Gastroenteritis and the rotavirus vaccine

This article looks at the clinical features, epidemiology and management of rotavirus-associated gastroenteritis. Particular emphasis is placed on recent advances in the development of rotavirus vaccines and their potential impact on disease burden in both industrialised and developing settings.

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Key points

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1. Rotavirus is the most common cause of gastroenteritis in childhood with almost all children having been infected by the age of five.
2. Rotavirus causes significant medical and economic burden and is responsible for around 600,000 deaths per year worldwide.
3. Phase III safety and efficacy trials have recently been published for two rotavirus vaccines, Rotarix and RotaTeq. Both were highly effective at reducing the incidence of rotavirus disease and reduced the number of hospitalisations due to rotavirus.
4. Neither vaccine was associated with an increased risk of intussusception in the age groups studied but continuing post-licensure surveillance is essential to confirm their safety.

Rotaviruses are double-stranded RNA viruses of the Reoviridae family. The viruses are divided into seven groups (A-G) which in turn are divided into types. Ninety per cent of disease in humans is due to group A viruses[1,2]. Rotaviruses are the most common cause of gastroenteritis in infants and young children worldwide: They are estimated to account for around 40% of cases of severe diarrhoea in childhood[3] and by age five almost all children have been infected[4-6]. Rotavirus-associated gastroenteritis accounts for 600,000 deaths per year worldwide. Most of these deaths occur in developing countries because of poor nutrition and inadequate access to rehydration therapy[6]. Rotavirus disease also causes great economic burden due to the high number of cases. Recent advances in the development of safe and effective commercial rotavirus vaccines could have a huge impact on this costly and potentially fatal disease.

Clinical features

Rotavirus infection can range from mild diarrhoeal illness that can be managed at home, to severe disease warranting hospital admission to correct dehydration and electrolyte imbalances (which can be life-threatening in infants and is a significant cause of mortality in the developing world). Symptoms usually become apparent after an incubation period of 24-72 hours and include vomiting and fever followed by watery, non-bloody diarrhoea; symptoms typically last 4-7 days[1]. The first episode of rotavirus infection is usually the most severe with subsequent infections causing progressively milder symptoms (although rotavirus is still shed in the stool and hence can still be transmitted from person to person)[7].

Transmission

Rotaviruses are highly contagious. Transmission is predominantly faecal-oral although it is suspected that they can also be transmitted via respiratory droplets[8]. Up to 1 trillion viral particles are shed in each millilitre of faeces[7]. Shedding begins before symptoms appear and persists after illness. Rotavirus can survive on human hands for up to four hours and for days on solid surfaces such as toys or food preparation counters[8]. Person-to-person spread via contaminated hands is therefore an important route of transmission. Alcohol-based hand hygiene products and disinfectants successfully inactivate the virus. Rigorous hand-hygiene and regular disinfection of environmental surfaces may therefore have a role in limiting disease spread.

Pathogenesis

The exact mechanisms by which rotaviruses cause diarrhoea are not fully understood. Multiple pathological processes are likely to be involved but a detailed discussion of the proposed hypotheses is beyond the scope of this article (a more in depth review of the pathogenesis of rotavirus disease can be found in Anderson and Weber, 2004)[7]. In short, rotaviruses infect the epithelium of the absorptive villi in the upper part of the small intestine. They replicate inside the cells and are subsequently shed resulting in the death of the infected intestinal cells. This leads to shortening of the villi, denudation of microvilli and hence impaired absorption from the gut. The viruses also appear to increase secretion of fluid and electrolytes into the gut and increase gut motility by stimulation of the enteric nervous system. The combination of increased secretion of fluid, reduced absorption and increased gut motility is

thought to be responsible for the profuse watery diarrhoea associated with rotavirus infection. This damage is reversible but diarrhoea will continue until the villi have regenerated[4,7]. Rotaviruses have also been known to spread from the gut to the bloodstream although the clinical relevance of this is unclear[9].

