

New Chapter September 2011

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Rotavirus

Introduction

Rotaviruses (RV) belong to the Reoviridae family of viruses. They are composed of 11 segments of double-stranded RNA enclosed in a three-layer protein capsid. The two outer capsid proteins are used to classify rotavirus strains into P (protease-sensitive) and G (glycoprotein) serotypes. There are at least seven antigenic groups, A-G. Five serotypes of Group A (G1P, G2P, G3P, G4P and G9P) cause over 90% of clinical rotavirus disease in temperate climates. A change in the major serotype typically occurs every two to three years.

Worldwide, rotaviruses are the commonest cause of community-acquired gastroenteritis in children, with a worldwide mortality of approximately 500,000/year. Most deaths occur in developing countries; death from rotavirus infection is very rare in the developed world where there is ready access to oral and parenteral rehydration.

Epidemiology

The virus is very infectious; up to ten million viral particles can be excreted per ml. of faeces, and only ten particles are required to cause infection. Spread is predominantly by person-to-person contact or from contaminated environmental surfaces, but infection can be transmitted by the respiratory route, and also through contaminated water and food.

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Animal-to-human transmission appears to be rare. Viruses may survive on hands for more than four hours, on environmental surfaces for days to weeks, and in recreational or drinking water for weeks. The incubation period is from 1-4 days.

The peak incidence of infection occurs between 4 and 36 months of age and in winter and spring. Virtually all children throughout the world are infected with RV by the time they are 5 years old, regardless of socioeconomic or environmental conditions. Infection is rare in those under 2 months of age, perhaps because of passively transferred maternal antibody; if infection does occur it is often asymptomatic or mild. Symptoms range from mild diarrhoea to severe gastroenteritis with dehydration, electrolyte imbalance and shock. Children may have multiple RV infections during the first years of life. Adults, especially the elderly, can develop rotavirus disease. Hospitalisation for rotavirus gastroenteritis is associated with low birth weight (a likely proxy for prematurity), daycare attendance, another child aged <2yrs in the household and maternal smoking. Breast feeding protects against hospitalisation.

Those who are immunocompromised because of congenital immunodeficiency or bone marrow or solid organ transplantation may experience severe or prolonged gastroenteritis. Severity of rotavirus disease in children infected with human immunodeficiency virus (HIV) may be similar to that occurring in those without HIV infection.

A single natural infection gives >85% protection against subsequent severe rotavirus gastroenteritis, >75% protection against subsequent rotavirus gastroenteritis, and >35% protection against subsequent rotavirus infection.

Different countries in Europe report widely different rates of disease and of admission to hospital because of RV disease. Hospitalisation rates of children <5 yrs of age vary from 3.8 per 1,000/year in Denmark to 12.8 in Ireland. The proportion hospitalised as a ratio of those medically assessed varied from 1 in 17 in Ireland to 1 in 80 in Spain

In Ireland, rotavirus became a notifiable disease in 2004 (under the category of Acute Infectious Gastroenteritis). Since then there has been a consistent and sustained rise in notifications. However, since almost all children are infected by their fifth birthday, there is very significant under-notification.

In 2009 there were 1748 cases of rotavirus reported to the Health Protection Surveillance Centre. Most were aged <24 months. There were 12 outbreaks of rotavirus notified during 2009 with 74 cases of associated illness. Of the 12 outbreaks, four occurred in crèches, four were family outbreaks in private homes, three were in hospitals and one was in a community hospital/long-stay unit. Since 2004, 8 outbreaks have been reported in hospitals.

Figure 1. Number of cases of Acute Infectious gastroenteritis (AIG) and rotavirus by year, 2004 to 2009 (Data courtesy of HPSC)

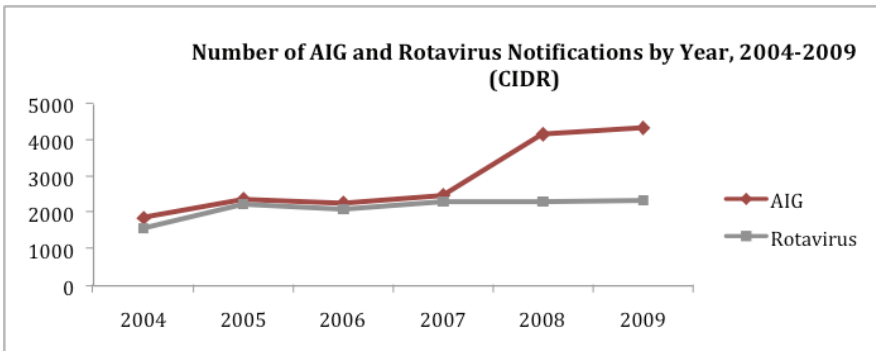
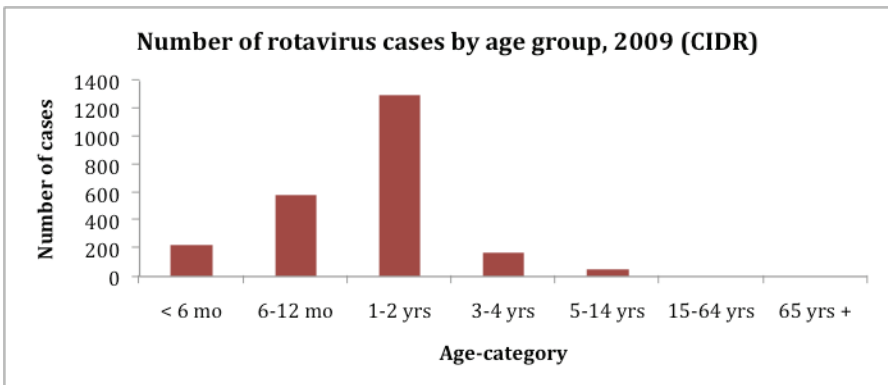


