EDITORIAL

# New Rotavirus Vaccines for Infant Gastroenteritis Arriving Soon

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## Burden of Rotavirus Gastroenteritis

Rotavirus gastroenteritis is the second most common disease of infants and young children. Each year, rotavirus causes approximately 111 million episodes of gastroenteritis requiring only home care, 25 million clinic visits, 2 million hospitalizations, and 352 000 – 592 000 deaths (median, 440 000 deaths) in children < 5 years of age, worldwide (1). By age five years, nearly every child will have an episode of rotavirus gastroenteritis, 1 in 5 will visit a clinic, 1 in 65 will be hospitalized, and approximately 1 in 293 will die (1). Children in the poorest countries account for 82% of rotavirus deaths. The most prevalent rotavirus serotypes which are responsible for over 80% of worldwide gastroenteritis infections are G1[P8], G2[P4], G3[P8] and G4[P8] (2). A previously licensed rotavirus vaccine in the United States of America was withdrawn from the market when it was associated with increased risk of infant intussusception (3).

In Jamaica (population 2.6 million, annual birth cohort 45 000), the burden of rotavirus illness remains significant. Rotaviruses were identified as the major cause of infantile diarrhoea by Dowe *et al*, occurring in 19% of 1020 cases of gastroenteritis in a hospital-based study sponsored by the World Health Organization (4). The National Sentinel Surveillance System (NSSS) had been established by the Ministry of Health in Jamaica in 1976. Each year, about 15 000 to 30 000 diarrhoeal cases were reported in Jamaica in infants aged less than five years, with 700 to 900 hospitalizations and 3 to 18 reported deaths. Active surveillance demonstrated that during 1998 to 2003, acute gastroenteritis occurred during the cooler months of the year, in children aged less than three years and deaths were relatively rare (2–3 per year). In 2003, the Jamaican Ministry of Health formally reported an unusually severe epidemic in over 4000 children which occurred during the summer months involving older children (up to 8 years) and young infants, with significantly increased case reporting from the community, increased hospital admissions and increased deaths, with 12 occurring during the short period of June to July (5, 6). Eight of the 12 deaths were directly attributable to diarrhoea and occurred in children aged four months to three years. All of the infants had watery diarrhoea and vomiting lasting for one to five days. This outbreak was uncommon in that it involved older children (aged > 3 years) and it occurred in the summer. Rotavirus was identified in 52% of 81 stool specimens, including 8 of 12 collected from children older than 3 years (6). Rotaviruses expressed the common serotypes and no vaccine strains were identified (5).

The United States Centers for Diseases Control and Prevention (CDC) opined that environmental exposures were the most likely cause of the outbreak, with heavy rains in the earlier months and subsequent flooding most likely causing faecal contamination of the water supply (5). The CDC also indicated that the deaths associated with acute gastroenteritis might have been attributable to inappropriate case management, as certain children received anti-emetic and anti-diarrhoeal injections, which are not part of the standard diarrhoea management (5). Since then, annual seasonal epidemics of infant gastroenteritis due to the rotavirus have continued unabated in Jamaica, with 21 total reported deaths in 2003 and 23 deaths in 2004; there was also a summer peak seen in sentinel sites in 2005. The Ministry of Health has also reported that public health education of healthcare providers, parents and caregivers regarding the use of oral rehydration therapy can reduce the severity and mortality from diarrhoea during outbreaks of acute gastroenteritis (7).

## New Rotavirus Vaccines

The extremely favourable results of two, international, industry-sponsored, clinical mega-trials of new rotavirus vaccines as published in the January 5, 2006 issue of the *New England Journal of Medicine* are therefore welcomed (8, 9) particularly in developing countries where the burden of rotavirus disease is high, such as in Jamaica. These two new rotavirus vaccines and the two clinical megatrials are compared in the Table.

## Challenges for the Developing World

In these huge clinical mega-trials, both rotavirus vaccines clearly demonstrated an impressive safety profile against infant intussusception, with proven efficacy against infant rotavirus gastroenteritis, thereby reducing healthcare contacts and therefore the economic costs that maybe related to infant rotavirus gastroenteritis (8, 9).

