

Can Changes to Scheduling Enhance the Performance of Rotavirus Vaccines in Low-Income Countries?

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(See the major articles by Armah et al on pages 1678–85 and Zaman et al on pages 1686–93.)

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Two live, oral, attenuated vaccines are licensed for use in infancy for the global prevention of rotavirus disease, and other vaccines are being developed. The current vaccines include a monovalent human rotavirus vaccine (Rotarix, GlaxoSmithKline Biologicals, Rixensart, Belgium; hereafter “RV1”) and a pentavalent human-bovine reassortant rotavirus vaccine (Rotateq, Merck, West Point, PA; hereafter “RV5”). Prior to rotavirus vaccine introduction into childhood immunization programs, rotavirus gastroenteritis was responsible for an estimated 453 000 childhood deaths globally each year [1]. Both vaccines were highly (>85%) efficacious in reducing the number of severe rotavirus gastroenteritis episodes in high-income and middle-income countries [2]. The high efficacy of these vaccines in clinical trials has translated into impressive effectiveness following their subsequent adoption into infant schedules, with a marked decline in the number of rotavirus hospitalizations reported from the Americas and from Europe. A sustained reduction in the number of diarrheal deaths in Mexico, Brazil, and Panama has been attributed to rotavirus vaccine use [2].

However, the bulk (>90%) of infant deaths due to rotavirus gastroenteritis occur in low-income countries in Africa and Asia. Clinical trials of rotavirus vaccines displayed substantially lower efficacy (approximately 50%) in low-income countries with a high disease burden, including Malawi and Bangladesh. Despite this modest efficacy, the World Health Organization (WHO) extended its recommendation for routine use of rotavirus vaccines to emphasize introduction in low-income countries because of the very high burden of rotavirus disease experienced by children in such settings [3].

Uptake of rotavirus vaccine has been rapid in high-income and middle-income countries and even in countries eligible for the Global Alliance for Vaccines and Immunization (GAVI) in Africa and Latin America, with 80 countries having introduced it by end of 2015: 57 are using RV1, 19 are using RV5, and 4 are using both vaccines [4]. Adoption of rotavirus vaccine in middle-income and low-income countries in Asia has been much slower. There are, so far, limited data on the effectiveness of rotavirus vaccines from GAVI-eligible countries. In Bolivia, where RV1 was introduced in 2008 for administration at 2 and 4 months of age, a case-control study demonstrated vaccine effectiveness against severe rotavirus gastroenteritis of 69% (95% confidence interval [CI], 54%–79%) [5]. Using the accelerated EPI schedule of administration at 6 and 10 weeks of age for the RV1 vaccine and a similar design, vaccine

effectiveness in Malawi was 64% (95% CI, 24%–83%) [6].

While these data from early adopter low-income countries offer hope that the rotavirus disease burden could be substantially reduced, the performance of the current live, oral rotavirus vaccines in the world’s poorest countries is clearly suboptimal. Reduced vaccine efficacy/effectiveness in the first year of life (where up to three quarters of the severe rotavirus disease burden lies) is a consistent finding in low-income countries and was documented with a further live, oral, monovalent human-bovine reassortant rotavirus vaccine (116E) in India [7], which showed 56% efficacy (95% CI, 37%–70%) in a phase 3 clinical trial but has not yet been evaluated in programmatic use. Even when the vaccine does protect in infancy, the longevity of such protection through the second year of life is uncertain. Thus, while rotavirus is known to continue as a significant pathogen into the second year of life in low-income countries [8], current rotavirus vaccines have not consistently demonstrated protection beyond 1 year of age in such settings [9]. However, protection was maintained in the second year of life in a postintroduction study of RV1 in South Africa [10] and in the clinical trial of 116E in India [7].

Many factors have been proposed to explain the lower efficacy/effectiveness of rotavirus and other live, oral enteric vaccines in low-income countries, including interference of concurrent oral poliovirus vaccine (OPV) administration,

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maternal antibody, breastfeeding, malnutrition, environmental enteropathy, and intestinal microbiome, but their relative contributions remain to be determined [11]. While the biologic reasons behind reduced performance and longevity of current vaccines in low-income countries are not yet understood, examining changes to rotavirus vaccine scheduling offers a pragmatic approach to optimizing the magnitude and duration of protection against severe rotavirus disease. In this issue of *The Journal of Infectious Diseases*, 2 studies investigated different schedules of RV1 in low-income countries in Africa and Asia.

Armah et al, in a postlicensure study from Ghana [12], examined the immunological benefit of an additional, third dose of RV1 administered at 14 weeks of age over the standard 2-dose schedule involving delivery at 6 and 10 weeks of age; statistically significant increases in immunoglobulin A (IgA) seroconversion rate and a higher geometric mean concentration were demonstrated in the 3-dose arm. A lesser benefit, not achieving statistical significance, in both IgA seroconversion rate and geometric mean concentration was observed using a delayed 2-dose schedule involving vaccination at 10 and 14 weeks of age. These data are consistent with findings from a placebo-controlled clinical trial of RV1 from South Africa and Malawi conducted prior to vaccine introduction, which compared 3 doses administered at 6, 10 and 14 weeks of age and 2 doses administered at ages 10 and 14 weeks to placebo; a suggested increase in immune responses and clinical benefit was observed with the 3-dose schedule over that provided by 2 doses, although the study was underpowered to definitively examine each individual schedule [13]. Clinical trials from Pakistan and India, however, did not document enhanced immune responses with a 3-dose or 5-dose RV1 schedule [14, 15]. Setting-dependent variability in rotavirus immunity and epidemiology has been shown in cohort studies of natural rotavirus infections and may help explain

discrepant result from vaccine studies in these different regions [16].

