Rotavirus Vaccine

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11.1 Burden of Rotavirus Disease

The clinical characteristics of severe rotavirus (RV) gastroenteritis (RVGE) include watery diarrhea, frequent vomiting, and high fever. About 20–30% of all children experience a clinically manifest episode of RVGE, and 10–20% of these (2–3% of all) are severe. Prevention of severe RVGE is the primary target of RV vaccination. In Europe, RV causes about one half of severe acute gastroenteritis (GE) in childhood requiring hospitalization. On average, RVGE is more severe than gastroenteritis caused by other viruses.

Moreover, it is now recognized that RV often causes a systemic infection and RV antigen and RNA can be detected in the circulation. RV vaccination also prevents some 20% of all febrile seizures. Rather than gastroenteritis, it is more appropriate to talk about RV disease. Prevention of RV disease by vaccination is a neutral term that puts RV vaccine in the same category as other viral vaccines, in contrast to being a "diarrheal disease vaccine."

Still, the first target of RV vaccination in Europe is the prevention of severe RVGE and, specifically, hospitalizations for RVGE. Hospital admission is also the major factor (about 90%) in calculations of financial burden associated with RVGE. The number of annual hospitalizations in Europe was at least 87,000 before RV vaccination was introduced. The rate of hospitalizations may vary according to local clinical practices, but there are probably also true differences between countries. For Europe, it has been estimated that the risk of hospitalization for RVGE before the age of 5 is 1 in 54, with a high of 1 in 33 in Finland and low of 1 in 67 in Denmark. It is plausible that in countries with long, cold winters, the RV season is longer and severe RVGE more common.

Some countries with a relatively low incidence of RVGE, such as Denmark and the Netherlands, have considered that there is no need to introduce RV vaccination into the immunization program. However, even if a country has decided not to introduce universal RV vaccination, at an individual level, the risk of severe RVGE in any European country is high enough to warrant prevention by vaccination.

Deaths from RVGE are rare in Europe (a 2006 estimate was 231 for European Union countries), but deaths may occur in cases of delayed admission to care. RVGE is still a potentially fatal disease in Europe, and the low mortality is only attributable to the availability of good case management at outpatient and hospital facilities.

Globally, RV is a major cause of childhood mortality. A recent estimate before large-scale RV vaccinations put the number of RV-associated deaths at 197,000 a year. Of individual countries, India had the highest number of deaths, followed by Nigeria, Pakistan, Bangladesh, and Indonesia. Introduction of RV vaccination in the high-mortality countries is a global public health priority, but has been slow in the named countries.

11.2 RV Epidemiology

Almost all RVs causing disease in humans belong to group A, determined by the common inner core group antigen VP6. VP6 is the most abundant protein in the RV particle and a powerful immunogen, and immune reaction against this antigen is likely the major mechanism of protection against severe RV disease. Protection may be induced by natural RV infection or vaccination alike. It takes two or three infections, or "hits," to induce solid protection against severe disease; the "hits" may also be administered in two or three doses of oral vaccine, and the protection is limited to RV disease and not infection. Protection against RV infection depends on immunity against the VP7 and VP4 surface antigens, and such protection is more variable and not durable.

The two surface antigens VP7 and VP4 determine the G- and P-types of RVs, respectively, and induce neutralizing antibodies. Although a large number of G- and P-combinations are possible, in reality a few fixed combinations prevail. The most common RV types are G1P[8], followed by G2P[4],

G3P[8], G4P[8], G9P[8], and, more recently, G12P[8]. Altogether, RV diversity has increased after RV vaccinations, but this has not reduced the effectiveness of the vaccine against severe RVGE, which is largely not dependent on immunity to G- or P-types. The surface antigen-induced antibodies protect against RV infection and have an effect on the RV strains that are prevalent in circulation, but the serotype-specific antibodies are not critical for the protection against severe RV disease.