Epidemiology and disease burden

Death from rotavirus in industrialised countries is rare. However, due to the high number of cases rotavirus is responsible for substantial medical and economic burden. In the UK this is particularly true in winter months where the winter seasonality of rotavirus coincides with peak incidence of other childhood diseases such as respiratory syncytial virus (RSV) bronchiolitis and influenza[4]. **FIGURE 1** illustrates the number of deaths due to rotavirus worldwide in 2004.

Rotavirus is estimated to cause 3.6 million cases of diarrhoea per year in the European Union (EU) (approximately 1 in 7 children aged five or under per year) of which around 700,000 will consult a healthcare professional as an outpatient and around 87,000 will require hospital admission[10]. Peak age of infection is 4-36 months[4]. Children under 3 months are rarely affected by severe rotavirus disease; this may be due to passive transfer of maternal antibodies via the placenta *in utero* and protection conferred by breastfeeding[11]. Due to the highly contagious nature of the virus, the incidence of rotavirus infection in settings where children are grouped together such as nurseries and day-care centres is higher than that of the general population[8]. The incidence of hospital-acquired rotavirus infection also exceeds that of community-acquired infection and results in extended length of hospital stay (by 4-10 days) and closure of wards[12]. A 2006 study reported 231 deaths per year in the EU due to severe rotavirus-associated gastroenteritis[10].

In addition to medical burden, rotavirus also has a substantial economic impact on healthcare systems, individual households and society. Direct medical costs such as GP consultation time, laboratory investigations and occupation of hospital beds, account for the majority of this financial burden; this is particularly true for cases requiring hospitalisation. Numerous studies have placed the annual cost of hospitalisations due to rotavirus in the EU in excess of €100 million (reviewed in Rheigans et al, 2006)[13]. Other economic effects of rotavirus illness include burden to individual households (e.g. loss of income due to time off work to care for a sick child and increased childcare costs) and burden to society (loss of worker productivity).

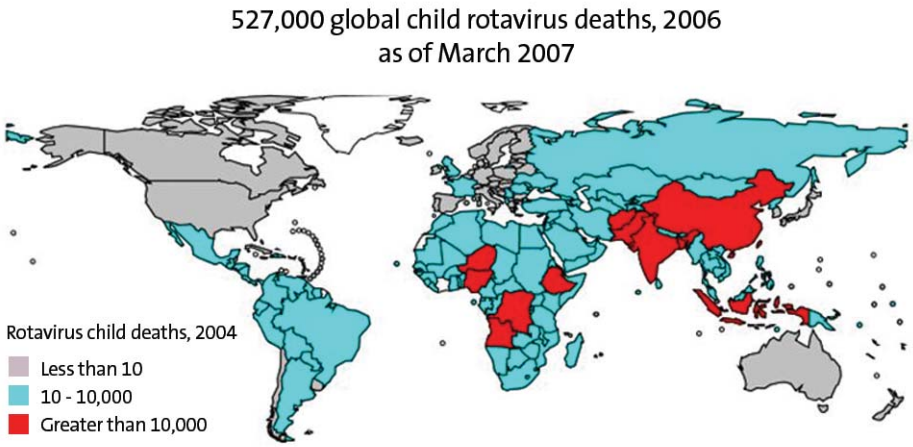

FIGURE 1 Global deaths due to rotavirus in 2004. *Reproduced with permission from the World Health Organisation (WHO).*

Management

The mainstay of management is prevention and treatment of dehydration and electrolyte imbalances and restoration of normal feeding as soon as possible. Oral rehydration solutions should be tried in the first instance but intravenous or subcutaneous rehydration may be required[14].

Up until the late 1990s it was thought that children with diarrhoeal illness should be starved for 24 hours as this would decrease the severity and duration of the diarrhoea. However, a study by the European Society of Paediatric Gastroenterology and Nutrition (ESPGAN) showed that early feeding does not prolong symptoms and results in significant weight gain when compared to children who are only given rehydration therapy for 24 hours[15].

