Rotavirus Vaccines
(WHO position paper — January 2013)

In accordance with its mandate to provide guidance to Member States on health policy matters, WHO issues a series of regularly updated position papers on vaccines and combinations of vaccines against diseases that have an international public health impact. These papers are concerned primarily with the use of vaccines in large-scale immunization programmes; they summarize essential background information on diseases and vaccines, and conclude with the current WHO position on the use of vaccines worldwide.

The papers have been reviewed by external experts and WHO staff, and are reviewed and endorsed by the WHO Strategic Advisory Group of Experts on Immunization (SAGE). [1] The position papers are intended for use mainly by national public health officials and managers of immunization programmes. They may also be of interest to international funding agencies, vaccine manufacturers, the medical community, the scientific media, and the public. A description of the processes followed for the development of vaccine position papers is available at http://www.who.int/immunization/position_papers/position_paper_process.pdf

This position paper replaces the corresponding WHO position paper of 2007 and its update of 2009; it summarizes recent developments in the field, in particular the potential of rotavirus vaccines to further reduce mortality by employing more flexible immunization schedules. All WHO recommendations appear at the end of this paper and reflect those offered by SAGE. Rotavirus vaccines were last discussed by SAGE at its meeting in April 2012; evidence presented at the meeting can be accessed at http://www.who.int/immunization/sage/previous/en/index.html.

BACKGROUND

Epidemiology

Rotaviruses infect nearly every child by the age of 3–5 years and are globally the leading cause of severe, dehydrating diarrhoea in children aged < 5 years. In low income countries the median age at the primary rotavirus infection ranges from 6 to 9 months (80% occur among infants < 1 year old) whereas in high income countries, the first episode may occasionally be delayed until the age of 2–5 years, though the majority still occur in infancy (65% occur among infants < 1 year old). [2]

In most low income countries in Asia and Africa, rotavirus epidemiology is characterized by one or more periods of relatively intense rotavirus circulation against a background of year-round transmission, whereas in high income countries with temperate climates a distinct winter seasonality is typically observed. This difference, as well as differences in health care availability and childhood co-morbidity, drive the marked inequality in rotavirus disease burden between low and high income countries. [3]

WHO estimates that in 2008, approximately 453 000 (420 000–494 000) rotavirus gastroenteritis (RVGE)-associated child deaths occurred worldwide (updated WHO estimates on global mortality due to RVGE are soon to be published). These fatalities accounted for about 5% of all child deaths and a cause-specific mortality rate of 86 deaths per 100 000 population aged < 5 years. About 90% of all rotavirus-associated fatalities occur in low income countries in Africa and Asia and are related to poor health care. National cause-specific mortality rates ranged from 474/100 000 (Afghanistan) to < 1/100 000 (63 countries); in 4 countries (Afghanistan, Burundi, Chad and Somalia) mortality rates of > 300/100 000 were recorded. [4]

Each year during the pre-vaccination area 1986–2000, > 2 million children worldwide were hospitalized for rotavirus infections. [5] In a recent report of sentinel hospital-based rotavirus surveillance from 35 nations representing each of the 6 WHO Regions and different economic levels, an average of 40% (range 34%–45%) of hospitalizations for diarrhoea among children aged < 5 years were attributable to rotavirus infection. [6] The universal occurrence of rotavirus infections even in settings with high standards of hygiene testifies to the high transmissibility of this virus.

PATHOGEN, DISEASE AND LABORATORY DIAGNOSIS

The pathogen

Rotaviruses are classified as a genus in the family of *Reoviridae*. The triple-layered viral particle encompasses a viral genome consisting of 11 segments of double-stranded RNA that encode 6 structural viral proteins (VPs) and 5 or 6 non-structural proteins (NSPs). Reassortment of the 11 gene segments may take place in coinfected host cells during the viral replication cycle. Formation of reassortants is in part responsible for the wide variety of rotavirus strains found in nature; even reassortants of animal-human strains have been identified. The outermost viral layer contains the viral proteins VP7 and VP4, which elicit the production of neutralizing antibodies in the host and hence are considered important for protective immunity. In human rotaviruses, at least 12 different VP7 antigens (G-types) and 15 different VP4 antigen (P-types) have been identified. As the combination of G- and P-types can vary independently, a binomial typing system is used to identify strains. Currently, 5 G-P combinations (G1P [8], G2P [4], G3P [8], G4P [8]) and G9P [8]) account for approximately 90% of all human rotavirus infections in many parts of the world; type G1P [8] is the most prevalent combination. However, data from countries in Asia and Africa show greater strain diversity with several rotavirus types circulating simultaneously. The prevalent types may vary from one season to the next, even within the same geographical area. The type of rotavirus does not usually correlate with the severity of the disease. There are currently no known laboratory markers for rotavirus virulence. [7, 8] During the first episode of rotavirus infection, rotaviruses are shed for several days in very high concentrations (> 10^{12} particles/gram) in the stools and vomitus of infected individuals. Transmission occurs primarily by the faecal-oral route directly from person to person, or indirectly via contaminated fomites.

World Health Organization, Geneva (Printed by «Weekly epidemiological record»)

Disease

Rotavirus infections affect primarily the mature enterocytes on the tips of the small intestinal villi. Destruction of these cells reduces the absorptive capacity of the villi, resulting in diarrhoea.