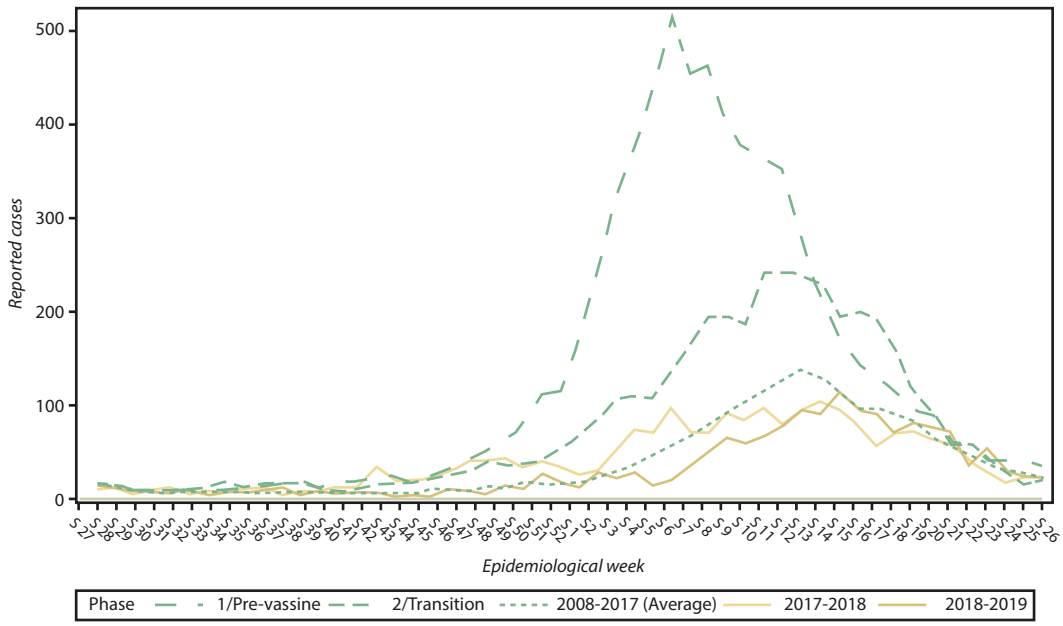
Although the predominant RV types vary by the year, no single type is predominant in the whole of Europe at the same time. Rather, there are multiple types of RV circulating at the same time in different regions. Thus, the rotavirus epidemic (season) does not have a single origin either, but RVs become prevalent in the winter season at various locations independently. Still, the seasonal pattern was very predictable until the introduction of universal RV vaccinations. In the countries with a high coverage of vaccinations, the RV season has shifted from peak winter toward spring and summer as first observed in Europe in Belgium (◘ Fig. 11.1).

Most cases of severe RV disease in Europe occur in the age group 6–18 months, i.e., in the first winter epidemic season of life. Therefore, vaccination schedules need to be completed by the age of 6 months. With introduction of vaccinations, there has been a shift in age distribution as discussed in ▶ Sect. 11.7 (◘ Fig. 11.2).

11.3 RV Vaccines

All RV vaccines are live attenuated tissue culture-grown RVs of human or animal origin or reassortants of human and animal

◘ **Fig. 11.1** Oral administration of rotavirus (RV) vaccine



◘ **Fig. 11.2** Rotavirus epidemic season with a winter peak before vaccination and the blunted peak after vaccinations in Belgium. (*Source*: sentinel lab Sciensano (Belgium))

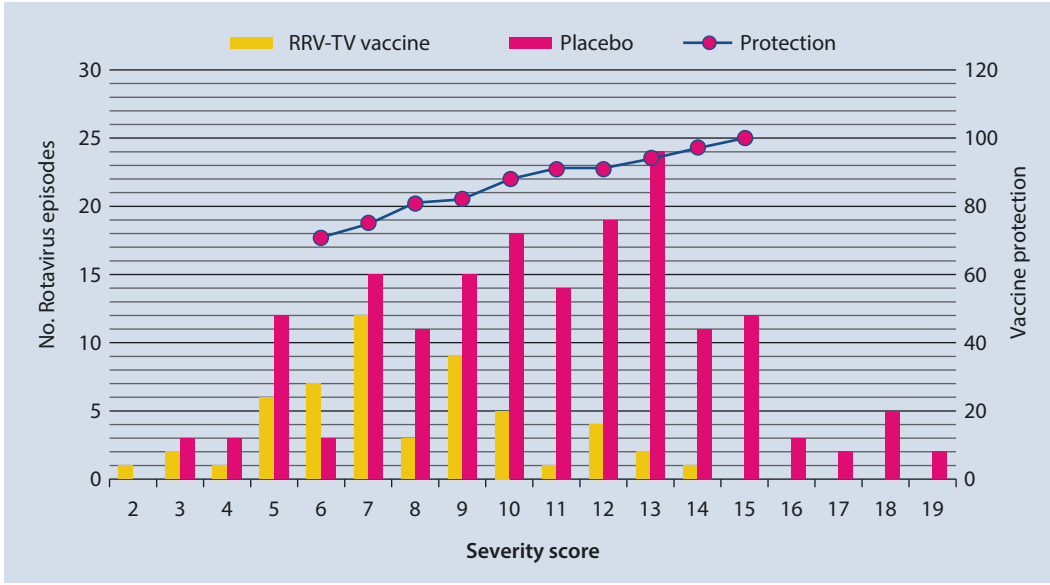


Fig. 11.3 Rotavirus disease severity and rhesus rotavirus tetravalent vaccine protection (Joensuu et al. 1997; Ruuska and Vesikari 1990)

RVs. RV vaccines are given orally (Fig. 11.1) to multiply in the intestine and to mimic asymptomatic wild-type RV infection. Vaccine virus infection is likely to induce natural-like immunity against RV disease, even if the mechanism of protection is not fully known.

