immunization programmes for infants [16–18]. Studies are urgently needed to define the safety and protection of Vi conjugate vaccines when given in the infant schedule of immunization in developing countries.

4. ADEQUATE EVIDENCE OF VACCINE SAFETY

Vaccines are the most cost-effective preventive tools in public health, with a remarkable record of safety and disease prevention. Nevertheless, in recent years, public health programmes have been besieged by a profusion of alleged associations between vaccines and severe side-effects, such as autism, inflammatory bowel disease and sudden infant death syndrome. In most instances, properly controlled studies have disproved the relationships. But certain vaccines have been associated with severe side-effects, as illustrated by the rare, but serious side-effect of intestinal intussusception due to the orally administered, rhesus-reassortant rotavirus vaccine, which resulted in the withdrawal of this vaccine from the US market by the manufacturer [19].

Crucial to the ability of public health vaccination programmes, including those in developing countries, to retain the confidence of the public are systems for evaluating alleged associations about vaccine safety in a rapid and credible fashion. In many industrialized countries, dynamic, large-linked databases, which link vaccine histories to medical outcomes in well-defined populations, have provided the basis for such evaluations. Unfortunately, in developing countries, surveillance for vaccine adverse events is weak, and population-based databases for evaluation of alleged vaccine side-effects are virtually non-existent. Prototype databases have been shown to be feasible in selected developing country settings [20]. Development of institutionalized, large databases in selected developing countries constitutes a major priority and will be needed to help ensure the sustainability of efforts to introduce new-generation enteric and other vaccines into developing countries.

Another aspect of enteric vaccine safety that has received relatively scant attention is the safety of vaccines in HIV-infected individuals. A recent case report has raised concern about the safety of live pentavalent human–bovine reassortant rotavirus vaccine in severely

Table 4. Adverse events after ingestion of CVD 103-HgR live oral cholera vaccine or placebo (adapted from [22]).

		no. of cases with symptoms after administration					
		during first 4 days of follow-up			during entire 12 days of follow-up		
HIV status	treatment	diarrhoea	fever	emesis	diarrhoea	fever	emesis
seronegative	vaccine	1/31 (3)	4/37 (11)	0/38 (0)	1/27 (4)	5/34 (15)	1/34 (3)
	placebo	1/31 (3)	3/37 (8)	0/38 (0)	2/27 (7)	6/34 (18)	1/34 (3)
seropositive	vaccine	2/30 (7)	4/37 (11)	0/27 (0)	2/27 (7)	6/36 (17)	1/34 (3)
	placebo	1/30 (3)	6/37 (16)	1/27 (3)	1/27 (4)	6/36 (17)	1/34 (3)

immunocompromised infants [21]. It is rarely feasible in developing countries to test individuals for HIV infection before administering a vaccine, and, as outlined above, systems for post-marketing surveillance for safety in developing countries are limited. It is therefore important that special studies of the safety of vaccines be undertaken in HIV-infected persons prior to their introduction into public health programmes in developing countries. While this has been done in small studies for certain cholera (table 4) and rotavirus vaccines, more attention to this issue and larger studies are warranted [22,23].

5. VACCINE EFFECTIVENESS WHEN GIVEN IN CONJUNCTION WITH 'COINTERVENTIONS'

Traditionally, the public health community has viewed the implementation of enteric vaccines in isolation from, or even in competition with, other interventions to control enteric infections. This has been especially evident for cholera, for which vaccines have often been seen as deterrents to disease control through improved water quality and sanitation, as well as provision of appropriate rehydration treatment. This tendency to view interventions in 'silos' is unfortunate, because there may be important complementarities between vaccination and non-vaccination interventions against enteric infections.

Co-administration of micronutrients may enhance the efficacy of enteric vaccines. A study in Bangladesh, for example, provided suggestive evidence that concomitant zinc supplementation enhances serum vibriocidal antibody responses to oral rBS-WC cholera vaccine in children [24]. The possibility of enhancement of immune responses to enteric vaccines by micronutrients requires further evaluation.

There are reasons to think that interventions to improve drinking water quality may act in a complementary fashion with the use of new-generation oral cholera vaccines to prevent cholera. An example of one such intervention is the use of sari cloth to filter drinking water in homes. In rural Bangladesh, one study found that household use of sari-filtration was associated with approximately 50 per cent reduction of the risk of cholera [25]. Such an intervention presumably prevents cholera by reducing the inoculum of ingested cholera vibrios, including reduction of the probability of disease even when cholera vibrios are ingested. Oral cholera vaccines prevent cholera by reducing the probability of disease at any ingested inoculum. It can, therefore, be predicted that the two interventions, which work by separate mechanisms, should yield a much lower incidence of cholera than either intervention implemented alone. The prediction that combined water-sanitation and oral cholera vaccine interventions may yield enhanced levels of disease prevention is now being tested in a cluster-randomized field trial in urban Bangladesh. More studies of this sort are needed for new-generation enteric vaccines.