The clinical spectrum of rotavirus disease is wide, ranging from transient loose stools to severe diarrhoea and vomiting causing dehydration, electrolyte disturbances, shock and death. In typical cases, following an incubation period of 1–3 days, the onset of disease is abrupt, with fever and vomiting followed by explosive watery diarrhoea. Without adequate fluid replacement, dehydration may ensue. Detailed clinical scoring systems have been developed to facilitate comparison of disease severity, particularly in vaccine trials. Gastrointestinal symptoms normally disappear within 3–7 days, but may last for up to 2–3 weeks. Although in most cases, recovery is complete, fatalities due to RVGE may occur, mainly in children ⩽ 1 year of age. [2, 9, 10] No specific therapy is currently available against rotaviruses. As with other childhood diarrhoeas, the cornerstones of treatment are fluid replacement to prevent dehydration, and zinc treatment which decreases the severity and duration of diarrhoea. Solutions of lowosmolarity oral rehydration salts (ORS) are more effective in replacing fluids than previous ORS formulations. Additional treatment measures during the diarrhoeal episode include continued feeding, including breastfeeding, and if ORS are not available, use of appropriate fluids available in the home. [11]

Laboratory diagnosis

An etiological diagnosis of rotavirus gastroenteritis requires laboratory confirmation. A range of diagnostic tests are commercially available: enzyme immunoassays for detection of rotavirus antigen directly in stool specimens are widely used, as are also the less sensitive, but rapid and simple-to-use test strips and latex agglutination assays. Reverse transcription polymerase chain reaction (RT-PCR), which is highly sensitive in detecting small concentrations of rotavirus in stool specimens, is also used for strain identification and further differentiation. [8]

PROTECTIVE IMMUNITY

Protection against rotavirus infection is mediated by both humoral and cellular components of the immune system. Following the first infection, the serological response is directed mainly against the specific viral serotype (i. e. a homotypic response), whereas a broader, heterotypic antibody response is elicited following ⩾ 1 subsequent rotavirus infections. [12]

A study that monitored 200 Mexican infants from birth to 2 years of age by weekly home visits and stool collections, detected on the basis of the fecal excretion of virus or a serologic response a total of 316 rotavirus infections, of which 52% were first and 48% repeated infections. Children with 1, 2, or 3 previous infections had progressively lower risk of subsequent rotavirus infection (adjusted relative risk, 0.62, 0.40, and 0.34, respectively) or of diarrhoea (adjusted relative risk, 0.23, 0.17, and 0.08) than children who had no previous infections. Subsequent infections were significantly less severe than first infections (p = 0.02) and second infections were more likely to be caused by another G type (p = 0.05).10

However, one study from India reported that the risk of severe disease continued after several reinfections. [9] In immunocompromised patients, natural rotavirus infection is not regularly associated with severe diarrhea or systemic disease, although shedding of the virus may be prolonged. However, individuals with congenital immunodeficiency, bone marrow transplantation or solid organ transplantation sometimes experience severe, prolonged and even fatal RVGE. [13]

In South Africa, the estimated incidence of acute RVGE was 2.3 fold (95% confidence interval: 1.8–2.9) higher in HIV-infected than in non-infected individuals. [14]

A study in Malawi found no differences in rotavirus disease severity for hospitalized children with and without HIV infection, but of 29 HIV-infected and 45 HIV-uninfected children who completed at least 3 weeks of follow-up, 6 (21%) HIV-infected children shed rotavirus, compared with 2 (4%) HIV-uninfected children (relative risk 4.7 [95% CI: 1.0–21.5], p = 0.05). Shedding was not associated with diarrhoea. [15]

The immune correlates of protection against rotavirus infection are incompletely defined, but the immune responses to the VP4 and VP7 proteins are generally believed to be important. Serum anti-rotavirus IgA antibody responses have been used as a measure of immunogenicity of all the live attenuated rotavirus vaccines evaluated. [16]

ROTAVIRUS VACCINES

Currently available vaccines are live, oral, attenuated rotavirus strains of human and/or animal origin that replicate in the human intestine. Two oral rotavirus vaccines are marketed internationally: the monovalent (RV1) Rotarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium) and the pentavalent (RV5) RotaTeq® (Merck & Co. Inc., West Point, PA, USA). In this document the 2 vaccines are referred to as RV1 and RV5, respectively. *Lanzhou* lamb rotavirus vaccine, manufactured by the Lanzhou Institute of Biomedical Products in China, and Rotavin-M1, manufactured by Polyvac in Viet Nam, are not available internationally and hence not further discussed here. WHO guidelines to assure the quality, safety and efficacy of live attenuated rotavirus vaccines are available. [15]

The monovalent human rotavirus vaccine (lyophilized and liquid)

RV1 is a live, oral vaccine originating from a G1P [8] strain that was isolated from a case of infantile gastroenteritis. This strain has undergone multiple passages in tissue culture and the resulting attenuated vaccine strain, RIX4414, is propagated in *Vero* cells. First prepared as a lyophilized vaccine, a ready-to-use liquid formulation containing the same RIX4414 strain has subsequently been developed for 2 presentations: oral applicator and squeezable tube. The vaccine should be kept at 2–8°C, protected from light, and should not be frozen. The vaccine shelf-life is 3 years. Each dose contains a suspension of at least 106.0 — the median cell culture infective dose (CCID50) — of live, attenuated human G1P [8] rotavirus particles. The volume is 1 ml for the lyophilized formulation and 1.5 ml for the liquid formulation. The vaccine should be used immediately after reconstitution (for the lyophilized formulation) or after opening (for the liquid presentation). If not used immediately, reconstituted RV1 can be stored either refrigerated (2–8°C) or at ambient temperature < 25°C but should be given within 24 hours. The vaccine vials and oral applicator do not have vaccine vial monitors (VVM); the tube presentation has a VVM 14.

The 2 vaccine doses are administered at an interval of at least 4 weeks. According to the manufacturer, the first dose should be administered to infants ⩾ 6 weeks of age and the second dose prior to 24 weeks of age. [17,18] For WHO recommended schedules see WHO recommendations below.

