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DETERMINANTS OF RESPONSIVENESS TO ORAL VACCINES IN DEVELOPING COUNTRIES

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SUMMARY

Vaccines can be a life saving tool to prevent infectious diseases. Oral vaccines are now being used for polio, typhoid, and cholera, and have recently been introduced for rotavirus. New oral vaccines are also being developed for other enteric infections. Unfortunately, oral vaccines tend to stimulate less consistent immune protective responses in children living in very poor countries. Several mechanisms have been proposed to explain this insufficient immune response, but the reasons for the poor response is not fully understood and no practical methods have yet been developed to correct this problem. Future studies are needed to insure that life saving vaccines can be developed which will be effective for children living in areas where the disease burden is the highest.

INTRODUCTION

Oral vaccines have been developed and are being used for polio, rotavirus, typhoid, and cholera. Others are under development for enterotoxigenic *E. coli*, Shigella and others. The vaccines for enteric bacterial infections are targeted to benefit children in developing countries where these diseases are endemic and most life-threatening, but children in the poorest countries tend to respond in a manner that is less than optimal, relative to those in industrialized countries. Enteric infections are major causes of deaths in children, and such vaccines have the prospect of preventing millions of deaths if they are able to induce protective immunity. However, it appears that that the children who are most at risk of severe infections do not respond well to these vaccines. Unless this problem is understood and corrected, the potential life-saving benefit of these vaccines will not be reached.

Figure 1 illustrates this point through a cartogram in which the area of each country is proportional to the annual number of children who die under the age of 5 years (*Sack*, 2008). The newer vaccines for rotavirus, RotaTeq and RotaRix, provide high levels of protection in children in the low mortality countries, but are much less protective in the high mortality countries, the ones which appear most prominently on the cartogram (*Madhi* et al., 2010). This paper reviews observations illustrating the problems of the relatively poor immune response in children who are at highest risk and examines the various explanations for the poor immune responses and lower protection.

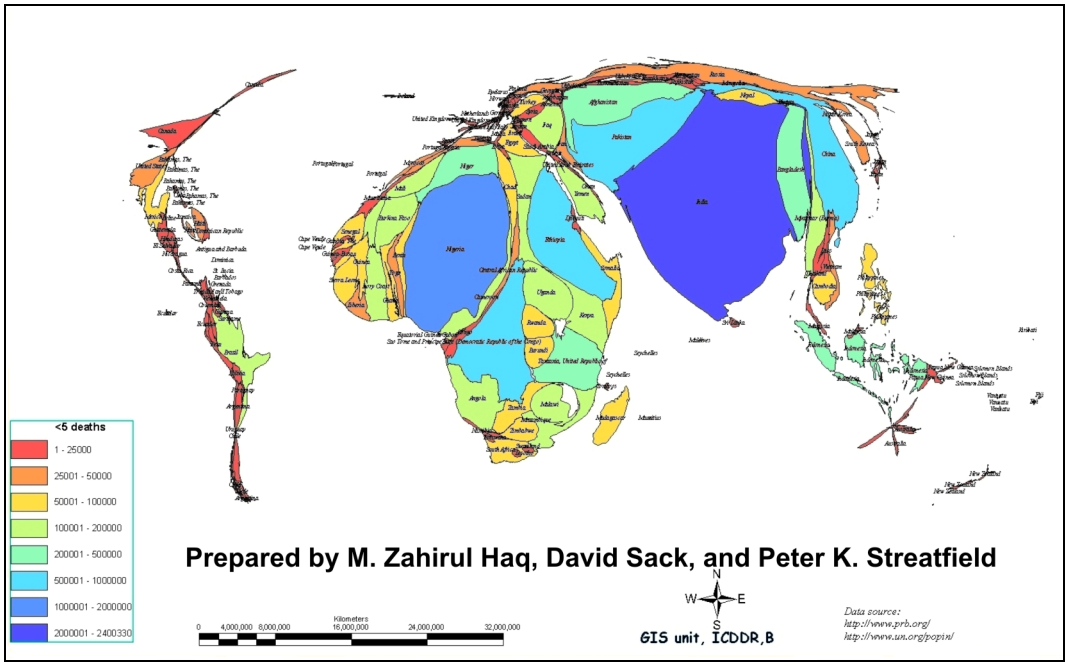

Figure 1: Under the age of 5 years deaths adjusted map of the world (2003).