The first experimental RV vaccine was a bovine rotavirus that was found to infect humans and to induce a high level of cross-protection against severe human RVGE in spite of having "non-human" G- and P-types. The early studies of bovine RV vaccine in the 1980s established some general principles of RV vaccination, which have been confirmed subsequently in numerous studies with other live RV vaccines: (1) vaccine-induced protection is higher against severe RVGE than any (including mild) RV disease; (2) oral RV vaccine needs to be given with a buffer because gastric acid may inactivate RV and reduce the uptake of RV vaccine; (3) breast milk or breast-feeding (despite RV IgA in the breast milk) does not negatively affect the uptake of RV vaccine; and (4) simultaneous administration of oral poliovirus vaccine (OPV) may interfere with live RV vaccine.

The first licensed RV vaccine (RotaShield®, Wyeth) in 1998 in the USA was a rhesus-human reassortant "tetravalent" vaccine, which contained three reassortants of rhesus rotavirus with human G-types G1, G2, and G4 plus the rhesus RV (G3) itself. This vaccine was given in three doses and after a full series induced a high level of protection, as shown in Fig. 11.3. With the use of a 20-point severity scale ("Vesikari scale"), the protection level against different severities of RVGE was determined with a greater accuracy. The protection reached 100% against disease with a severity score of 15/20; using the most commonly applied cutoff score of 11/20 for severe RVGE, the protection was about 90%. The same scale has been used to measure protection of other RV vaccines as well.

RotaShield® induced febrile reactions in about one third of the recipients and about 3% had high fever. After a million doses given in the USA by 1999, the vaccine was found to be associated with intussusception (IS) and was withdrawn. Other rotavirus vaccines are not reactogenic like RotaShield®. Still, the current RV vaccines may also cause IS, even though the risk is lower than that associated with RotaShield®.

The current major licensed RV vaccines are human RV vaccine (Rotarix™, GSK) and bovine–human reassortant RV vaccine (RotaTeq®, Merck), both of which are available and widely used in Europe and globally. The recommendations of the European Society for Pediatric Infectious Diseases (ESPID) take the position that both vaccines can be recommended to protect European children from RVGE and that the performance of the vaccines in Europe is equal. No formal head-to-head comparison of the vaccines has been done.

11.4 Human RV Vaccine Rotarix™

Human RV vaccine (Rotarix™, GSK), also termed RV1, is the most extensively used RV vaccine today. It was derived from a G1P[8] RV isolate in Cincinnati, passaged 33 times in cell culture and designated 89–12. The strain was acquired by GSK, cloned (by plaque purification) and passaged another 12 times in MRC-5 cells. In this process, the virus lost its residual reactogenicity and is generally regarded as nonreactogenic for humans. Rotarix™ multiplies effectively in humans, as characterized by a high rate of shedding (60% or even more) after the first dose, but does not cause diarrhea or systemic reactions; in other words, it is highly attenuated for its original host.Rotarix™ is given in two doses. The uptake and immunogenicity are excellent (90%) even after the first dose when given in the presence of a low level of maternal antibody, such as in European populations. The uptake of the second dose may be prevented by the antibodies induced after the first dose, as indicated by the lack of shedding and lack of a booster response after the second dose. Therefore, the second dose mainly fills the immunity gap remaining after the first dose, but does not induce an increase in the level of antibodies if the first dose has been successful. The pivotal safety and efficacy trial for licensure was carried out in 60,000 children in Latin America. Before licensure in Europe, the vaccine was tested in five European countries. Rotarix™ was the first new RV vaccine to be licensed after the withdrawal of RotaShield®, with European licensure in 2006.

The results of the major European efficacy trial of Rotarix™ are illustrative for the performance of this vaccine. The primary endpoint was severe RVGE, as defined by score 11/20. Against such severe RVGE, the efficacy for 2 years was 91%, with 96% efficacy in the first season and 86% in the second season, showing a decline over time. Against any RVGE the efficacy was 78% and 68% in the first and second year, respectively, for a total efficacy of 72% over 2 years. The efficacy against severe RVGE by G-type ranged from 96% for G1P[8] to 86% for G2P[4]; these differences were not statistically significant (Fig. 11.4a). For any RVGE, the efficacy point estimates were higher for G1, G3, G4, and G9 with P[8] than G2P[4] with 58%. The interpretation would be that a G1P[8] vaccine cannot well control the circulation of G2P[4] RV, but remains efficacious against severe RVGE caused by this "fully heterotypic" RV. G2P[4] has often become more prevalent after universal RV vaccination with Rotarix.

Description of Rotarix™ According to the Summary of Product Characteristic (SPC)

► https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Rotarix/pdf/ROTARIX-PI-PIL.PDF

ROTARIX, for oral administration, is a live, attenuated rotavirus vaccine derived from the human 89–12 strain, which belongs to the G1P[8] type. The rotavirus strain is propagated on Vero cells. After reconstitution, the final formulation (1 mL) contains at least 10^6 median Cell Culture Infective Dose (CCID50) of live, attenuated rotavirus.