The pentavalent human-bovine reassortant rotavirus vaccine

RV5 is an oral vaccine that contains 5 reassortant rotaviruses developed from human and bovine (WC3) parent rotavirus strains. Four WC3-based reassortants express one of the VP7 proteins G1, G2, G3 or G4 from the human strains and the VP4 protein P7 [5] from the bovine strain, whereas the fifth reassortant virus expresses the VP4 protein P1A [8] from a human strain and the G6 protein from the bovine parent strain. The reassortants are subsequently propagated in *Vero* cells using standard cell-culture techniques.

Each dose (2 ml) of the vaccine contains a minimum titre of approximately $2.0–2.8\times10^6$ infectious units per reassortant, and not greater than 116×10^6 infectious units per aggregate dose. The 5 reassortant strains are suspended in a solution of buffer and stabilizer that should be stored at 2–8°C. RV5 should not be frozen. Following removal from refrigeration, the vaccine should be used as soon as possible. The vaccine tubes do not have VVMs.

The manufacturer's recommended schedule prescribes 3 oral doses at ages 2, 4 and 6 months. The first dose should be administered between ages 6–12 weeks and subsequent doses at intervals of 4–10 weeks. The manufacturer recommends that all 3 doses should be administered by age 32 weeks. [19] For WHO recommended schedules see WHO recommendations below.

Efficacy and effectiveness of the rotavirus vaccine

A recent Cochrane review [20] shows that RV1 and RV5 are most efficacious against severe RVGE in subregions with very low or low child and adult mortality (WHO mortality strata A and B as defined below), [21] although the vaccines are also efficacious in subregions with high child mortality and high or very high adult mortality (WHO strata D and E). [20] Based on 11 RCTs of RV1 and 6 RCTs of RV5, this Cochrane review showed protection against severe RVGE after 1 and/or 2 years of follow up, ranging from approximately 80%–90% with modest waning over the period of observation in stratum A as compared to approximately 40%–60% efficacy over 2 years of follow up in stratum E.

However, since the incidence of severe rotavirus disease is significantly higher in high child mortality settings, the numbers of severe disease cases and deaths averted by vaccines in these settings are likely to be higher than in low mortality settings, despite the lower vaccine efficacy. [3, 22]

A descriptive review of observational studies mostly from high income and middle income countries, and a systematic review of observational and impact studies from industrialized countries have reported a substantial reduction in disease burden within a few years of vaccine implementation and also some evidence of herd protection in unvaccinated older children and adults. Data also suggest that rotavirus vaccination has delayed the onset and decreased the magnitude of the yearly seasons in several high income countries. [23, 24]

Observational studies in Mexico and Brazil after the introduction of RV1 reported a reduction in diarrhoearelated deaths in infants and young children. [25, 26]

In Mexico, the estimated decline in the rate of diarrhoearelated deaths was greatest among infants < 11 months of age (a relative reduction of 41% (95% CI: 36%–47%). There was also a relative reduction among children aged 1223 months (29%, 95% CI: 17%–39%) but no significant reduction was observed in children 24–59 months of age (7%, 95% CI: 14%–26%). [25] In Brazil, a study reported that compared to expected rates based on pre-vaccine era trends, rates for diarrhoea-related mortality were 22% (95% CI: 6%–44%) lower than expected. The largest reductions in deaths (22%–28%) were among children younger than 2 years, who had the highest rates of vaccination. In contrast, lower reductions in deaths (4%, 95% CI: 30%–29%) were noted among children 2–4 years of age, who were not ageeligible for vaccination during the study period. [26]

No randomized control trials (RCTs) have been conducted to specifically assess differences in all-cause mortality between different vaccine schedules or among studies in different WHO mortality strata. [20] Data from case-control studies show that RV1 and RV5 are more efficacious when the full course is given, but some protection may also be achieved following an incomplete vaccination series. For example, RV5 exhibits substantial effectiveness against RVGE before completion of the full 3 dose regimen. [20, 27]

The interchangeability of RV1 and RV5 has not been studied.

RV1 and RV5 have similar efficacy against severe RVGE in countries where a high diversity of strains co-circulate, suggesting an important role for heterotypic protective immunity. However, indirect evidence suggests that homotypic immunity also plays a role in protection against subsequent RV infection. Characterization of RV strains present in the environment post-vaccination is needed to exclude population-based selection of 'escape' strains due to long-term pressure exerted by homotypic immunity. [11]

Duration of protection

Published RCTs are not adequately powered to conclude definitively whether or not efficacy wanes for either RV1 or RV5. With RV5, RCTs that enrolled subjects from 11 countries, reported an efficacy against severe disease estimated at 98% (95% CI: 88%–100%) during the first rotavirus season and 88% (95% CI: 49%–99%) during the second season. 28 An extension of this trial demonstrated a sustained reduction in the number of hospitalizations for rotavirus disease also 3 years after vaccination. [29]

Reports from RCTs were consistent with little decrease in the efficacy of RV1 against severe rotavirus disease during the second season of follow-up, from 83% (95% CI: 67%–92%) to 79% (95% CI: 66%–87%) in Latin America 30 and from 96% (95% CI: 90%–99%) to 86% (95% CI: 76%–92%) in Europe.31 A RCT of RV1 conducted in 3 high income settings in Asia reported sustained efficacy against severe RVGE of 100% (95% CI: 67.5%–100%) during the third year of life.32 In contrast, a study of RV5 conducted in 3 countries in sub-Saharan Africa reported an estimated efficacy of 39.3% (95% CI: 19.1%–54.7%) against severe RVGE over the full follow-up period with an estimated 64.2% (95% CI: 40.2%–79.4%) during the first year after vaccination and 19.6% (95% CI: 15.7%–44.4%) in the second year after vaccination. [33] For RV1 in South Africa, results from the extended follow-up of a RCT are inconclusive given the lack of power in the extension study. [34] There is currently insufficient evidence to make a general recommendation on the need for a third dose of RV1 in the primary series. A RCT directly assessing vaccine efficacy against severe RVGE in South Africa and Malawi did not show statistically significant differences between 2 doses and 3 doses of RV1; 58.7%, (95% CI: 35.7%–74%) and 63.7%, (95% CI: 42.4%–77.8%), respectively. [35] However, in South African children, the efficacy of 2 or 3 doses of RV1 against severe RVGE over 2 consecutive rotavirus seasons was 32% ($p = 0.487$) and 85% ($p = 0.006$), respectively, as compared to the placebo group. [34] Similarly, although significant reduction of RVGE