Finally, as pointed out elsewhere, the contention that interventions to improve care for cholera and to provide oral cholera vaccines are competitive with one another is a false dichotomy [26]. Provision of proper rehydration has revolutionized the care of cholera and reduced case-fatality to negligible levels. However, the impact of rehydration therapy at the population level will always depend on access to suitable care, which is difficult to ensure for the most difficult to reach populations, i.e. populations that are often at high risk in cholera-endemic countries. Provision of oral cholera vaccines to these marginalized populations is highly feasible, especially since trained medical personnel are not required to administer these vaccines. This complementarity needs to be evaluated in future research.

6. VACCINE PROTECTION AGAINST ALL RELEVANT OUTCOMES

It is important that future studies of enteric vaccines evaluate vaccine protection against the most relevant outcomes. For pathogens that are phenotypically heterogeneous, it is important that studies are done to demonstrate that vaccines protect against all epidemiologically prevalent phenotypes. The DOMI Programme conducted population-based, surveillance for treated episodes of shigellosis among *ca* 500 000 persons of all ages among all persons residing in field sites in Bangladesh, China, Pakistan, Indonesia and Vietnam. In each site, *Shigella flexneri* was the predominant aetiological species, but the phenotypic diversity of *S. flexneri* serotypes was great: a vaccine would have to protect against nine different serotypes and subserotypes to protect against 90 per cent or more of cases in each of the five sites [27]. A shigellosis vaccine that protects in all geographical areas will have to be highly multivalent, or will have to protect against shigellosis in a species- and serotype-independent fashion, using a common protein or other approach. Whatever the construct, it will be important to evaluate future *Shigella* vaccines against all epidemiologically prevalent phenotypes.

Table 5. Protection against death among three-dose recipients of killed oral cholera vaccines or placebo in a field trial in Bangladesh (adapted from [29]).

age at dosing	deaths (protective efficacy, 95% CI) among recipients of B subunit-killed whole cell vaccine	deaths (protective efficacy, 95% CI) among recipients of killed whole cell vaccine	deaths among recipients of placebo
2–15 years (males and females)	42 (−9%, −71 to 28%)	38 (3%, −49 to 39%)	39
>15 years (females only)	42 (45%, 20–62%)	50 (33%, 5–53%)	76
total	84 (26%, 3–46%)	88 (23%, −1 to 42%)	115

Increasingly, policymakers are focusing on disability-adjusted life years prevented as a metric for comparing the predicted impact of different public health interventions for developing countries. Conventional studies of enteric vaccines have focused only on the ability of the vaccines to prevent infection or disease *per se*. Relatively few studies have addressed the ability of enteric vaccines to reduce the burden of enteric disease disability and mortality. A large body of evidence documents that much of the disability caused by diarrhoeal infections of children in developing countries results from the nutritional and neurobehavioural sequelae of these infections [28]. Unless future evaluations of enteric vaccines in developing countries evaluate the ability of these vaccines to improve these outcomes, an important dimension of their public health impact will be missed.

Few clinical trials of enteric vaccines have evaluated their impact on mortality. Measuring mortality is challenging in vaccine studies done before licensure, as pre-licensure trials are typically conducted in populations well-served by medical treatment. In practice, the greatest impact on mortality of these vaccines will be seen in medically underserved populations. Still, it may be possible to gain some insight into the mortality-preventing potential of these vaccines in pre-licensure trials, as was illustrated by a phase III trial of oral BS-WC and WC only cholera vaccines in rural Bangladesh, in which a pronounced decline in mortality was seen in vaccinated adult women, whose access to care for cholera may have been limited by cultural constraints (table 5) [29]. Post-licensure documentation of the impact of enteric vaccines on mortality is also vital for vaccines that have been licensed and introduced into public health practice, as recently illustrated by a pronounced impact on diarrhoeal deaths among children 23 months of age or younger in Mexico following the introduction of routine immunization against rotavirus with a human monovalent rotavirus vaccine [30]. It is important that future studies of enteric vaccines, both pre- and post-licensure, are designed to assess vaccine impact on mortality.