This paper concentrates on oral vaccines rather than injectable vaccines since most evaluations of injectable vaccines find that children in developing and industrialized countries respond in a similar manner to injectable vaccines. Measures of the lowered immunogenicity include lowered take rate, lower geometric mean titres following immunization, higher doses required to induce an immune response, reduced efficacy against disease, and shorter durations of protection.

EXAMPLES OF SUB-OPTIMAL VACCINE RESPONSES

It appears that most vaccines given orally yield sub-optimal responses when given to children in developing countries. Some children who have received multiple doses of oral polio vaccine have developed paralytic polio, and many other immunized children may be infected with wild type virus, even though asymptomatic (*Grassly* et al., 2010). In a recent study, only 70% of Bangladeshi infants had a serological take to polio serotype 3 following immunization with OPV even though they responded to the other serotypes (*Zaman* et al., 2009). The sub-optimal responses to the vaccine has impeded efforts to totally eradicate polio from certain geographic areas where wide-type virus continues to circulate, such as India, Pakistan, Afghanistan and Nigeria (*Paul*, 2009; *Hasan* et al., 2004).

Rotavirus vaccines have had lower rates of protective efficacy when tested in countries in sub-Saharan Africa and South and South East Asia, as well as lower take rates and lower geometric mean titres following immunization (*Madhi* et al., 2010; Zaman, K., personal communication). Although the

protective efficacy and immunogenicity of these rotavirus vaccines is lower in these poor countries, they still have the potential to be important public health tools because of the large numbers of cases of severe diarrhoea which can be averted. Still, their public health effectiveness is lessened by the sub-optimal immune responses.

A live attenuated Shigella vaccine (SC602) which was immunogenic and protective in North America volunteers did not colonize or stimulate detectable serological responses in Bangladeshi children (*Katz* et al., 2004). Doses of vaccine, from 10^4 to 10^6 were given to children in Bangladesh but with no detectable responses, even though a dose of 10^6 induced some dysentery symptoms in North American volunteers (Sack, D., unpublished data,). Though a higher dose might have been immunogenic in Bangladeshi children, it was felt that a higher dose would not have been acceptable.

Besides inducing a lesser serological response, sub-optimal vaccination may also be exhibited by a shorter duration of protection. This was seen in the trial of Dukoral (killed oral cholera vaccine) when given to subjects in Bangladesh. Children <5 years of age were protected against cholera for the first six months, but then protection was lost during the second six months. By contrast, the older children and adults continued to be protected for up to three years (*Clemens* et al., 1990).

Another oral cholera vaccine is the live attenuated oral vaccine (CVD103HgR). Among North American volunteers, a dose of $5x10^8$ bacteria was adequate to stimulate vibriocidal responses, but among Indonesian subjects, this same dose induced such responses rarely. Thus, the dose was increased to $5x10^9$ to stimulate an adequate take rate. Even with this higher dose, the vaccine did not protect against cholera (*Richie* et al., 2000).

Thus, there are several examples of reduced immune responses to many types of oral vaccines when used in developing countries.

RELEVANCE OF THE SUB-OPTIMAL RESPONSES TO ORAL VACCINES

These vaccines are intended to be "life-saving" interventions. The deaths, which could potentially be prevented with these vaccines, occur among the poor groups within these poor countries. For example, it is estimated that between 500,000 and 600,000 children die from rotavirus diarrhoea annually. However, these deaths are not equally distributed among the world's children; rather, they nearly all occur within the poorest countries and within these poor countries, they occur most often in the poorest families. These same groups are the ones who appear to respond in the least consistent manner. Although a rotavirus vaccine with an efficacy of 50% in the poor countries might be estimated to reduce rotavirus deaths by 50%, in fact, the reduction could be much less. This is because children who are most at risk of a rotavirus death are likely the same as the ones who respond less well to the vaccine.

Generally, vaccines are among the most equitable health interventions because they can be given to many who may not receive treatment if they do become ill. Depending on treatment for a treatable illness is much less equitable because, in reality, treatment many not be available or provided. Thus, prevention of illness is especially critical for those without access to care.