of any severity was observed in the 2-dose group (49%; $p = 0.007$), the reduction was lower than that in the 3-dose group (68%; $p < 0.001$). Further adequately powered studies would be helpful to explore whether additional doses have a favourable risk/benefit ratio in high mortality settings and whether partial vaccination is also efficacious against severe rotavirus diarrhoea. [36]

Vaccine safety and precautions

In a recent review of efficacy and safety of the current rotavirus vaccines that included 41 trials with 186 263 participants, no differences were observed between the vaccine groups and the placebo groups in terms of events that required discontinuation of the vaccination schedule. 19 A RCT that enrolled a total of 100 HIV-positive infants aged 6–10 weeks in South Africa found that 3 doses of RV1 were tolerated well and elicited a satisfactory immune response without aggravating the immunologic or HIV condition. [37] Similarly, a RCT in Kenya showed no significant differences in serious or non-serious adverse events between the 88 HIV-exposed RV5 recipients versus the 89 HIV-exposed placebo recipients who were vaccinated at approximately 6, 10, and 14 weeks of age. [38] Simultaneous administration of RV1 or RV5 with other vaccines of the infant immunization programme, including combined diphtheria, tetanus toxoid and acellular pertussis vaccine (DTaP), inactivated poliovirus vaccine (IPV), *H. influenzae* type b conjugate (Hib), hepatitis B vaccine, and pneumococcal conjugate vaccine have been shown not to interfere significantly with the protective immune responses or safety profile of the respective vaccines. [39,40]. Although OPV may have an inhibitory effect on the immune response to the first dose of both rotavirus vaccines, this interference does not persist after administration of subsequent doses of rotavirus vaccines. [41]

Breastfeeding and prematurity (< 37 weeks' gestation) do not seem to significantly impair the response to the rotavirus vaccines. [20, 42] Contraindications for using rotavirus vaccines are severe hypersensitivity to any of their components and severe immunodeficiency including severe combined immunodeficiency (SCID). Vaccination should be postponed in case of ongoing acute gastroenteritis or fever with moderate to severe illness. These vaccines are not routinely recommended for infants with a history of intussusception or intestinal malformations possibly predisposing for intussusception.

In 2010, contamination of RV1 with full length DNA from porcine circovirus was reported and subsequently, low levels of DNA fragments of this virus were also detected in bulk lots of RV5. [43] Porcine circovirus is not known to infect or cause disease in humans. GACVS has concluded that given the extensive clinical data supporting the safety of both RV1 and RV5 and the benefits of rotavirus vaccination for children, the benefits of vaccination far outweigh any currently known risk associated with use of either rotavirus vaccine. [44]

The risk of intussusception

Post-licensure surveillance showed that the previously marketed rotavirus vaccine, RotaShield® (Wyeth-Lederle), carried an attributable risk of intussusception estimated at 1:10 000 recipients. [45] Intussusception, an intestinal invagination resulting in obstruction, is characterized clinically by intermittent severe abdominal pain, blood in the stools, a palpable lump in the abdomen, and vomiting. This serious and potentially fatal condition was associated primarily with the first of the 3 oral vaccine doses and the highest attributable risk was found in infants > 3 months of age. The pathogenic mechanisms involved in intussusception following rotavirus vaccination remain poorly defined.

RCTs conducted so far have lacked power to rule out very small relative risks of association between RV1 or RV5 and intussusception in narrow risk windows, for example the 1–7 day period after dose 1. [20, 46] However, no increased risk of intussusception was detected with either RV1 or RV5 in 2 RCTs, each of which including approximately 60 000–70 000 infants (30 000–35 000 received rotavirus vaccine) and designed to detect a risk similar to that seen with Rotashield®. [28, 47]

Using self-controlled case-series and case-control methods the potential association between RV1 and intussusception was investigated after routine immunization of infants in Mexico and Brazil. [48] The study included 615 case patients (285 in Mexico and 330 in Brazil) and 2050 controls. An increased risk of intussusception 1–7 days after the first dose of RV1 was identified among infants in Mexico using both the self-controlled case-series method (incidence ratio, 5.3; 95% CI: 3.0–9.3) and the case-control method (odds ratio, 5.8; 95% CI: 2.6–13.0). Among infants in Brazil no significant risk was found after the first dose, but an increased risk by a factor of 1.9 to 2.6 was seen 1–7 days after the second dose. A combined annual excess of 96 cases of intussusception in Mexico (approximately 1 per 51 000 infants) and in Brazil (approximately 1 per 68 000 infants) and of 5 deaths due to intussusception was attributable to RV1.

A prospective, active surveillance study for intussusception in infants following RV1 vaccination was performed in Mexico during the period 2008–2010. [49] The relative incidence of intussusception within 31 days of vaccination was 1.8 (95% CI: 1.2–2.5; $p = 0.001$) post dose 1 and 1.1 (95% CI: 0.8–1.5; $p = 0.8$) post-dose 2. The relative incidence of intussusception within 7 days of vaccination was 6.5 post-dose 1 (95% CI: 4. 2–10.1; $p < 0.001$) and 1.3 post-dose 2 (95% CI: 0.8–2.1; $p = 0.3$). The attributable risk of intussusception within 7 days of vaccine dose 1 was estimated at 3 to 4 additional cases of intussusception per 100 000 vaccinated infants.

