World Health Organization
Global Vaccine Safety
Essential Medicines & Health Products
20, Avenue Appia, CH-1211 Geneva 27
Switzerland

INFORMATION SHEET
OBSERVED RATE OF VACCINE REACTIONS
ROTAVIRUS VACCINE

April 2014

The Vaccines

Rotaviruses are non-enveloped RNA viruses which are classified according to 2 surface proteins contained on the outer layer of the viral capsid - the VP7 (glycoprotein or G protein) and the VP4 (protease cleaved protein or P protein). The rotavirus strains are commonly referred to by their G type with G1, G2, G3, G4, and G9 accounting for 90% of virus types globally. Among P types found with these G types P[4], P[6], and P[8] are most prevalent [Kobayashi 2007].

A number of rotaviral vaccines have been developed that vary depending on the source of the virus and the virus types used. The currently prequalified oral rotaviral vaccines are live attenuated and include: Rotarix (GSK – referred to as RV1) an attenuated human virus of the G1P[8] strain which protects against non G1 serotypes on the basis of their common P[8] antigen; and RotaTeq (Merck – referred to as RV5) a pentavalent product with reassortant virus from human and bovine origin that express human serotypes G1, G2, G3, G4, and P[8].

Type of vaccines

Route	Vaccine antigens	Excipients
Oral	Rotarix (GSK) Attenuated human strain R1X4414 of G1P[8] strain	Sucrose, dextran 40, sorbitol, amino acids, Dulbecco's modified eagle medium, calcium carbonate, xanthum gum. Calcium carbonate buffer as diluent.
	Rotateq (CSL/Merck) Pentavalent rotavirus reassortant with human G1, G2, G3, G4 and P[8]	Sucrose, sodium citrate, sodium phosphate, sodium hydroxide, polysorbate 80, cell culture media, trace amounts of fetal bovine serum.

Adverse events

Mild adverse events

A recent review of 31 RV1 and 12 RV5 studies examined occurrence of fever, diarrhoea and vomiting at several time points: after the first, second, third doses, and at the end of follow-up period. There were no differences between the vaccines and placebo for each of these outcomes and time points (Soares-Weiser et al. 2012).

Severe adverse events

Because of the prior experience with the rhesus-human reassortant rotavius vaccine (Rotashield) the pre-licensure clinical trials for the RV1 and RV5 were powered to exclude a similar incidence of intussusception. Hence, subsequent phase III clinical trials of alternate candidate rotaviral vaccines were designed to include over 60,000 vaccinated infants, in order to be able to better assess the risk of intussusception. Prior to licensure no association was identified between receipt of either of these candidate vaccines and the development of intussusception (Ruiz-Palacios et al. 2006; Vesikari et al. 2006).

Post-licensure surveillance studies of both vaccines in some settings identified a small increased risk of intussusception shortly after the first dose is administered (Patel et al. 2011; Buttery JP et al. 2011). Post-licensure surveillance indicates the possibility of an increased risk of intussusception shortly after the first dose of rotavirus vaccine in some populations. In Mexico, within 1–7 days after administration of the first dose of rotavirus vaccine, the rate of intussusception was elevated about 5-6 fold, corresponding to a risk of about 1–2 additional hospitalizations for intussusception per 100 000 infants vaccinated. In Australia, studies found a temporal increase in intussusception with both rotavirus vaccines during the first week after vaccination, although these findings were based on relatively few cases. In the United States, data from both the CDC and from an evaluation sponsored by Merck & Co., Inc., did not show evidence of an increased risk of intussusception with RotaTeq; however, the population of children under active surveillance in the United States who have received RotaTeq is not yet large enough to rule out the level of risk during the first week after vaccination that has been suggested for Rotarix in Mexico and with both vaccines in Australia. Recent surveillance of RV5 in the United States did not demonstrate an increased risk (Shui et al. 2012).

If the findings in Mexico, Brazil and Australia are confirmed, the level of risk observed in these studies is substantially lower than the risk of 1 case/5000–10 000 in infants who received the Rotashield vaccine, and the benefits from hospitalizations and deaths prevented by vaccination greatly exceed these risks.