The lyophilized vaccine contains amino acids, dextran, Dulbecco's Modified Eagle Medium (DMEM), sorbitol, and sucrose. DMEM contains the following ingredients: sodium chloride, potassium chloride, magnesium sulfate, ferric (III) nitrate, sodium phosphate, sodium pyruvate, D-glucose, concentrated vitamin solution, L-cystine, L-tyrosine, amino acids solution, L-glutamine, calcium chloride, sodium hydrogencarbonate, and phenol red.

In the manufacturing process, porcine-derived materials are used. Porcine circovirus type 1 (PCV-1) is present in ROTARIX. PCV-1 is not known to cause disease in humans.

The liquid diluent contains calcium carbonate, sterile water, and xanthan. The diluent includes an antacid component (calcium carbonate) to protect the vaccine during passage through the stomach and prevent its inactivation owing to the acidic environment of the stomach.

ROTARIX is available in single-dose vials of lyophilized vaccine, accompanied by a prefilled oral applicator of liquid diluent. The tip caps of the prefilled oral applicators may contain natural rubber latex; the vial stoppers are not made with natural rubber latex.

ROTARIX contains no preservatives.

11.5 Bovine–Human Reassortant RV Vaccine, RotaTeq®

The "pentavalent" bovine–human reassortant RV vaccine (RotaTeq®, Merck, also termed RV5) is a combination of four G-type reassortants (for G1–G4) and one P-type (P[8]) reassortant on the WC-3 bovine RV genetic backbone. As WC-3 is a G6P[5] virus, these bovine G- and P-types are also present in the vaccine. The terms "pentavalent" and RV5 refer to the five mono-reassortant strains in the vaccine. However, it is now well established that the protection against severe RVGE induced by the vaccine is not limited to the G or P types contained in the product (see below).The RotaTeq® vaccine is given in three doses. This was determined early on to accommodate the US childhood immunization program (2, 4, and 6 months of age), but has an additional basis in the demonstration of incremental immunogenicity and protection by each dose. RotaTeq® vaccine virus is also shed after vaccination, and the shedding may rarely be associated with diarrhea. The G1 and P[8] reassortants included in the RotaTeq® vaccine may re-reassort with each other and form vaccine-derived (vd) double reassortants on the bovine RV VP6 core, which may be more virulent than the original single reassortant vaccine viruses, and vdG1P[8] may be responsible for most of the diarrhea seen after vaccination in about 1% of the vaccine recipients.

The efficacy and safety of the RotaTeq® vaccine were established in the large (70,000 infants) Rotavirus Efficacy and Safety Trial (REST). The overall efficacy against severe RVGE as determined by healthcare utilization (combined endpoint of hospital admission and outpatient clinic treatment) was 95%