In Australia, an excess of observed compared to expected cases of intussusception was reported for both RV1 and RV5 among children 1–3 months of age. With RV1, the relative risk was 3.5 (95% CI: 0.7–10.1) 1–7 days after the first dose and 1.5 (95% CI: 0.4–3.9) 1–21 days after the first dose. The corresponding figures for RV5 were 5.3 (95% CI: 1.1–15.4) and 3.5 (95% CI: 1.3–7.6). [46]

Two large cohort studies with active follow-up assessed the risk of intussusception following receipt of RV5 in the USA. In one US study, covering the period 2006– 2010, a total of 786 725 RV5 doses, including 309 844 first doses, were administered to infants 4–34 weeks of age. Comparing the incidence of intussusception between rotavirus vaccine recipients and similarly aged recipients of other infant vaccines, no statistically significant increased risk of intussusception with RV5 was observed for either comparison group following any dose in either the 1–7 day or 1–30 day risk window. [50] The other US study, which compared the risk of intussusception between 85 397 RV5 recipients and 62 820 DTaP recipients found 6 and 5 confirmed cases of intussusception, respectively, within 30 days following either dose. The relative risk of intussusception was 0.8 (95% CI: 0.2–3.5). [51]

Thus, in some but not all settings, post-marketing surveillance of both currently available rotavirus vaccines has detected a small increased risk of intussusception

(about 1–2/100 000 infants vaccinated) shortly after the first dose. Where present, this risk is 5–10 times lower than that observed with the previously licensed RotaShield®, and the benefits of rotavirus vaccination against severe diarrhoea and death from rotavirus infection far exceeds the risk of intussusception. [52] Administration of the first and last dose of RV1 and RV5 at different ages inside the recommended age window has not shown any impact on the incidence of serious adverse events including intuss usception. [53] No data are available on the possible risk of such events outside the recommended age window. There is limited information on the background rates of intussusception in settings of high mortality due to RVGE and no data on the risk of intussusception following rotavirus vaccination in such settings.

Optimizing immunization schedules

Ideally, vaccination schedules should be designed to provide benefits to those at highest risk of severe disease and death. Based on pooled data from studies of 38 populations, at least 3 of which are from each WHO Region, 1%, 3%, 6%, 8%, 10%, 22% and 32% of all RVGE events had occurred by age 6, 9, 13, 15 and 17, 26 and 32 weeks, respectively, although with substantial heterogeneity between populations. Mortality was limited to RVGE events before 32 weeks of age. [2] Although in many parts of the world there are relatively few admissions for RVGE before the scheduled first dose of the rotavirus vaccine (at the age 6–12 weeks), RVGE in very young children is more common in low income settings. Children in the poorest, typically rural, households with the highest risk of mortality seem to have the earliest exposure to rotavirus and the lowest level of vaccine protection. [2]

To maximize its impact, the rotavirus vaccine has to be given before RVGE occurs and before a sizeable proportion of the target population acquires natural infection. The impact of rotavirus vaccination depends on effectiveness, timeliness and coverage. In developing countries where natural infection occurs early, completion of the immunization schedule early in infancy is desirable, though programmatically challenging. [54]

Previously, WHO recommended that rotavirus immunization be initiated by 15 weeks of age when background intussusception rates are reportedly low. However, this policy could exclude a substantial number of children from vaccination, especially in low income countries where delays in vaccination are common. A model was used to predict the number of deaths prevented by rotavirus vaccination and the number of intussusception deaths caused by rotavirus vaccination when administered on the previously recommended, restricted schedule (initiate by 15 weeks and complete by 32 weeks) versus a schedule allowing vaccination up to 3 years of age. Countries were grouped by WHO child mortality strata and the inputs were stratum-specific estimates of rotavirus mortality, intussusception mortality, and predicted vaccination rates by week of age, and vaccine efficacy and vaccine-associated intussusception risk. [23]

The model estimated that a restricted schedule would prevent 155 800 rotavirus deaths (5th–95th centiles, 83 300–217 700) while causing 253 intussusception deaths (76–689). Vaccination without age restrictions would prevent 203 000 rotavirus deaths (102 000–281 500) while causing 547 intussusception deaths (237–1160). Thus, the model predicted that removing the age restrictions would avert an additional 47 200 rotavirus deaths (18 700–63 000) and cause an additional 294 (161–471) intussusception deaths for an incremental benefit-risk ratio of 154 deaths averted for every death caused by the vaccine. These additional deaths prevented under an unrestricted versus restricted schedule reflect additional 21%–28% children who would potentially be eligible for rotavirus vaccination. Thus, in low and middle income countries, the additional lives saved by removing age restrictions for rotavirus vaccination would by far outnumber the excess vaccine-associated intussusception deaths. [22]

Cost effectiveness of vaccination against rotavirus infection

Estimates of the annual cost per disability-adjusted life year (DALY) averted and of the proportion (%) of rotavirus deaths averted through introduction of rotavirus vaccines vary between US$ 8 and US$ 87, and 32% and 44%, for Afghanistan and Bangladesh, respectively. For India, the country with the highest number of recorded deaths due to RVGE, the corresponding figures were US$ 57 and 34%, whereas for the Democratic Republic of Congo, Ethiopia, and Nigeria these figures varied between US$ 19–27 and 28–31%. The estimates are based on the expected introduction of rotavirus vaccination into the respective national immunization programmes within the next few years (2012–2018) and on forecasts of the vaccination coverage that can then be expected for a first dose administered before the age of 15 weeks and a second dose by age 32 weeks.