A number of other interventions have varying degrees of efficacy against rotavirus infection: There is some evidence that probiotics such as Lactobacillus shorten the duration of diarrhoea[16]. Passive immunisation with orally administered immunoglobulins has been shown to have some benefit in expatiating recovery from rotavirus gastroenteritis, but this approach is costly and at present there are no commercial preparations available[17]. Drugs that decrease gut motility such as codeine and loperamide are used for symptom control in adult disease but their use is not encouraged in children[7].

On the whole these novel treatment strategies have been shown to have limited efficacies in clinical trials. Preventative measures are therefore thought to be more important in reducing the impact of rotavirus. For this reason there is much interest in vaccinating healthy children against this widespread, costly and potentially life-threatening disease.

Rotavirus vaccines

Exposure to rotavirus leads to the development of natural immunity which reduces the frequency and severity of subsequent clinical episodes. One rotavirus infection is thought to protect 40% of children against further rotavirus infection, 75% are protected against further diarrhoea due to rotavirus and 88% are protected against severe rotavirus disease[18]. Subsequent infections further increase and broaden protection. Rotavirus vaccines therefore seek to duplicate this natural protection with the aim of preventing moderate to severe disease.

The first rotavirus vaccine to be licensed (RotaShield, Wyeth Laboratories) was a live oral rhesus-human reassortant vaccine. RotaShield was shown to have efficacy in limiting the frequency and severity of rotavirus disease and was recommended for the universal vaccination of infants[19]. However, the vaccine was withdrawn by the manufacturer shortly after its release in 1999 due to a temporal association with intussusception (where a section of bowel telescopes into adjacent proximal bowel causing obstruction)[20,21]. Children receiving their first dose of vaccine at an older age (over 90 days) appeared to be at greater

risk[22]. The pathogenic mechanism of this association remains poorly understood. Studies have estimated the risk of intussusception with RotaShield to be between 1 in 10,000 and 1 in 32,000 vaccinated infants. All recommendations were subsequently withdrawn; this proved to be a major set back in attempts to prevent rotavirus disease.

Phase III safety and efficacy trials of two new rotavirus vaccines have recently been published; each study involved at least 60,000 children[23,24]. Rotarix (GlaxoSmithKline Biologicals) is an oral attenuated monovalent vaccine derived from the most common human strain of the virus (G1P)[8] while RotaTeq (Merck Research Laboratories) is an oral live human-bovine reassortant vaccine.

The studies report that these vaccines reduced the incidence of severe rotavirus-associated gastroenteritis by between 85-98% and reduced the need for either medical consultation or hospitalisation by 85-95%. Both vaccines were well tolerated with few adverse effects when administered alone and both can be co-administered with other vaccines given at the same age such as *Haemophilus influenzae* type B, hepatitis B, inactivated polio vaccine, diphtheria-tetanus-acellular pertussis, diphtheria-tetanus-whole cell pertussis and pnuemococcal conjugate vaccines[25]. Critically, neither vaccine was associated with an increased risk of intussusception[23,24]. These trials highlight the potentially huge public health impact rotavirus vaccines could have if universally introduced. It should be noted that direct comparison of the two vaccines is difficult as their respective trials used different classifications of disease severity and because different populations were studied: The RotaTeq trial mainly studied industrialised countries (Finland and the USA) whereas the Rotarix trial included developing countries (poor and middle income families in Latin America).

Although both vaccines have passed large safety trials and neither was associated with an increased incidence of intussusception, anxieties remain over their use in older children. Naturally occurring intussusception is uncommon in the first 3 months of life and RotaShield seemed to increase risk of intussusception mainly in children older than 3 months. Thus it may be that the lack of association with intussusception for RotaTeq and Rotarix was because these vaccines were only trialled at ages where intussusception is uncommon anyway. Both manufacturers have therefore recommended that the vaccines should not be used in children older than the age range studied. For Rotarix (2-dose regimen), the first dose may be administered from 6 weeks of age, there should be an interval of 4 weeks between doses and the course must be completed by age 24 weeks. For RotaTeq (3-dose regimen), the first dose must be administered between 6 and 12 weeks of age, there must be an interval of 4-10 weeks between doses and the course must be completed by 32 weeks. This highlights the need for continuing post-licensure surveillance of the safety and efficacy of the vaccines.