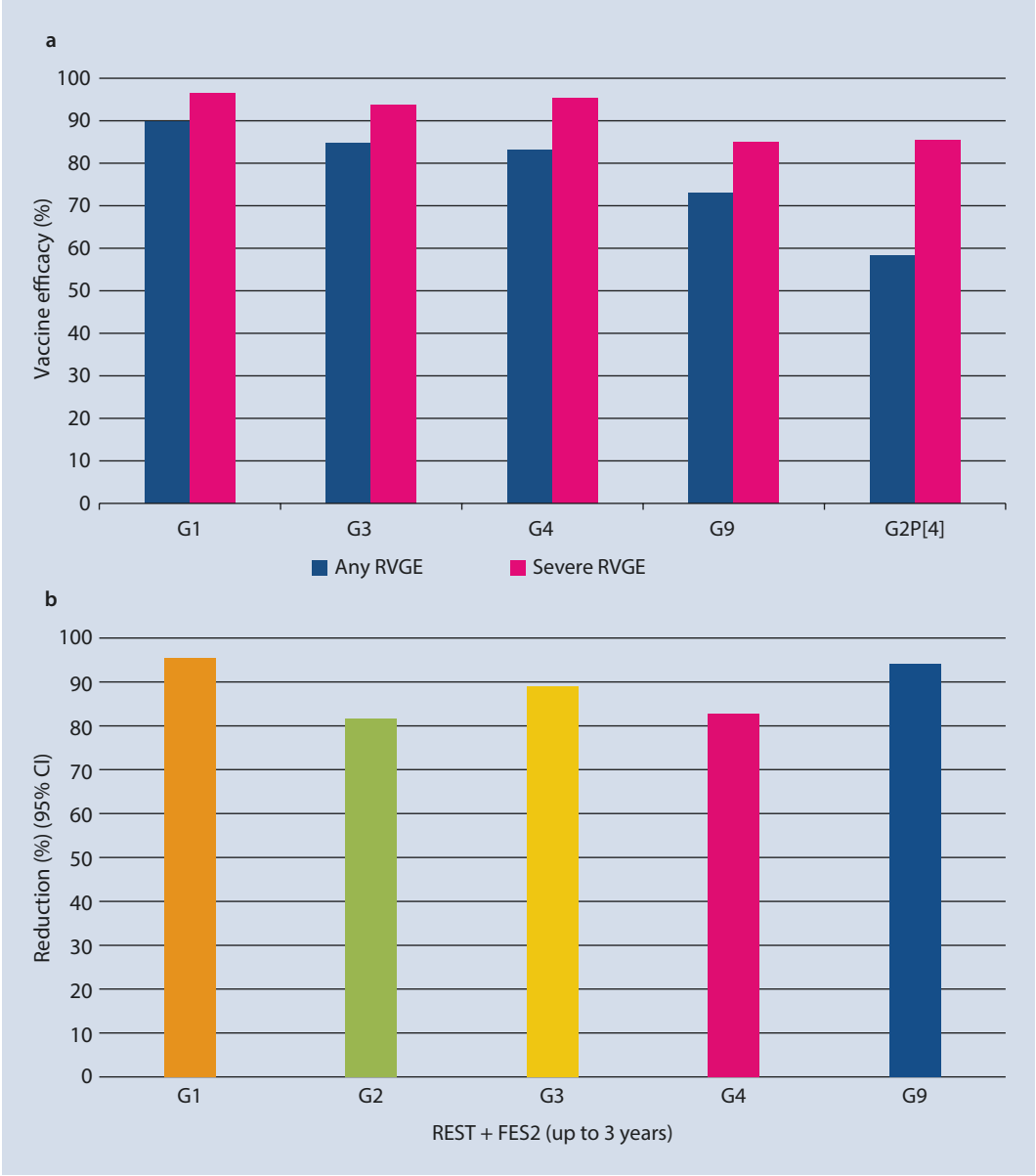


Fig. 11.4 **a** European efficacy trial of Rotarix. Vaccine efficacy against rotavirus gastroenteritis (RVGE) caused by specific RV types. **b** Finnish Extension Study of Rotateq vaccine: serotype-specific efficacy of RV5 against hospitalizations and emergency department visits

(Fig. 11.4b). An extension study of the REST in Finland involving 21,000 children confirmed that RotaTeq was efficacious against severe RVGE associated not only with G1, G3, and G4, all P[8], but also against G9P[8], which is not among the G-types in the vaccine, and G2 P[4], with a different P-type. RotaTeq® was licensed in 2006 and is now one of the two major RV vaccines used globally.

Description of RotaTeq® According to the SPC

► http://www.merck.com/product/usa/pi_circulars/r/rotateq/rotateq_pi.pdf

RotaTeq is a live, oral pentavalent vaccine that contains five live reassortant rotaviruses. The rotavirus parent strains of the reassortants were isolated from human and bovine hosts. Four reassortant rotaviruses express one of the outer capsid proteins (G1, G2, G3, or G4) from the human rotavirus parent strain and the attachment protein (serotype P7) from the bovine rotavirus parent strain. The fifth reassortant virus expresses the attachment protein, P1A (genotype P[8]), herein referred to as serotype P1A[8], from the human rotavirus parent strain and the outer capsid protein of serotype G6 from the bovine rotavirus parent strain.

The reassortants are propagated in Vero cells using standard cell culture techniques in the absence of antifungal agents.

The reassortants are suspended in a buffered stabilizer solution. Each vaccine dose contains sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, cell culture media, and trace amounts of fetal bovine serum. RotaTeq contains no preservatives.

In the manufacturing process for RotaTeq, a porcine-derived material is used. DNA from porcine circoviruses (PCV) 1 and 2 has been detected in RotaTeq. PCV-1 and PCV-2 are not known to cause disease in humans.

RotaTeq is a pale yellow clear liquid that may have a pink tint.

The plastic dosing tube and cap do not contain latex.

11.6 Comparative Efficacy

Both the Rotarix™ and the RotaTeq® vaccines have been tested for efficacy in different environments, from developed to "intermediate" to developing countries. In general, the overall and serotype-specific efficacy against severe RVGE of the two vaccines are remarkably similar in all settings, being highest in Europe (around 95%) followed by Latin America (80–85%) and Africa (50–70%). No formal head-to-head comparative efficacy trial has been conducted. In a recent comparative immunogenicity study in the USA, three doses of RotaTeq® was more immunogenic by RV IgA response than two doses of Rotarix™. The same study showed that a mixed schedule of two doses of RotaTeq® and one dose of Rotarix™ was even more immunogenic.

11.7 Real-Life Effectiveness

Studies on the real-life effectiveness of RV vaccines after the introduction of immunization programs have been conducted in several countries and areas. On the whole, there seems to be a similar gradient in vaccine effectiveness to that in prelicensure efficacy trials among developed, "intermediate," and developing countries.

In Europe, the examples of Finland and Belgium are representative. In these countries, which have reached a high coverage with RV5 (Finland) and RV1 (Belgium), respectively, the real-life vaccine effectiveness in the target population has been well above 90% against hospitalization for RVGE. In Austria, with coverage of 72–74%, the reduction of RVGE hospitalizations in the target age group was 81–84%, and this was sustained for up to 3 years. The direct impact of RV vaccination in the target age group has shifted the occurrence of RVGE to older unvaccinated children (◘ Fig. 11.5).