Recent cost-effectiveness modeling in Kenya predicted that cumulated over the first 5 years of life, the estimated prevented costs totaled US$ 1 782 761 (direct and indirect costs) with an associated 48 585 DALYs saved. Irrespective of the vaccine used, vaccination against rotavirus disease was found to be cost effective. [55]

A generic approach to the development of cost-effectiveness models for rotavirus vaccines in national immunization programmes has been proposed. [56]

WHO RECOMMENDATIONS

Rotavirus vaccines should be included in all national immunization programmes and considered a priority, particularly in countries with high RVGE-associated fatality rates, such as in south and south-eastern Asia and sub-Saharan Africa.

The use of rotavirus vaccines should be part of a comprehensive strategy to control diarrhoeal diseases with the scaling up of both prevention (promotion of early and exclusive breastfeeding, handwashing, improved water supply and sanitation) and treatment packages. WHO/UNICEF recommend that all children receive solutions of low-osmolarity ORS to prevent and treat dehydration due to diarrhoea. Breast milk is also an excellent rehydration fluid and should be given to children still breastfeeding along with ORS. In addition to fluid replacement, children with diarrhoea should continue to be fed during the episode. Food intake supports fluid absorption from the gut into the bloodstream to prevent dehydration and helps maintain nutritional status and ability to fight infection. Children should also simultaneously receive zinc treatment which reduces the duration and severity of diarrhoea episodes, stool volume and the need for advanced medical care. [57, 58]

Plans for introduction of rotavirus vaccines should consider the epidemiology of the disease by age, the coverage and actual age at vaccination and an evaluation of the estimated public health impact and potential risks. In addition, cost-effectiveness assessment, issues of affordability of the vaccine, financial and operational impact on the immunization delivery system, and careful examination

of current immunization practices should be taken into account.

Introduction of rotavirus vaccine should be accompanied by measures to ensure high vaccination coverage and timely administration of each dose.

Following a review of new evidence on age-specific burden of rotavirus disease and deaths, timeliness of vaccination, and the safety and effectiveness of different immunization schedules, WHO continues to recommend that the first dose of rotavirus vaccine be administered as soon as possible after 6 weeks of age, along with diphtheria-tetanus-pertussis (DTP) vaccination, to ensure induction of protection prior to natural rotavirus infection. Although early immunization is still favoured, the manufacturers' conventional age restrictions on the first and last dose of rotavirus vaccines may have prevented vaccination of many vulnerable children in settings where the DTP doses are given late (i. e. after 15 weeks for DTP1 or after 32 weeks for DTP 2 or DTP3). By allowing infants to receive rotavirus vaccine together with DTP regardless of the time of vaccination, immunization programmes will be able to reach children who were previously excluded from the benefits of rotavirus vaccines. Because of the typical age distribution of RVGE, rotavirus vaccination of children > 24 months of age is not recommended.

RV1 should be administered orally in a 2-dose schedule at the time of DPT1 and DPT2 with and interval of at least 4 weeks between doses. RV5 should be administered orally in a 3-dose schedule at the time of the DTP1, DTP2, and DTP3 contacts, with an interval of at least 4 weeks between doses. With both vaccines, prematurely born infants should follow the vaccination schedules recommended for their chronological age.

Rotavirus vaccinations can be administered simultaneously with other vaccines in the infant immunization programme. Apart from a low risk of intussusception (about 1–2 per 100 000 infants vaccinated) the current rotavirus vaccines are considered safe and well tolerated.

Proper planning and training of staff to conduct pharmacovigilance should take place before the vaccine is introduced. Countries should develop a strategy to inform relevant health staff that although the benefits outweigh the risks, a small potential risk of intussusception after rotavirus vaccination remains. Countries should also ensure that caregivers are adequately counseled to recognize danger signs of dehydration or intussusception that should prompt immediate medical consultation. Given the background rate of natural intussusception and the large number of children included in national immunization programmes, intussusception cases are expected to occur by chance alone following rotavirus vaccination. It is important to establish the baseline incidence of intussusception at sentinel sites and to use epidemiological studies, such as the self-controlled case series method, to assess the safety of rotavirus vaccines. [59] Severe allergic reaction (e. g. anaphylaxis) after a previous dose, and severe immunode ficiency including severe combined immunodeficiency, are contraindications for rotavirus vaccination. Precautions are necessary if there is a history of intussusception or intestinal malformations, chronic gastrointestinal disease, and severe acute illness.

Vaccination should be postponed in case of ongoing acute gastroenteritis or fever with moderate to severe illness. The epidemiological impact of rotavirus vaccination should be monitored. High-quality surveillance should be conducted in selected countries and defined populations, including high child mortality settings. However, lack of population-based surveillance should not be an impediment to the introduction of rotavirus vaccine.