With regard to other serious adverse events the recent Cochrane review did not identify any differences in the numbers of deaths or serious adverse events in vaccinated groups compared with placebo groups (Soares-Weiser et al. 2012).

Other safety issues

Intussusception with rhesus-human reassortant rotavius vaccine (Rotashield) - The first oral rotavirus vaccine was licensed in the United States of America was the rhesus-human reassortant tetravalent vaccine (Rotashield, RRV-TV: Wyeth Lederle Vaccines). Pre-licensure trials demonstrated a possible association between vaccination and intussusception but because of the limited number of subjects included these trials no statistical association was established (Rennels et al. 1998). Following widespread use of the vaccine a number of cases of intussusception were reported to the Vaccine Adverse Events Reporting System (VAERS) eventually leading to a suspension of vaccination. Subsequent studies demonstrated a causal relationship between vaccination and intussusception. Statistical significance was demonstrated for between 3 to 14 days following vaccination with the first dose of the vaccine (odds ratio 21.7) (Murphy et al. 2001). The estimated incidence of intussusception following the Rotashield vaccine is thought to be 1 per 2,500-9,500 vaccinees, with the range depending on a number of factors which include the methods used to analyse the adverse event data, case definitions and the estimated baseline rates of intussusception (Murphy et al. 2003). Importantly, no cases occurred in infants less than 2 months of age although 16% of all first doses were given at this age (Simonsen et al. 2005). In the United States, intussusception rates vary markedly by age in the first year of life, with the lowest rates under 9 weeks of age, peaking at 62 per 100,000 infants among those 26 to 29 weeks of age, and then decreasing to 26 per 100,000 infants by 52 weeks of age (Tate JE et al, Pediatrics 2008).

Age of vaccine administration -Because of the difference in background rate, if there is an increase in relative risk, more cases of intussusception would result among older infants than younger infants, even if the relative risk is the same. This has led to the current product labelling to administer the last scheduled dose of rotaviral vaccines prior to an upper age limit. This upper age limit recommended by manufacturers varies according to type of vaccine used (For Rotarix the 2nd dose should be administered by the 25th week of age and for RotaTeq the third dose should be administered by the 33rd week of age). WHO, based on the advice from the Strategic Group of Experts (SAGE), recommends that the first dose of either RotaTeq or Rotarix be administered at age 6–15 weeks. The maximum age for administering the last dose of either vaccine should be 32 weeks (WHO 2009). There are no safety data of administration of the vaccine beyond this recommended age group and specifically if administering the vaccine beyond this age is associated with an increased risk of intussusception.

Route of vaccine administration - The vaccine should not be injected.

Use in infants in households with pregnant women – there is no contraindication to the vaccine being administered to infants who share households with pregnant women.

Use in the immunocompromised – Limited evidence is available to date about vaccination in immunocompromised infants (acquired or primary). In one study, rates of adverse events in children infected with HIV were not increased compared with non-HIV-infected infants. Children with severe combined immunodeficiency syndrome (an uncommon condition affecting about 1 in 100000 infants) who have been vaccinated have demonstrated prolonged shedding of the live attenuated vaccine virus strains (Patel et al 2009). However, the benefit and risks of vaccination require additional assessment.

Use in preterm infants - Premature infants can be immunised at their chronological age. In one study of 2070 preterm infants (gestation median 34 weeks, range 25-36) there was no increase in adverse events in the vaccinated group (Goveia et al. 2007; Van den Wielen et al. 2008).

Use after blood transfusion – Ideally vaccination should not occur within 42 days of the administration of an antibody-containing blood product. However, if this would then preclude administration of the last dose of the vaccine then the vaccine should be given (American Academy of Pediatrics Committee on Infectious Diseases 2007).

Past history of intussusception – There is no information on the risk of vaccinating infants who have a past history of intussusception.

Kawasaki disease – Kawasaki disease following receipt of both vaccines a pre-licensure vaccine trial has been described in a small number of infants. However, it is unclear whether the rates observed among vaccinated infants are higher than expected in the normal population. Further studies are needed to investigate this potential association and given the current evidence a casual association is not thought to be likely (WHO 2008; Soares-Weiser et al. 2012).