The indirect effect of RV vaccinations on unvaccinated children remains unsettled. In Austria, there was initially an indirect effect on unvaccinated children, but after 3 years, this was followed by an increase in RVGE hospitalizations in 5- to 14-year-old children. In Finland, with an RV vaccination coverage of 95%, the reduction in cases of RVGE seen in hospitals was 94% in a period of 4 years after vaccination, but specifically in the age group 5–14 years, no significant reduction was seen over this period. It seems that large-scale RV

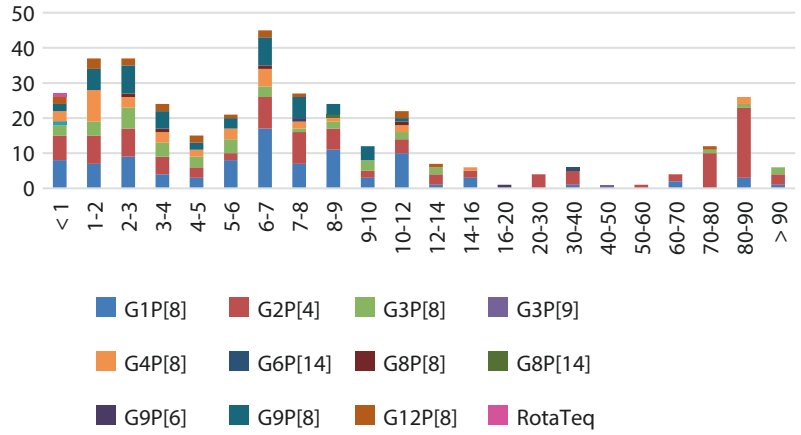


Fig. 11.5 Age distribution and associated genotypes in all RVGE cases in Finland after universal RV vaccinations. (Adapted from Markkula et al. (2020))

vaccinations interrupt the circulation of wild-type RVs after initial introduction, but do not eliminate RV circulation. Over time, the circulating wild-type RVs find susceptible individuals, and some of these will come down with severe RVGE. In addition, RV circulates and causes small outbreaks of disease in the elderly, seemingly unaffected by vaccination of children (Fig. 11.5).

The impact of vaccines on all hospitalizations due to acute gastroenteritis depends on the share of RV in all severe gastroenteritis and the vaccine coverage. At best, the total reduction of hospitalizations from any gastroenteritis may be as high as 70%, as observed in Finland over a period of 4 years.

11.8 Effects beyond Gastroenteritis

Over the years since introduction, it has become clear that RV vaccination has positive effects beyond prevention of acute gastroenteritis. RV causes a systemic infection with high degree of antigenemia and low degree of viremia. Severe RVGE may be associated with seizures. RV vaccination has been found to decrease all seizures in children by 20% or more.

RV vaccination has also been shown to prevent chronic disease. An extension study of REST in Finland found that RV vaccination reduced celiac disease by one third and possibly stopped the increase of type 1 diabetes (DM1) (Fig. 11.8). A US study found a reduction of 3–4% in the incidence of DM1 in young children in the time since the introduction of RV vaccination.

The impact on DM1 and celiac disease beyond RVGE is of such magnitude that they provide an additional argument for introduction of universal RV vaccination (Fig. 11.6).

11.9 Introduction of RV Vaccination

After Austria (both vaccines), Belgium (Rotarix™), and Finland (RotaTeq® exclusively), there was a gap of a couple of years until Germany started universal vaccinations state by state. The most significant recent step forward is perhaps the introduction into the UK in 2014. The map in Fig. 11.7 shows the status of universal RV vaccinations in Europe in 2020.

No country that has initiated a universal program has stopped it. However, in 2015, France recalled the recommendation for RV vaccination over concerns of safety (IS) and is unlikely to relaunch a universal RV vaccination program. Spain has withdrawn the Rotarix vaccine for concerns over porcine circovirus (PCV-1) contamination (see below).