REFERENCES

1. See http://www.who.int/immunization/sage/en
2. Sanderson C. et al. Global review of rotavirus morbidity and mortality data by age and WHO region. Report to WHO/IVB, 2011 (www.who.int/entity/immunization/sage/meetings/2012/april/presentations_background_docs/en/ — 45k).
3. Detailed review paper on rotavirus vaccines (presented to the WHO Strategic Advisory Group of Experts (SAGE) on Immunization in April 2009). *Geneva, World Health Organization*. 2009. Available from (http://www.who.int/immunization/sage/3_Detailed_Review_Paper_on_Rota_Vaccines_17_3_2009.pdf).
4. WHO estimate for January 2012: http://www.who.int/immunization_monitoring/burden/rotavirus_estimates/en/index.html
5. Parashar D.U. et al. Global illness and deaths caused by rotavirus disease in children. *Emerging Infectious Diseases*, 2003, 9: 565–572.
6. *Weekly Epidemiological Record*. 2008; 47: 421–425. URL: http://www.who.int/wer
7. Hu L. et al. Rotavirus non-structural proteins: structure and function. *Current Opinion in Virology*. 2012, 2: 380–388.
8. Manual of rotavirus detection and characterization methods (WHO/IVB/08.17). *Geneva, World Health Organization*. 2009. Available from http://www.who.int/nuvi/rotavirus/WHO_IVB_08.17_eng.pdf, accessed January 2013.
9. Gladstone B.P. et al. Protective effect of natural rotavirus infection in an Indian birth cohort. *New England Journal of Medicine*, 2011, 365: 337–346.
10. Velazquez F.R., Matson D.O., Calva J.J. et al. Rotavirus infection in infants as protection against subsequent infections. *New England Journal of Medicine*, 1996, 335: 1022–1028.
11. Oral rehydration salts. Production of the new ORS (WHO/FCH/CAH/06.1). *Geneva, WHO/UNICEF*. 2006. Available from http://whqlibdoc.who.int/hq/2006/WHO_FCH_CAH_06.1.pdf, accessed January 2013.
12. Angel J. et al. Rotavirus immune responses and correlates of protection. *Current Opinion in Virology*. 2012. P. 419–425.
13. Clark H.F. et al. Rotavirus vaccines. In: Plotkin S., Orenstein W., Offit P., eds. *Vaccines, 6 th ed. Elsevier Saunders*. 2013. P. 669–687.
14. Groome M.J. et al. Five-year cohort study on the burden of hospitalisation for acute diarrhoeal disease in African HIV-infected and HIV-uninfected children: potential benefits of rotavirus vaccine. *Vaccine*. 2012; 30 (Suppl. 1): A173–178.
15. Cunliffe N.A. et al. Effect of concomitant HIV infection on presentation and outcome of rotavirus gastroenteritis in Malawian children. *Lancet*. 2001; 358 (9281): 550–555.
16. Guidelines to assure the quality, safety and efficacy of live attenuated rotavirus vaccine Annex 3). *Geneva, World Health Organization*. 2007. WHO Technical report series 941.
Available from http://www.who.int/entity/biologicals/publications/trs/areas/vaccines/rotavirus/Annex %203 %20rotavirus %20vaccines.pdf, accessed January 2013.
17. See http://www.who.int/entity/immunization_standards/vaccine_quality/Rotarix_ liquid_tube_product_insert_text_2009.pdf
18. See http://www.who.int/entity/immunization_standards/vaccine_quality/Rotarix liquid_oral_applicator_product_insert_text_2009.pdf
19. See http://www.who.int/entity/immunization_standards/vaccine_quality/RotaTeq_ Product_Insert.pdf and http://www.merck.com/product/usa/pi_circulars/r/rotateq/rotateq_pi.pdf
20. Soares-Weiser K. et al. Vaccines for preventing rotavirus diarrhoea: vaccines in use. *Cochrane Database Systematic Review*. 2012; 11: CD008521.