FIGURE 2 Vaccination against Rotavirus infection can protect infants against severe gastroenteritis.

In addition to RotaTeq and Rotarix there are a number of other potential vaccines on the horizon. Phase II trials have been completed for two other vaccines: In Australia another attenuated human vaccine was shown to be well tolerated but with poor immunogenicity (further trials are underway using larger doses)[26] and another human-bovine reassortant (UK) vaccine was effective at limiting rotavirus disease[27,28].

In India two attenuated neonatal strains have shown promise as vaccine candidates in phase I trials[29] and a vaccine derived from a lamb strain is licensed in China but studies of this vaccine are lacking[30,31]. It is unclear whether regulatory authorities will insist that these newer vaccines be subjected to large clinical trials of sufficient size and studying a range of age groups to be able to detect an association with intussusception. If so this could have major cost and feasibility issues for smaller vaccine manufacturers.

Safety and efficacy in preterm infants

There is some evidence to suggest that preterm infants are at increased risk of hospitalisation due to viral gastroenteritis in the first year of life[32]. It follows that vaccination against rotavirus may be even more important in these vulnerable infants but practitioners must consider potential risks. For RotaTeq, 2070 preterm infants (25-36 weeks gestation) were studied in the phase III trial; safety and efficacy seemed to be similar in preterm and term infants[24,25]. The American Academy of Paediatrics (AAP) has therefore recommended that preterm infants can be vaccinated with RotaTeq from six weeks after birth and that the vaccine should be given according to the usual schedule at calendar age[33]. Data for Rotarix in this group are more limited (140 preterm infants of 29-36 weeks gestation were studied in the phase III trial) but the available evidence suggests that it is well tolerated[23,25].

Rotavirus vaccines in the developing world

Clinical trials to date suggest that rotavirus vaccines are an effective means of preventing rotavirus-associated gastroenteritis in industrialised nations. However the effectiveness and safety of rotavirus vaccines in the developing world (where the burden of rotavirus is greatest and where the disease can often be fatal) is not well documented.

There is a greater diversity of circulating rotavirus strains in developing settings with higher frequency of mixed infection and greater reassortment between human and animal strains; this will test the protection offered by rotavirus vaccines[11]. Host factors such as malnutrition, chronic disease (e.g. HIV) and interference from other enteric bacterial and viral pathogens may also affect the efficacy of vaccines. Different safety issues also need to be addressed such as safety and immunogenicity of the vaccines when administered to immunocompromised infants with HIV. Clinical trials of both Rotarix and RotaTeq have started in the developing world which should clarify these issues[31,34].

Rotavirus vaccines also carry high costs and therefore making vaccines affordable and universally available in the developing world is perhaps the greatest challenge. Collaboration between governments, drug companies and the global healthcare community is essential if this is to be made a reality. Organisations such as the World Health Organisation (WHO), the Global Alliance for Vaccines and Immunisation (GAVI), and the Bill and Melinda Gates Foundation are supporting the development and introduction of rotavirus vaccines to developing nations where they are needed the most.

Conclusion

Rotavirus associated gastroenteritis affects most children by the age of five, causes significant medical and economic burden and is responsible for 600,000 deaths per year worldwide. Natural exposure to rotavirus protects against further clinical episodes and rotavirus vaccines therefore seek to mimic this protection. Both Rotarix and RotaTeq have been shown to be effective at reducing frequency and severity of rotavirus disease and are predicted to have a huge impact on the associated burden in industrialised nations when introduced universally. Importantly, neither vaccine increased the risk of intussusception in the age groups studied; post-licensure surveillance is essential to confirm the safety of these two vaccines.

Further studies are needed to look at whether rotavirus vaccines have the same impact on disease in developing countries. Once efficacy and safety have been established in the developing setting, the global healthcare community should make it a priority to make these vaccines affordable and widely available in these areas where the burden of rotavirus is heaviest and where the disease can often still be fatal.

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