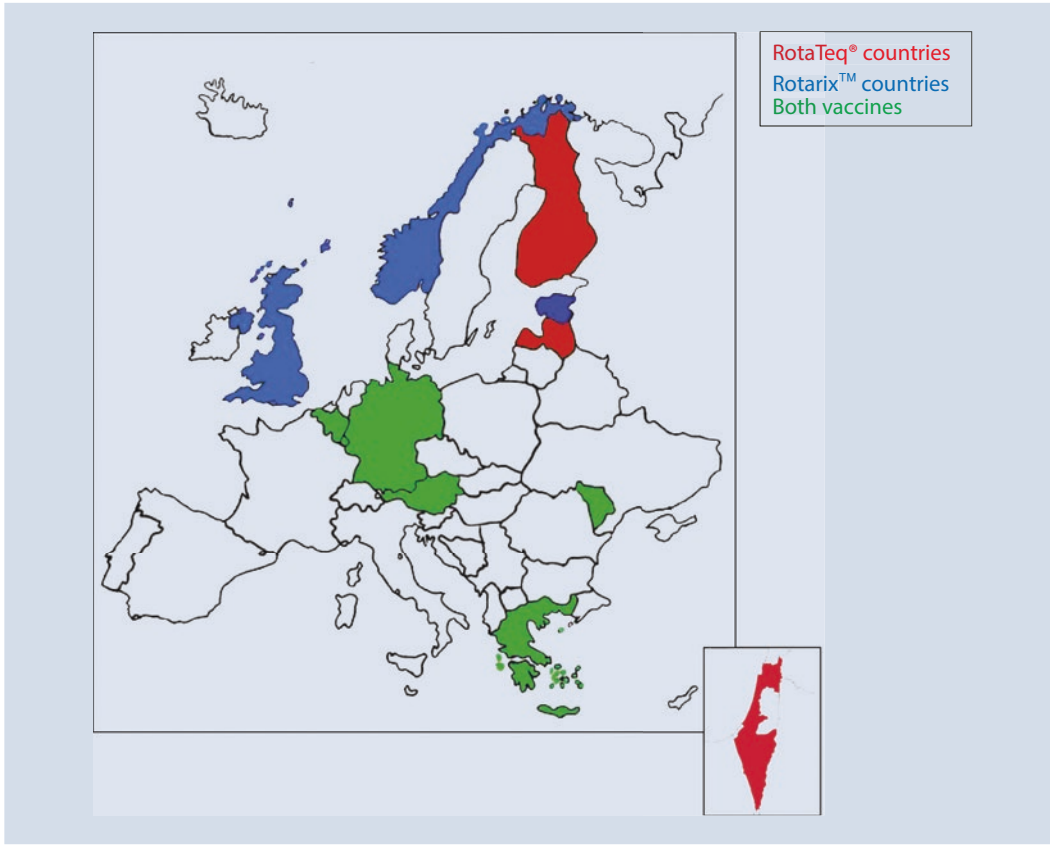


Fig. 11.7 Universal RV vaccination programs in Europe

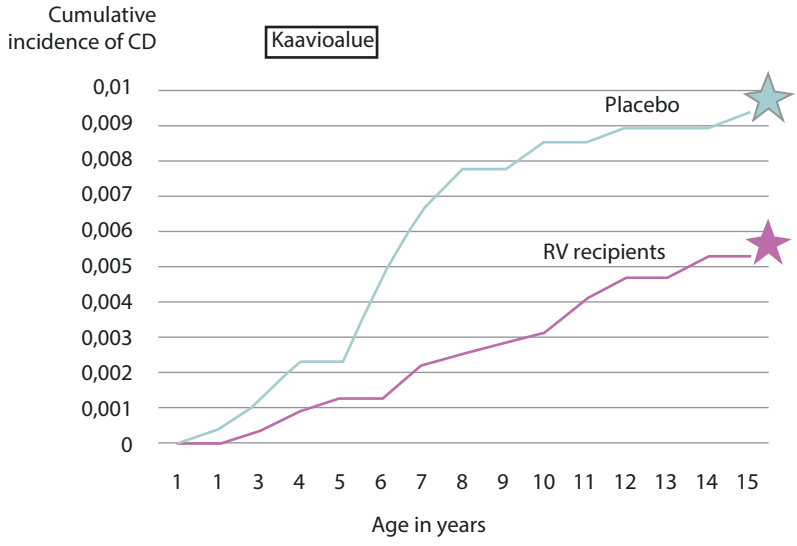


Fig. 11.6 Reduction in celiac disease between ages 11 and 14 years in children participating in REST study and receiving RotaTeq vaccine or placebo. (Adapted from Hemming-Harlo et al. (2019))

11.10 Intussusception

Intussusception is the most important adverse effect of RV vaccination. Association with IS led to the withdrawal of the first licensed RV vaccine, RotaShield®, in 1999. IS occurred mostly 3–7 days after the first dose of RotaShield®, and the attributable risk was estimated at 1:10,000. However, the risk of IS was shown to be age-dependent, and most of the cases occurred in the catch-up vaccination program in infants who were over 90 days of age at the time of the first dose.

Both of the leading licensed RV vaccines, Rotarix™ and RotaTeq®, are also associated with IS, albeit with a lower risk than RotaShield®. The prelicensure trials did not detect the risk, as they were designed to rule out a risk of IS of similar magnitude to that with RotaShield®. Later, in a post-marketing surveillance study, the risk estimates of IS for both vaccines are between 1:50,000 and 1:80,000 after the first dose.