21. To aid in cause of death and burden of disease analyses, WHO subregions are stratified (A through E) based on levels of child and adult mortality: Stratum A., very low child and very low adult mortality; Stratum B., low child and low adult mortality; Stratum C., low child and high adult mortality; Stratum D., high child and high adult mortality; Stratum E., high child and very high adult mortality. The 9 low- and middle-income subregions included in the model are: African Region: D and E; Region of the Americas: B and D; South-East Asia Region: B and D, Eastern Mediterranean Region: B and D, and Western Pacific Region: B. Please consult the List of Member States by WHO region and mortality stratum available at www.who.int/entity/whr/2003/en/member_states_182–184_en.pdf, accessed January 2013.
22. Grading of scientific evidence — Tables 1–4: Does RV1 and RV5 induce protection against rotavirus morbidity and mortality in young children both in low and high mortality settings? Available from http://www.who.int/immunization/position_papers/rotavirus_grad_rv1_rv5_protection
23. Patel M.M. et al. Removing the Age Restrictions for Rotavirus Vaccination: A Benefit-Risk Modeling Analysis. *PLoS Medicine*. 2012; 9: e1001330.
24. Giaquinto C. et al. Summary of effectiveness and impact of rotavirus vaccination with the oral pentavalent rotavirus vaccine: a systematic review of the experience in industrialized countries. *Human Vaccines*. 2011; 7: 734–748.
25. Richardson V. et al. Effect of rotavirus vaccination on death from childhood diarrhea in Mexico. *New England Journal of Medicine*. 2010; 362: 299–305.
26. do Carmo G.M. et al. Decline in diarrhoea mortality and admissions after routine childhood rotavirus immunization in Brazil: a time-series analysis. *PLoS Medicine*. 2011; 8: e1001024
27. Wang F.T. et al. Effectiveness of an Incomplete RotaTeq® (RV5) Vaccination Regimen in Preventing Rotavirus Gastroenteritis in the United States. *The Pediatric Infectious Disease Journal*. 2012. [Epub ahead of print].
28. Vesikari T. et al. Safety and efficacy of pentavalent human-bovine (WC3) reassortant rotavirus vaccine in preventing rotavirus gastroenteritis and reducing associated health care resource utilization. *The New England Journal of Medicine*. 2006; 354: 23–33.
29. Vesikari T. et al. Efficacy of the pentavalent rotavirus vaccine, RotaTeq®, in Finnish infants up to 3 years of age: the Finnish Extension Study. *European Journal of Pediatrics*. 2010; 169: 1379–1386.
30. Linhares A.C. et al. Efficacy and safety of an oral live attenuated human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in Latin American infants: a randomised, double-blind, placebo-controlled phase III study. *Lancet*. 2008; 371: 1181–1189.
31. Vesikari T. et al. Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study. *Lancet*. 2007; 24 (370): 1757–1763.
32. Phua K.B. et al. Rotavirus vaccine RIX4414 efficacy sustained during the third year of life: a randomized clinical trial in an Asian population. *Vaccine*. 2012; 30: 4552–4557.
33. Armah G.E. et al. Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in sub-Saharan Africa: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2010; 376:606–614.
34. Madhi S.A. et al. Efficacy and immunogenicity of 2 or 3 dose rotavirus-vaccine regimen in South African children over two consecutive rotavirus-seasons: a randomized, double-blind, placebo-controlled trial. *Vaccine*. 2012; 30 (Suppl. 1): A44–51.
35. Madhi S.A. et al. Effect of human rotavirus vaccine on severe diarrhoea in African infants. *New England Journal of Medicine*. 2010; 362: 289–298.
36. Grading of scientific evidence — Tables 5–6: Is giving a third dose of RV1 superior to the currently recommended 2-dose schedule? (Table 5); Is partial vaccination also efficacious against severe rotavirus diarrhoea? (Table 6).
Available from http://www.who.int/immunization/position_papers/rotavirus_grad_rv1_3rd_dose
37. Steele A.D. et al. Safety, reactogenicity, and immunogenicity of human rotavirus vaccine RIX4414 in human immunodeficiency virus-positive infants in South Africa. *Pediatric Infectious Disease Journal*. 2011; 30: 125–130.
38. Laserson K.F. et al. Safety of the pentavalent rotavirus vaccine (PRV), RotaTeq (®), in Kenya, including among HIV-infected and HIV-exposed infants. *Vaccine*. 2012; 30 Suppl 1: A61–70.
39. See http://us.gsk.com/products/assets/us_rotarix.pdf
40. See http://www.merck.com/product/usa/pi_circulars/r/rotateq/rotateq_pi.pdf
41. Soares-Weiser K. et al. Rotavirus vaccine schedules: a systematic review of safety and efficacy from RCTs and observational studies of childhood schedules using RV1 and RV5 vaccines. Report to WHO/Initiative for Vaccine Research, 2012. Available from http://www.who.int/immunization/sage/meetings/2012/april/Soares_K_et_al._SAGE_April_rotavirus.pdf, accessed January 2013.
42. Goveia M.G. et al. Efficacy of pentavalent human-bovine (WC3) reassortant rotavirus vaccine based on breastfeeding frequency. *The Pediatric Infectious Disease Journal*. 2008; 27: 656–658.
43. McClenahan S.D. et al. Molecular and infectivity studies of porcine circovirus in vaccines. *Vaccine*. 2011; 29: 4745–4753.
44. Global illness and deaths caused by rotavirus disease in children. *Emerging Infectious Diseases*. 2010; 30: 285–292.
45. Acute intussusception in infants and young children (WHO/V&B/.02.19). *Geneva, World Health Organization*. 2002. Available at http://www.who.int/vaccinesdocuments/DocsPDF06/www640.pdf, accessed January 2013.
46. Buttery J.P. et al. Intussusception following rotavirus vaccine administration: postmarketing surveillance in the National Immunization Program in Australia. *Vaccine*. 2011; 29: 3061–3066.
47. Ruiz-Palacios G.M. et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *New England Journal of Medicine*. 2006; 354: 11–22.
48. Patel M.M. et al. Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. *New England Journal of Medicine*. 2011; 364: 2283–2292.
49. Velazquez F.R. et al. Postmarketing Surveillance of Intussusception Following Mass Introduction of the monovalent human Rotavirus Vaccine in Mexico_(UGG)_(EPI PLAN). *The Pediatric Infectious Disease Journal*. 2012; 31: 736–744.
50. Shui I.M. et al. Risk of intussusception following administration of a pentavalent rotavirus vaccine in US infants. *JAMA: the Journal of the American Medical Association*. 2012; 307: 598–604.
51. Loughlin J. et al. Postmarketing evaluation of the short-term safety of the pentavalent rotavirus vaccine. *The Pediatric Infectious Disease Journal*. 2012; 31: 292–296.
52. *Weekly Epidemiological Record*. 2012; 6: 53–60. URL: http://www.who.int/wer
53. Grade table 7: Is it safe to administer the first dose of vaccine at different ages? Available from http://www.who.int/immunization/position_papers/rotavirus_grad_safe_first_dose_ages
54. Cherian T. et al. Rotavirus vaccines in developing countries: the potential impact, implementation challenges, and remaining questions. *Vaccine*. 2012; 30 (Suppl. 1): A3–6.
55. van Hoek A.J. et al. (2012) A cost effectiveness and capacity analysis for the introduction of universal rotavirus vaccination in Kenya: Comparison between Rotarix and RotaTeq Vaccines. *PLoS ONE*. 2012; 7: e47511.
56. Postma M.J. et al. Comparative review of 3 cost-effectiveness models for rotavirus vaccines in national immunization programs; a generic approach applied to various regions in the world. *BMC Medicine*. 2011; 9: 84.
57. Diarrhoea: why children are still dying and what can be done. *Geneva, WHO/UNICEF*. 2009. Available from http://www.who.int/maternal_child_adolescent/documents/9789241598415/en/index.html, accessed January 2013.
58. Pneumonia and diarrhoea: tackling the deadliest diseases for the world's poorest children. *New York, UNICEF*. 2012. Available from http://www.unicef.org/media/files/UNICEF_P_D_complete_0604.pdf, accessed January 2013.
59. *Weekly Epidemiological Record*. 2011; 8: 61–72. URL: http://www.who.int/wer