However, when a vaccine is less effective among the most vulnerable groups, there is a "mismatch" between those who respond to the vaccine and those whose lives are at most risk. Such vaccines, which provide high efficacy to the groups, which are the least vulnerable, but lower efficacy to the most vulnerable, might be said to be "inequitable vaccines." This mismatch emphasizes the critical importance of finding a solution to the problem of sub-optimal responses to immunization.

APPROACHES TO SOLVING THE PROBLEMS OF SUB-OPTIMAL RESPONSES

Because the experience with past vaccines, vaccine programs have adopted empiric strategies to correct for sub-optimal vaccine responses. In the case of polio, national programs have provided additional doses of OPV to children through "national immunization days (NIDS)" (*Centers for Disease Control and Prevention [CDC]*, 2004, 2005, 2008). These NIDS aim to provide OPV vaccine to all children regardless of previous receipt of OPV. Many children end up receiving 10 to 15 doses of OPV over a lifetime. From a programmatic perspective, these NIDS have been very successful in reaching a very high proportion of all children. Due to the wide and massive coverage in countries with inadequate sanitation, the live vaccine virus spreads in the environment and immunizes many others who may not have received vaccine directly, thereby enhancing herd immunity. This strategy has essentially stopped transmission of wild type virus in many countries. Unfortunately in some areas, asymptomatic transmission of wide-type polio virus has continued in spite of this wide scale immunization through the NIDS (*Grassly* et al., 2010). Thus, this strategy of giving additional doses on a massive scale has been successful in many areas, but has not been adequate to eradicate the disease as was hoped it would.

For rotavirus, RotaRix is now recommended as a two-dose vaccine given during the first two immunization visits. Is it possible that a third dose as a potential way to increase protection? Unfortunately, one study from Africa did not show an improvement in protection with a third dose (*Madhi* et al., 2010).

In the case of the live attenuated cholera vaccine (CVD103HgR), the strategy used was to give a ten-fold higher dose. In theory, it may be possible to have a specific formulation with a higher dose for use in developing countries; however, this is certainly not optimal and could only be used if the vaccine was shown to be extremely safe. It would seem more logical to adopt the higher dose, appropriate for use in developing countries, as the "standard" dose and use this dose in all countries.

Whether giving higher doses or more doses will improve vaccine performance is not clear. In the case of live attenuated vaccines, the effectiveness of additional doses may be blocked by "immune exclusion" resulting from the first dose, so it is not clear that simply giving additional doses will result in more robust immune responses.

The underlying mechanism responsible for the sub-optimal immune response is not known. Since children living in tropical countries often have an inflamed intestinal mucosa with shortened villi it is possible that "tropical enteropathy" contributes to the

problem (*Lagos* et al., 1999). Malnutrition, including specific micronutrient deficiencies have also been implicated, as have intestinal parasites (*Cooper* et al., 2001). It seems unlikely that a single factor will provide an explanation with all vaccines. Some vaccines, e.g. rotavirus, are given at a very young age, prior to the age where malnutrition, micronutrient deficiency or intestinal worms are commonly found. By contrast, other vaccines, e.g. cholera vaccine, are given at 1 or 2 years. By this time, tropical enteropathy, malnutrition, micronutrient deficiency, and infestations are frequent.

Studies have been carried out to determine if supplements with vitamin A, zinc or a combination of these would improve immunogenicity of killed cholera vaccine. In a group of children who were not vitamin A deficient, supplemental vitamin A did not change the immunogenicity, but zinc did stimulate a higher titre of vibriocidal antibodies (*Albert* et al., 2003). Vitamin A is thought to be critical for healthy mucosa as well for immunity; however, when a routine vitamin A distribution program is providing vitamin A, it appears that additional vitamin A is not helpful.

Maternal antibodies via placental route or via breast milk may inhibit vaccine responses. This is well established in the case of measles vaccine, but is unclear in the case of oral vaccines (*Griffin* et al., 2008; *Triki* et al., 1997). There is some evidence that breast milk may neutralize antigens and that the immune response may be blunted (*John* et al., 1976). Studies are ongoing to determine the extent to which withholding breast feeding temporarily may improve rotavirus vaccine immunogenicity. Results from this study will be informative; however, a strategy of withholding breast-feeding is neither practical nor feasible, and could interfere with messages in favour of breast-feeding more generally.