The issues for the developing world remain whether intussusception would become more evident if these vaccines are given to older children (as may be necessary in Jamaica

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**Table: Comparison of two new rotavirus vaccines and two clinical mega-trials**

| Characteristics | Merck's *Rotateq*$^{TM}$ Vaccine | Glaxo-SmithKline's *Rotarix*$^{TM}$ Vaccine |
|---|---|---|
| New vaccines | Live pentavalent, human-bovine reassortants, WC3 bovine strain, with viral surface proteins of human rotavirus serotypes G1,G2,G3,G4,P [8] | Live attenuated monovalent, human G1P [8] serotype RIX4414 vaccine strain |
| | Orally administered, three doses given 4-10 weeks apart given with normal diphtheria, tetanus, pertussis (DTP) vaccination schedule | Orally administered, two doses, administered one to two months apart with normal infant (DTP) immunization schedule |
| | Liquid preparation, 2 ml volume | Lyophilized vaccine, reconstituted to 1 ml |
| | Not tested concurrently with oral polio vaccine (OPV), inactivated polio vaccine given instead, (concurrent studies with OPV now underway) | Oral polio vaccine given two weeks after first and second dose |
| Clinical Trials | Randomized, double-blind, placebo controlled, phase 3, vaccine:placebo ratio of 1:1 | Randomized, double-blind, placebo controlled, phase 3, vaccine:placebo ratio of 1:1 |
| Countries involved | 11 countries, primarily developed nations of USA and Finland (but Jamaica was included and enrolled 1805 subjects) (10). | 11 Latin American countries, primarily from poor and middle income populations, (but Finland was included) |
| Enrollment | 70 321 subjects enrolled, data for 69 274 available | 63 225 infants enrolled |
| Safety against acute infant Intussusception | 11 cases of acute infant intussusception diagnosed within 42 days of any dose; 6 in vaccine recipients and 5 in placebo recipients (RR=1.6) | 13 cases of intussusception diagnosed within 31 days of receiving any dose; 7 in vaccine recipients and 6 in placebo recipients (difference in risk – minus 0.32 per 10 000 infants) |
| Efficacy subset | 98% efficacy against severe gastroenteritis | 85% efficacy against severe rotavirus gastroenteritis and rotavirus-associated hospitalization |
| | 95% reduction in emergency department visits and hospitalization for G1-G4 rotavirus gastroenteritis | 42% reduction in hospitalization for diarrhoea of any cause |
| | 74% efficacy against G1-G4 rotavirus gastroenteritis | —— |
| | 86% reduction in clinic visits for G1-G4 rotavirus gastroenteritis | —— |
| Regulatory approval | United States Food and Drugs Administration (FDA) has approved it; The Immunizations Practices Advisory Committee of the United States Centers For Disease Control and Prevention has also recommended it for use in the USA in infants aged six to 32 weeks | Approved and in use in Mexico and Brazil |
| Use in Jamaica | Mid 2006, via private practitioners and paediatricians | Early 2006, via private practitioners and paediatricians |
| Estimated cost | $US62.50 per dose when purchased as a pack of 10 single-dose tubes | $US50.00 per dose to the practitioner (mark-up to patient) |

where epidemic cases in older children have been described after widespread flooding) and when given to children in larger numbers (11). The right price will always be an issue to negotiate, although the cost-benefit ratio of eliminating infant rotavirus gastroenteritis from the developing world may well be worth any effort. Challenges of immunizing young infants who maybe immuno-suppressed from HIV/AIDS (which is likely undiagnosed when infant immunizations begin at 6–10 weeks), malnutrition and tropical bacterial, viral and parasitic inter-current childhood illnesses may yet become evident. The potential challenges of administering two live viral vaccines (rotavirus and oral polio vaccine) in a staggered manner to infants in the developing world, such as Jamaica, will need to be overcome, especially as this relates to the potential of creating missed opportunities for immunizations in the first few months of life (about 8–9 total visits for immunizations would now be required in infancy). Evolving partnerships between these two Vaccine Manufacturers, the Global Alliance for Vaccines and Immunization, the World Health Organization, Pan American Organization and the Bill and Melinda Gates Foundation are welcomed, as plans are galvanized to roll out these vaccines to children in the developing world, where these products are desperately needed in the continued fight to eliminate infant gastroenteritis.

The arrival of these two rotavirus vaccines represents the first meaningful step towards universal access to vaccines and control of infant rotavirus gastroenteritis, similar to the

advent and widespread use of oral polio vaccine in the 1950s with the last case of acute poliomyelitis reported over 20 years ago in this region.

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