Rotavirus vaccines. WHO position paper November 2012.

Summary
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Epidemiology

• Rotaviruses (RVs) are highly contagious and globally the leading cause of severe, dehydrating diarrhoea in young children
• Nearly every child has been RV-infected by age 3-5 years
• The majority of severe rotavirus gastroenteritis (RVGE) occurs in low-income countries and affect infants <1 year old
• In 2008, approximately 453 000 RVGE-associated child deaths occurred world-wide (WHO estimate)
• In low income countries, the RV-epidemiology is characterized by episodes of intense viral transmission against a background of year-round RV-circulation
• In high income countries of temperate climate, a distinct winter seasonality is typically observed.
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Virology

• RVs belong to the *Reoviridae* family. The RV-genome consists of 11 segments of double stranded RNA and encodes 6 structural viral proteins (VPs) and 6 non-structural proteins (NSPs) Reassortments between the RNA segments occur frequently

• The outer viral layer contains the proteins VP7 and VP4 which elicit production of neutralizing antibodies. In human rotaviruses, there are at least 12 different VP7 antigens (G-types) and 15 different VP4 antigen (P-types)

• A binomial typing system is used: 5 G-P combinations (G1P[8], G2P[4], G3P[8], G4P[8]) and G9P[8]) account for approximately 90% of all human rotavirus infections
Clinical aspects

• RVs damage the enterocyte lining of the small intestinal villi resulting in reduced absorptive capacity and diarrhoea

• The wide clinical spectrum of rotavirus disease ranges from transient loose stools to severe diarrhoea and vomiting causing dehydration, electrolyte disturbances, shock and in untreated cases, death

• The cornerstones of treatment of severe RVGE are fluid replacement and zinc supplementation.

• An etiological diagnosis of rotavirus gastroenteritis requires laboratory confirmation
Rotavirus vaccines (a)

- Currently available vaccines are based on live, oral, attenuated RV strains of human and/or animal origin that replicate in the human gut.
- Two RV vaccines are marketed internationally: the monovalent (RV1) Rotarix™ (GlaxoSmithKline Biologicals, Rixensart, Belgium) and the pentavalent (RV5) RotaTeq™ (Merck & Co. Inc., West Point, PA, USA).
- RV1 originates from a human G1P[8] strain, whereas RV5 contains 5 reassortants developed from human and bovine parent rotavirus strains.
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Rotavirus vaccines (b)

- RV1 and RV5 show 80%-90% efficacy against severe RVGE in countries with very low or low child and adult mortality, and 40% - 60% efficacy in countries with high child mortality and high or very high adult mortality
- In industrialized countries, a substantial reduction in RVGE was observed within a few years of vaccine implementation
- In Mexico and Brazil, vaccination resulted in 22%–28% reduction in diarrhea related deaths in children aged ≤ 2 years
- In most cases, vaccination in infancy provides protection against severe RVGE for at least 2 years (the period of highest risk)
- Breastfeeding and prematurity (<37 weeks’ gestation) do not significantly impair the response to the rotavirus vaccines
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Rotavirus vaccines (c)

• In large controlled studies, no differences were observed between the vaccine groups and the placebo groups in terms of serious adverse events
• In some, but not all settings, post-marketing surveillance of these vaccines has detected a small increase in the risk of intussusception (~1–2/100 000 infants vaccinated) shortly after the first dose
• The benefits of the protection these vaccines provide against severe RV diarrhoea and death far exceed the risk of intussusception
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WHO recommendations (a)

• 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 and should include, among other interventions, breast-feeding, improvements in hygiene and sanitation, zinc supplementation, community-based administration of oral rehydration solution, and overall improvements in case management.
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WHO recommendations (b)

• 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 by the recommended age
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WHO recommendations (c)

Following a review of new evidence on the 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 vaccination against diphtheria-tetanus-pertussis (DTP), to ensure induction of protection prior to natural rotavirus infection.
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WHO recommendations (d)

• Although early immunization is still favoured, 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 recommended time of DTP vaccination in the existing national schedules, 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
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WHO recommendations (e)
immunization schedules

• RV1 should be administered orally in a 2-dose schedule at the time of DPT1 and DPT2 with an 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 of the infant immunization programme
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WHO recommendations (f)

intussusception

• 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

• 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
Proper planning and training of staff to conduct pharmacovigilance should take place before the vaccine is introduced.

Given the background rate of natural intussusception and the large number of children involved 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–control case-series, to assess the safety of rotavirus vaccines.
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WHO recommendations (h)

• Severe allergic reaction (e.g. anaphylaxis) after a previous dose and severe immunodeficiency including combined immunodeficiency (SCID) are contraindications for rotavirus vaccines, whereas precautions for their use include 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 rotavirus vaccine introduction