Addressing the issue of reduced duration of protection, Zaman et al, also in this issue, conducted a noninferiority trial in Bangladesh, in which a third dose of RV1 was administered concomitantly with measles-rubella vaccine at age 9 months [17]. Importantly, seroresponses to measles-rubella vaccine were not negatively affected by RV1 administration. The third dose of RV1 resulted in enhanced rotavirus antibody levels, with responses particularly prominent among those infants who were either seronegative or had low rotavirus antibody titers prior to the third dose of RV1 (seroresponses following the primary 2-dose RV1 series were not available).

In both trials of alternate schedules, no adverse effects were attributed to RV1 administration. Both trials were too small to detect rare events such as intussusception, which is associated with oral rotavirus vaccination [18], although the trial in Bangladesh immunized children at an age when the incidence of naturally occurring intussusception is higher. Because intussusception was reported to be age dependent with the first licensed rotavirus vaccine (a tetravalent rhesus-human reassortant rotavirus vaccine, RRV-TV [RotaShield]), with the relative risk of intussusception considered to be higher among those receiving the first dose beyond 3 months of age, age restrictions were placed on the timing of administration of RV1 and RV5. These restrictions were included in the product information that was reviewed by regulatory authorities. When the WHO endorsed global use of rotavirus vaccines, it was recommended that the first dose be given by 15 weeks of age and the last dose by 32 weeks of age [3]. Postintroduction studies have shown that RV1 and RV5 were associated with an increased risk of intussusception primarily following receipt of the first dose, but at a much lower level than that associated with RotaShield [18]. Since it is appreciated that infants in low-income, high-mortality countries often

present late for vaccination, and because any increase in deaths from intussusception is expected to be far outweighed by rotavirus deaths averted through vaccination, the age restriction recommendation was subsequently altered by the WHO to give countries the maximum opportunity for infants to be immunized [18]. Recently, India has extended the immunisation window to one year of age. In this and other settings where immunisation is delayed, risk must continue to be assessed for a better understanding of the consequences, or lack of consequences, of later immunisation with rotavirus vaccines.

While vaccination later in infancy would be expected to decrease the impact of maternal antibody in reducing immune responses when vaccine is administered in early infancy [19], timely protection in low-income countries is required because of early natural exposure to rotavirus in such settings [16]. Administration of the first dose of RRV-TV during the neonatal period was undertaken during a clinical trial in Ghana, with a reported vaccine efficacy of 61% (95% CI, 30%–78%) against rotavirus gastroenteritis of any severity, using 2 doses [20]. A live, attenuated rotavirus vaccine developed from a neonatal rotavirus strain (RV3) is being evaluated in neonatal and infant schedules [21]. A potential advantage of neonatal administration is that naturally occurring intussusception is rare in the neonatal period.

Although both studies in this issue of *the Journal* demonstrate that there may be potential value of an additional dose of RV1, caution is required since serum antirotavirus IgA, although used as a measure of vaccine response, has an imprecise correlation with protection from rotavirus disease [22]. As the identification of an immune correlate of protection remains elusive, studies with clinical end points are required. Since placebo-controlled studies of an intervention (rotavirus vaccine) with proven effectiveness would be hard to justify ethically, large-scale, expensive postintroduction studies are required to demonstrate the public health benefit of changes to the vaccine

schedule. Furthermore, the total benefit of a rotavirus vaccine program in reducing the burden of severe diarrhea will be realized through a combination of direct and indirect effects. Protection of children too old to have been vaccinated has been reported from high-income and middle-income countries worldwide [23]. This herd protection is thought to have occurred as a consequence of reduced rotavirus transmission. Whether this benefit will be observed in low-income countries, where direct protection is lower and virus epidemiology and social demographic patterns differ from those in middle-income and high-income countries, will be determined by careful postintroduction surveillance.

It is important to consider rotavirus vaccine scheduling in the context of current issues pertaining to other vaccine-preventable diseases of childhood; these include the switch from oral polio vaccine to inactivated polio vaccine, optimization of pneumococcal conjugate vaccine schedule, introduction of malaria vaccine in malaria-endemic areas, and ensuring maximum beneficial heterologous effects [24]. Since the incidence of diseases, other than pertussis, for which the accelerated 6-, 10-, and 14-week schedules were implemented in low-income countries have declined significantly and there is potential to address early pertussis with maternal immunization, perhaps it is time to consider alternate schedules with later dosing or multiple doses. Large-scale cluster randomized trials could be powered to evaluate the impact of scheduling on vaccine effectiveness in populations in Africa and Asia with a high disease burden. Such studies should also address mechanistic questions underlying vaccine underperformance. A clear opportunity

exists to refine the childhood immunization programs in vulnerable populations with a high disease burden, to maximize the magnitude and longevity of vaccine protection against major infective causes of childhood illness and death.

Note

Potential conflict of interest. N. A. C. has received research grant support and honoraria from GlaxoSmithKline Biologicals for participation in rotavirus vaccine advisory board meetings. G. K. certifies no potential conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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