7. POPULATION-LEVEL VACCINE PROTECTION

Conventional clinical evaluations of enteric vaccines in developing countries have focused only on the assessment of direct protection of vaccinated individuals [14,31]. While valuable, such evaluations are restricted in that they ignore a major potential benefit of these vaccines: the ability to confer herd immunity either by reducing the transmission of the pathogen in the targeted population or, for excreted live vaccines, by immunizing non-vaccinees through exposure to the vaccine organism excreted by vaccinees. Vaccine herd protective effects are demonstrated when the protective impact of a vaccine in a population exceeds that expected on the basis of the proportion of population that is vaccinated and the individual level protective efficacy of the vaccine [32]. Importantly, vaccine herd protective effects can result in protection of persons who do not receive vaccine, as well as enhanced protection of vaccinees. These extended protective effects of vaccines in populations can dramatically improve the benefits of vaccination at the population level, as well as the cost-effectiveness of vaccination. The measurement of vaccine herd protection may, therefore, yield crucial pieces of evidence in policy deliberations about the introduction of new vaccines into developing countries, where resources for new interventions are limited.

Traditionally, vaccine herd effects have been assessed after licensure for vaccines that have already been introduced into practice. Such evaluations are needed and valuable, but reliance on such evaluations for policy on vaccine introduction creates a 'catch-22' situation for vaccines that have not yet been introduced. Recent methodological developments have created approaches for evaluating vaccine herd effects before licensure with use of either individually randomized or cluster-randomized trials [33].

In the case of killed oral cholera vaccines, a re-analysis of an individually randomized efficacy trial in Bangladesh, using an innovative geographical information systems approach, found that these vaccines conferred substantial herd protection (table 6) [34]. These important data were then used to calibrate a dynamic transmission model of cholera in rural Bangladesh, which predicts that the incidence of endemic cholera could be nearly extinguished with these vaccines, at a population coverage level of only 60 per cent [35]. In addition, these analyses were used in cost-effectiveness analyses of killed oral cholera vaccines, which found the vaccines to be very cost-effective in several settings if vaccine herd effects are taken into account [36]. In aggregate, these analyses of the projected population impact of using killed oral cholera vaccines provided crucial evidence for a recent strengthened World Health Organization recommendation on the use of these vaccines for the control of endemic and epidemic cholera [37]. Analysis of vaccine herd effects before introduction into public health programmes with use of either cluster-randomized or individually randomized trials constitutes an important

Table 6. Cholera risk by the level of cholera vaccine coverage of the neighbourhood, in an individually randomized field trial in Bangladesh (adapted from [34]).

level of vaccine coverage (%)	target population		vaccinated group			placebo group		
	n	%	*n*	cases	risk per 1000 persons*	*n*	cases	risk per 1000 persons**
<28	24 954	20.6	5627	15	2.66	2852	20	7.01
28–35	25 059	20.7	8883	22	2.47	4429	26	5.87
36–40	24 583	20.3	10 772	17	1.57	5503	26	4.72
41–50	24 159	19.9	11 513	26	2.25	5801	27	4.65
51+	22 394	18.5	12 541	16	1.27	6082	9	1.47
total	121 149	100	49 336	96	1.94	24 667	108	4.37

*$p = 0.05$ for trend.
**$p < 0.0001$ for trend.

priority for future efforts to accelerate the introduction of enteric vaccines into developing countries.

8. COMMENT

We live in a very exciting age in which the fruits of biotechnology are being brought to bear on the health problems of the world's poorest people living in developing countries. Enteric infections remain a major source of morbidity and mortality in these populations, as illustrated by a recent analysis of the global burden of mortality among children under 5 years of age, in which diarrhoea, estimated to cause 1.336 million deaths, ranked as the second leading cause of infectious disease mortality [38]. The robust ensemble of vaccines already licensed and vaccines in the pipeline provides breathtaking opportunities for disease prevention.

At the same time, the track record of introducing existing, licensed vaccines against rotavirus, cholera and typhoid fever into programmes for the poor has been dismal. It is incontestable that limited financial resources have constituted a major impediment to the introduction of these vaccines into developing countries. But responsibility also lies with the clinical and public health research community, for not having adequately addressed cogent policy questions in their evaluations of these vaccines in developing countries.

In this paper, I have outlined several types of studies that can help to better inform the policy debate about introduction of present and future enteric vaccines. My inventory of studies is not meant to be comprehensive. Moreover, although this paper has focused on enteric vaccines, many of the considerations raised and types of studies cited are generally applicable to new vaccines for developing countries. I hope that the issues raised in this paper will contribute to a future research agenda that is well designed to provide the evidence needed to accelerate rational introduction of new-generation enteric vaccines to populations that need them.

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