MATERNAL INTERVENTIONS

There is increasing interest in attempting to improve the health of the infant through interventions that are directed toward the mother during or prior to pregnancy. When examining risk factors that are associated with high infant mortality, many of these are related to mother's education and health. Mothers of children who are most vulnerable are frequently underweight, suffer from frequent illnesses, have short birth intervals between children, are anaemic and under stress. It seems likely that some of these factors can influence the immune system and the health of the infant.

An example of the relation between mother's toxic stress and the infant's immune system is the information showing that women who are exposed to arsenic during pregnancy have a smaller thymus (*Raqib* et al., 2009). While this is only one example, addressing the health needs of women before and during pregnancy may be more effective than focusing only on the infant.

INTERACTION BETWEEN IMMUNITY AND ENVIRONMENT

The focus on poor immune response of the infant should not exclude consideration of the lack of sanitation in the environment in which the infant lives.

Intestinal immunity can be overwhelmed if an inoculum is very high, at least for bacterial infections and possibly for viral infections. Areas where protection is lower tend to be areas of very poor sanitation. Is it possible that the heavy environmental faecal contamination results in a very high inoculum, and that this results in vaccine failures and increased transmission of the enteric pathogens? The cycle of immune and environmental failure could be a key concept to reducing the predisposing factors for hyporesponsiveness to vaccination as well as continued transmission of pathogens.

RESEARCH AGENDA

The cause of oral vaccine hyporesponsiveness is not known, but solving the puzzle is clearly critical if the effectiveness of vaccines for rotavirus, polio and other enteric diseases are to be improved and be more equitable. Risk factors for vaccine and immunological failure need to be identified. A limitation of past efficacy studies for rotavirus has been their study designs which did not allow for identifying many risk factors for vaccine failure. Data on potential risk factors such as birth weight, illnesses in the infants, maternal nutrition and micronutrient deficiency, birth interval, chemical exposures, and maternal illnesses need to be correlated with vaccine failures. Based on data from such case control studies, rational interventions can be devised to test hypotheses.

Pending data from such case control studies, potential interventions can be attempted such as micronutrients and calories for mothers, maternal immunizations, and micronutrients for the infant. Breast milk can be withheld for a period during the time of immunization to understand the role of breast milk antibody, but this will not be a practical strategy for the future.

While attempting to understand vaccine hyporesponsiveness, it may be that a practical solution is not possible and that a different approach is needed. For polio it seems clear that children who do not respond to OPV will respond to injectable polio vaccine (IPV) (*Sutter* et al., 2000). Until now, the very low cost of OPV and the relatively high cost of IPV has favoured the use of OPV for developing countries. For limited areas where polio has not been able to be eradicated with OPV, use of IPV may need to be reconsidered.

An injectable vaccine for rotavirus was never tested in children, but in view of the effectiveness of IPV, this might be considered. Many years ago, it might have been possible to have a parallel track to evaluate an injectable vaccine for rotavirus, but this was not attempted because of the belief that local intestinal immunity was best stimulated with an oral vaccine. In the field, it seems that the current oral rotavirus vaccines protect against symptomatic rotavirus disease, but they are much less efficient in protecting against rotavirus infection even in populations where high-level protective efficacy is seen. It would seem that an injectable vaccine could be prepared in relatively straightforward manner and could be tested in humans.

Other vaccine strategies could also be attempted with the current rotavirus vaccine. These might include a booster dose at 7 to 9 months of age. Giving rotavirus vaccine at an older age is not currently approved because of the fear of intussusceptions from the previous vaccine, RotaShield (*Peter* and *Myers*, 2002). The current vaccines, RotaTeq and RotaRix have not been associated with any increased risk for this compli-

cation, and it would seem that this strategy might be evaluated. An obvious limitation to a booster dose at 9 months is that it would not prevent the cases which occur earlier in life. The proportion of cases occurring prior to 9 months of age varies depending on the geographic region, though with a successful rotavirus vaccine program, the median age may increase as the disease burden lessens.

Other vaccination methods are being considered as well, such as sublingual or transdermal approaches. These are currently experimental approaches and have not been attempted, but they do appear promising.

Finding strategies to overcome the sub-optimal immune responses to oral vaccines among children in poor countries is a challenge. Finding solutions to the problem will be critically important if these oral vaccines are to accomplish their role as life saving interventions for the most vulnerable.

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