Figure 2. Number of Rotavirus Cases by age group 2009.



Effects of Rotavirus

The virus damages the mature enterocytes of the small intestinal villi, where it produces an enterotoxin which causes epithelial necrosis, atrophy and desquamation. This results in reduced absorption of carbohydrates, salt and water, and in secretory and osmotic diarrhoea. Excretion of virus in faeces precedes the onset of illness, and may continue for weeks after resolution of symptoms.

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There is a wide spectrum of symptoms, ranging from none through mild diarrhoea to severe gastroenteritis with dehydration, electrolyte imbalance and shock. Rarely, encephalitis and meningitis may occur. Severe illness is more likely in those aged 4-24 months. Up to one third of children have a temperature of $>39^{\circ}\text{C}$. Vomiting usually lasts <48 hrs, but may persist for 8-10 days. Other gastrointestinal symptoms generally resolve in 3-7 days. Occasionally diarrhoea may last for up to 3 weeks. Asymptomatic infections are common among neonates, older children and adults

Diagnosis

The most widely used diagnostic laboratory method is antigen detection in the stool by an enzyme immunoassay (EIA) directed at an antigen common to all group A rotaviruses, the principal cause of human disease. Rotavirus-specific IgG, IgA and neutralising antibodies can be measured in serum; at present this is only done in research settings.

Rotavirus Vaccines

Two vaccines are currently available.

Rotarix (RV1) is a live monovalent attenuated human type G1P1A virus vaccine. It is supplied as a powder and solvent with an oral applicator, providing an oral dose of 1ml. Successive doses give cross protection against different strains.

Rotateq (RV5) is a live pentavalent reassortant human-bovine virus vaccine, containing five reassortant strains developed from human and bovine strains, which stimulates production of type-specific antibodies against the commonest types of rotavirus. It is supplied as a liquid, given orally in a dose of 2mls.

Both vaccines should be stored between $2-8^{\circ}\text{C}$.

Both vaccines give at least 95% (C.I. 88-100%) protection against severe RV disease and over 70% protection against any RV disease.

In 1998, a tetravalent rotavirus vaccine, RRV-TV (Rotashield) was recommended for routine vaccination of U.S. infants at ages 2, 4, and 6 months. Evidence of significant association with intussusception emerged in its first year of use and it was withdrawn

Post-marketing surveillance of both currently available rotavirus vaccines has detected a small increased risk of intussusception (about 1-2/100 000 infants vaccinated) in some settings shortly after the first dose. This risk is

5-10 times lower than that observed with the previously licensed vaccine, and the benefits of rotavirus vaccination against severe diarrhoea and death from rotavirus infection far exceed the risk of intussusception. As a precaution, healthcare professionals should follow-up on any symptoms indicative of intussusception (severe abdominal pain, persistent vomiting, bloody stools, abdominal bloating and/or high fever). Parents/guardians should be advised promptly to report such symptoms.

Dose and route of administration

1. Rotarix (RV1, live attenuated human vaccine). **Two** oral doses of 1ml doses are given at 2 and 4 months of age. No restrictions are placed on the infant's feeding in relation to rotavirus vaccine. If an infant regurgitates or vomits during or after administration of vaccine that dose should not be repeated. The infant should receive any remaining dose 2 months later.
2. Rotateq (RV5, live human-bovine reassortant vaccine). **Three** oral doses of 2mls are given at 2, 4 and 6 months of age. No restrictions are placed on the infant's feeding in relation to rotavirus vaccine. If an infant regurgitates or vomits during or after administration of vaccine do not repeat that dose. The infant should receive remaining doses after the recommended interval.

Age and interval restrictions for administration

The minimum age for dose 1 of any rotavirus vaccine is 6 weeks; the maximum age for dose 1 is 14 weeks and 6 days. There is insufficient data on the safety of a first dose of rotavirus vaccine in older infants. The minimum interval between doses is 4 weeks; no maximum interval is set, however no dose should be given after 32 weeks of age.

No dose should be administered after 32 weeks of age (even if the course is incomplete) because of lack of safety and efficacy data in those older than 32 weeks.