Summary of mild and severe adverse events

Nature of adverse event	Description	Rate/doses
Mild	None identified to date	
Severe	Intussusception	Attributable risk 1-2 cases per 100,000 first dose in some populations. No apparent increase identified with subsequent doses

References

American Academy of Pediatrics Committee on Infectious Diseases. Prevention of rotavirus disease: guidelines for use of rotavirus vaccine. Pediatrics. 2007 Jan;119(1):171-82.

Buttery JP, Danchin MH, Lee KJ, et al. Intussusception following rotavirus vaccine administration: post-marketing surveillance in the National Immunization Program in Australia. Vaccine 2011;29:3061-66.

Goveia MG, Rodriguez ZM, Dallas MJ, Itzler RF, Boslego JW, Heaton PM, DiNubile MJ; REST Study Team. Safety and efficacy of the pentavalent human-bovine (WC3) reassortant rotavirus vaccine in healthy premature infants. Pediatr Infect Dis J. 2007 Dec;26(12):1099-104.

Kobayashi N, Ishino M, Wang YH, Chawla-Sarkar M, Krishnan T, Naik TN. Diversity of G-type and P-type of human and animal rotaviruses and its genetic background. In: Mendez-Vilaz A and Diaz J, eds. Modern Reseach and educational topics in microscopy. Formatex. 2007, 847-858.

Murphy, B. R., D. M. Morens, et al. Reappraisal of the association of intussusception with the licensed live rotavirus vaccine challenges initial conclusions." J Infect Dis 2003 187(8): 1301-8.

Murphy, T. V., P. M. Gargiullo, et al. Intussusception among infants given an oral rotavirus vaccine." N Engl J Med 2001 344(8): 564-72.

Patel MM, López-Collada VR, Bulhões MM, et al. Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. N Engl J Med. 2011;364:2283-92.

Rennels, M. B., U. D. Parashar, et al. Lack of an apparent association between intussusception and wild or vaccine rotavirus infection. Pediatr Infect Dis J 1998 17(10): 924-5.

Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. New England Journal of Medicine 2006;354:11-22.

Shui IM, Baggs J, Patel M, et al. Risk of intussusception following administration of a pentavalent rotavirus vaccine in US infants. JAMA 2012;307:598-604.

Soares-Weiser K, Maclehose H, Bergman H, Ben-Aharon I, Nagpal S, Goldberg E, Pitan F, Cunliffe N. Vaccines for preventing rotavirus diarrhoea: vaccines in use. Cochrane Database Syst Rev. 2012.

Simonsen L, Viboud C, Elixhauser A, et al. More on RotaShield and intussusception: the role of age at the time of vaccination. J Infect Dis 2005 192 Suppl 1: S36-43.

Van der Wielen M, Van Damme P. Pentavalent human-bovine (WC3) reassortant rotavirus vaccine in special populations: a review of data from the Rotavirus Efficacy and Safety Trial. Eur J Clin Microbiol Infect Dis. 2008l;27:495-501.

Vesikari T, Matson DO, Dennehy P, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. New England Journal of Medicine 2006;354:23-33.

WHO. Global Advisory Committee on Vaccine Safety, 12–13 December 2007.Weekly Epidemiological Record 2008;83:37-44.
WHO. Rotavirus vaccines: an update. Weekly Epidemiological Record 2009;84:533-7.

Patel NC, et al. Vaccine-acquired Rotavirus infection in two infants with severe combined immunodeficiency: late breaking abstracts. J Allergy Clin Immunol 2009.

This information sheet has been developed in close collaboration with the Global Advisory Committee on Vaccine Safety (GACVS). GACVS experts are independent and have declared no interests related to the expertise displayed in this product. Information displayed has been developed using primary sources such (Plotkin et al 2008, Institute of Medicine of the National Academies 2011) and from data derived from a literature search on Pubmed in 2008 using key words “vaccine antigen”, “Safety” and “adverse events”. An independent expert provided a first draft which was reviewed by nominated experts and the GACVS. Data of different vaccines that may be found in this product should only be compared if there is indication that a comparative randomised controlled trial has been undertaken. The information sheets will be updated as new information may become available at the following web link:
http://www.who.int/vaccine_safety/vaccrates/en/index.html

World Health Organization

Essential Medicines & Health Products
Safety & Vigilance
Global Vaccine Safety

Email: vaccsafety@who.int