

Rotavirus Immunization in Africa: A Perspective Re-visited

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In August 1998, the sun was shining on the rotavirus world as the first rotavirus vaccine candidate was licensed in the United States. RotaShield® was licensed by the Food and Drug Administration (FDA) in the United States [1] and was soon recommended for routine use in American Children and inclusion in the immunization schedule [1,2]. It was hoped that the rotavirus vaccine would rapidly be evaluated in African and Asian children and soon be available for use in the developing world [3,4].

However, within a few short months, the dream of an effective rotavirus vaccine for introduction into many countries including Africa was ended. By July 1999, 15 cases of intussusception were reported in children receiving the RotaShield® vaccine, by the Vaccine Adverse Events Reporting System (VAERS) which is in place for every new vaccine in the United States [5]. VAERS is a passive surveillance system operated by the FDA and the Centres for Disease Control and Prevention (CDC). The CDC recommendation that the use of the rotavirus vaccine should be withdrawn soon followed [6].

Intussusception

Intussusception is a rare type of bowel blockage, where a portion of the intestine invaginates into an adjacent section and causes a compression and blockage. Unless treated, the intussusception can result in an ischemic necrosis and may result in perforation and peritonitis [7]. Thus, although rare, intussusception has a serious consequence with high mortality if untreated. However, it remains unclear how the RotaShield® vaccine would cause the intussusception and several hypotheses have been proposed, but await further investigation.

Almost two years of investigation into the background of intussusception in American Children and a re-examination of the RotaShield® experience in the United States [8,9] has confirmed the risk of the vaccine for intussusception. RotaShield® seems to be associated with a risk of an extra case of intussusception in every 10 000 children vaccinated [8]. The risk seems to be concentrated in the period within 3-10 days post dose 1, although some elevated risk also occurs after dose 2 and dose 3.

Need for a Rotavirus Vaccine

However, the development of an effective rotavirus vaccine is a priority for the developing world. In fact, this priority for the development of a rotavirus vaccine has been in place since the mid-1980s by the Institutes of Medicine [10] and the World Health Organization [11]. The pressure for the development and licensure of a rotavirus vaccine has come because of the high mortality associated with this virus in the developing world [3,12].

In developing countries, rotavirus was estimated to cause almost one million deaths each year, accounting for an estimated 20-25% of all deaths due to diarrhoea and 6% of all deaths among children less than five years old [12]. The magnitude of the disease associated with rotavirus infections in the developing world and the acknowledgement that public health interventions to provide clean water and improved sanitation will not decrease the incidence of this disease, have driven the need to develop a rotavirus vaccine [13].

It is clear from studies in infants and young children in both developed and developing countries that rotavirus accounts for over one

third of severe cases of diarrhoea that require hospitalization and that can potentially lead to death [3,12]. It has been estimated that the administration of an efficacious rotavirus vaccine could prevent 16% of all diarrhoeal deaths in children less than 5 years of age [11].

Rotavirus in Africa

In Africa, it has recently been estimated that approximately 110-150 000 young children less than 5 years of age die annually due to rotavirus infection [14,15]. This is one region of the globe, where a rotavirus vaccine is urgently required. However, despite the WHO recommendations and prioritization in 1985, only three rotavirus vaccine trials have been completed in Africa [16-18]. All were undertaken in mid 1980s and none with RotaShield®, which was eventually licensed. Clinical trials with the FDA-Licensed

RotaShield® only began in Africa in 1999 and, to the best of my knowledge, all ended on "clinical hold" due to the intussusception issue. None was completed successfully.

Although the new rotavirus vaccine candidates have demonstrated high efficacy in trials in developed countries, the history of rotavirus vaccine in Africa has not been good. The earlier rotavirus vaccine candidates, based on bovine rotavirus strains, were reported to have lower efficacy or to have completely failed [16-18] (Table 1). Two of the earlier African trials were conducted with the GSK Biologicals' bovine vaccine candidate (RIT4237) and both showed poor immunogenicity and poor protection in African Children [16,17]. The initial Merck bovine rotavirus candidate (WC3) also showed poor efficacy in a trial in the Central African Republic [18].

Table 1. Rotavirus Vaccine Trials in Africa in the 1980s

Vaccine Strain	Site	Number of Subjects	Number of doses	Protection against Severe RV Disease	Protection against Any RV Disease	Reference
RIT4237	Rwanda	245	1	0	0	16
RIT4237	Gambia	185	3	31	0	17
WC3	Central African Republic	472	2	36	0	18

Many factors are likely to have played a role in the failure of these vaccine candidates in Africa, not least of which may have been the trial design and interpretation, as occurred with the trials in Peru and Brazil [19,20]. Other more obvious reasons may include vaccine-related issues (such as the antigenic make-up of the bovine rotavirus candidates, which are G6, a VP7 type not found generally in humans, or the vaccine concentration used), or host-related issues (such as malnutrition and microbial load in African infants), or in fact differences in the epidemiology of rotavirus strains in these countries.

The reasons for these apparent differences in efficacy need to be investigated and elucidated, since they may hold important clues to completing

development of a vaccine suitable for the children of Africa. In addition, further research questions in Africa remain to be answered. These questions include the actual burden of disease due to rotavirus infection in Africa, which rotavirus VP7 serotypes are circulating and whether the new vaccine candidates will protect against them and how immunogenic these vaccines will be in a typical African population?

WHO recommendations

At a meeting held at the World Health Organization in Geneva, Switzerland on "Rotavirus Vaccines for Immunization of Children in Developing Countries" (1997), it was decided that two important aspects of rotavirus

infection in Africa needed to be addressed. First, there was a paucity of data of the VP7 and VP4 rotavirus types circulating in Africa. The African Rotavirus Network, which is funded by the WHO has contributed significantly to addressing this void since 1998, and there has been an increase in the data available for many African countries. However, the second aspect—the lack of data on the immunogenicity and efficacy of current rotavirus vaccine candidates in African children—remains unresolved.

A second meeting at WHO "Future Directions for Rotavirus Research in Developing Countries" (2000), stressed the need for the parallel development of new rotavirus vaccine candidates in the developing world, especially in Africa and Asia, where this vaccine would be needed. To date, only GlaxoSmithKline Biologicals' have shown the initiative to pioneer the parallel development through clinical trials in Africa and Asia with their rotavirus candidate. Thus the heritage set by this pharmaceutical company in the mid 1980s is to be continued in a new development programme of rotavirus vaccine trials in Africa. Let us hope that his human rotavirus candidate will be more successful in African children than its predecessor almost 20 years ago.

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