If the first dose is given inadvertently at age 15 weeks or older, the rest of the rotavirus vaccination series should be completed before 32 weeks of age, because the timing of the first dose should not affect the safety or efficacy of any subsequent doses. Infants who get rotavirus gastroenteritis before receiving the full series of rotavirus vaccination should still be immunised, because the initial rotavirus infection might provide only partial protection against subsequent rotavirus disease. Rotavirus vaccine can be given to infants with minor acute illness

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including mild gastroenteritis or mild upper-respiratory tract infection, with or without a fever.

Indications

Rotavirus vaccines are indicated for the prevention of rotavirus gastroenteritis when given to infants aged between 6 and 32 weeks.

Rotavirus vaccination is not included as part of the routine childhood immunisation schedule. However parents may choose to have their healthy children immunised.

Vaccination of special groups:

a. Preterm Infants (<37 Weeks Gestation)

Preterm infants are at increased risk for hospitalisation from rotavirus gastroenteritis during the first one to two years of life. In clinical trials, rotavirus vaccine was generally well tolerated in preterm infants, although relatively small numbers have been evaluated. Thus, the benefits of rotavirus vaccination of preterm infants outweigh the risks of adverse events.

b. Immunocompromised persons

No safety or efficacy data are available for the administration of rotavirus vaccine to infants who are immunocompromised or potentially immunocompromised. Vaccine strains of rotavirus are considerably attenuated. Those with severe combined immunodeficiency should not be given either vaccine. If in doubt, consult an immunologist or Infectious Disease (ID) specialist.

c. Infants with a history of intussusception

Compared with infants who have never had intussusception, infants with a history of intussusception are at higher risk for a repeat episode of intussusception. No data are available on the administration of rotavirus vaccine to such infants. Neither vaccine should be given to an infant who has had an intussusception.

Simultaneous Administration with other vaccines

Rotavirus vaccine can be administered together with the following vaccines: DTaP, Hib, IPV, Hepatitis B, Men C, PCV and BCG. It may be administered at any time before, along with, or after administration of any blood product, including antibody-containing products.

Interchangeability of Rotavirus Vaccines

Whenever possible the same rotavirus vaccine should be used to complete the series. However, if the brand is not available or is unknown, continue or complete the series with the vaccine available, unless there is a contraindication. If any dose in the series was RV5 or the vaccine product is unknown for any dose in the series, a total of 3 doses of rotavirus vaccine should be administered.

Do not administer on or after 32 weeks, even if fewer than three doses have been administered.

Contraindications

1. Anaphylactic reaction to any of the vaccine constituents.
2. Uncorrected congenital GIT malformation (e.g., Meckel's diverticulum) that would predispose an infant to intussusception.
3. Previous intussusception.
4. Severe combined immunodeficiency(SCID).

Precautions

1. Acute severe febrile illness – defer until recovery. Vaccination should not be delayed because of the presence of a mild acute illness with or without fever.
2. Moderate or severe vomiting or diarrhoea – defer until recovery. However, infants with mild acute gastroenteritis can be vaccinated, particularly if the delay in vaccination might make the infant ineligible to receive the vaccine (e.g., aged >15 weeks before the vaccine series is started), even though the immunogenicity and efficacy of the vaccine could be reduced.
3. Immunodeficiency (other than SCID). No safety or efficacy data are available for administration of rotavirus vaccine to infants who are immunocompromised or potentially immunocompromised. Vaccine strains of rotavirus are considerably attenuated. Consult with an immunologist or ID specialist.
4. Infants with Spina Bifida or Bladder Extrophy. These infants are at high risk for acquiring latex allergy. Latex is contained in the Rotarix oral applicator whereas the RV5 dosing tube is latex-free. Such infants should be given Rotateq (RV5) instead of Rotarix (RV1) to minimize latex exposure in these children.
5. There is a possibility that both vaccine viruses can be transmitted to non-vaccinated contacts. The potential for transmission of vaccine virus following vaccination should be weighed against the possibility of acquiring and transmitting natural rotavirus.
6. Caution is advised when considering whether to administer RotaTeq to

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individuals with close contacts who are immunocompromised such as:

- Individuals with malignancies;
- Individuals with primary immunodeficiency; or
- Individuals receiving immunosuppressive therapy.

It is prudent for all members of the household to employ measures such as good handwashing after changing a nappy or otherwise coming in to contact with the faeces of the vaccinated child.

Adverse Reactions

Generally rotavirus vaccines are very well tolerated. Irritability, loss of appetite, diarrhoea, vomiting, rash and pyrexia may occur, but are no more common than when compared with placebo.

Post-marketing surveillance indicates the possibility of an increased risk of intussusception shortly after the first dose of both currently licensed rotavirus vaccines in some populations. If confirmed, the level of risk observed in these post-marketing studies is substantially lower than the risk of one case of intussusception in 5,000-10,000 vaccinees identified after Rotashield vaccination.

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