The age pattern of RV vaccine-associated IS, whether by RotaShield® or the current vaccines, may follow that of naturally occurring IS (Fig. 11.6). Therefore, it is important not to administer the first dose of any RV vaccine after 90 days of age, but it is prudent to follow the current ESPID recommendation and give the first dose of RV vaccine as early as possible, i.e., at 6–8 weeks of age (Fig. 11.8).

The small risk of IS is often weighed against the benefits of RV vaccination, and this comparison comes out in favor of vaccination in developed countries as well. However, everything should be done to minimize the risk, and early administration of the first dose is of key importance.

11.11 Porcine *Circovirus*

In 2010, both licensed RV vaccines were found to have porcine *circovirus* (PCV) as a contaminant. PCV is not known to infect humans, and the WHO and European Medicines Agency have held that RV vaccines may continue to be used. Some European countries withdrew Rotarix™ temporarily, but this position is maintained only in Spain. In Rotarix™, PCV contamination was traced to virus seed, but the manufacturer is committed to providing a PCV-free vaccine in the future.

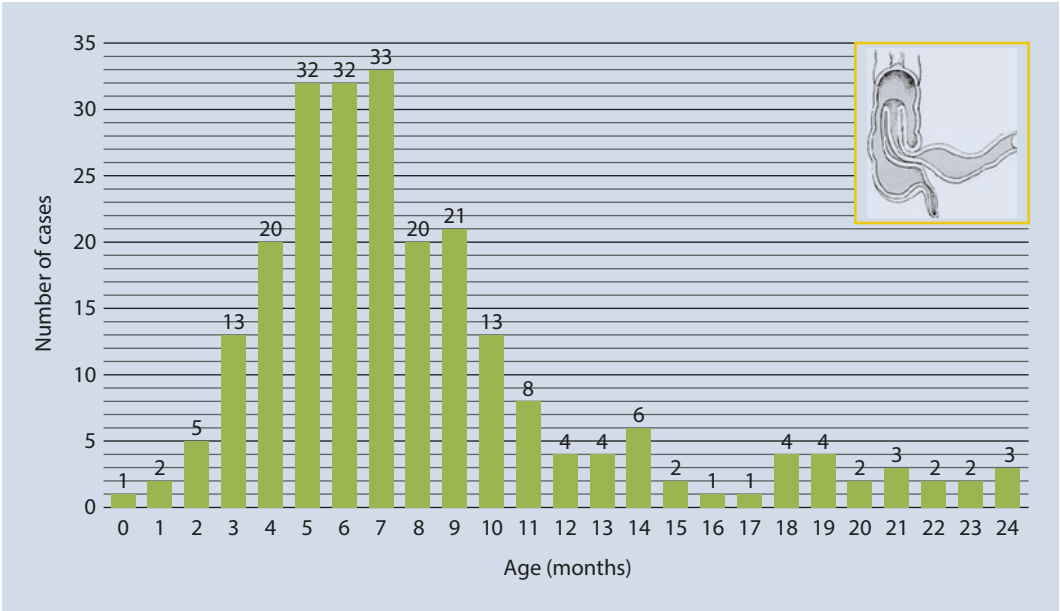


Fig. 11.8 Age distribution of naturally occurring intussusception in Finnish children. Timo Vesikari, unpublished

In RotaTeq®, the source of contamination was traced to batches of trypsin used in the manufacturing process, and with changes in the process, PCV-free vaccine should be available. However, at the present time neither RV vaccine is explicitly PCV-free.

11.12 RV Vaccine Recommendations

In Europe, there is no formal recommendation-issuing body, but the pediatric societies, the ESPID and the European Society for Paediatric Gastroenterology Hepatology and Nutrition, issued recommendations in 2008 that were updated as ESPID recommendations in 2015. The US Advisory Committee on Immunization Practices recommendations are also widely followed. Globally, the most important one is the WHO position for universal recommendation.

All major recommendations hold that RV vaccination should be given to all children, because no special "risk groups" for RVGE can be identified. However, two European countries, Croatia and the Netherlands, make an exception of the rule and recommend RV vaccination for only "high risk groups," including prematurely born infants.

11.12.1 Premature Infants

Both RotaTeq® and Rotarix™ vaccines can be given to prematurely born infants regardless of gestational age, following the recommendations according to calendar age. If the infant is still in hospital, a possible risk of transmission of the vaccine virus must be considered.

11.12.2 HIV-Infected Children

Asymptomatic HIV-infected infants can be vaccinated normally according to calendar age without any safety issues using either Rotarix™ or RotaTeq®. Screening for maternally acquired HIV infection can often be done by the time of RV vaccination at 6–8 weeks of age, but the result is not needed for decision-making on RV vaccination.

11.12.3 Immunodeficiency

The RV vaccine causes symptomatic disease (prolonged diarrhea and viral shedding) in children with severe combined immunodeficiency, and therefore vaccination is contraindicated and exposure to RV vaccine shedders should be avoided in such children. Other immunodeficiencies may be regarded similarly. Selective IgA deficiency may result in the prolonged shedding of the RV vaccine, but does not constitute a safety problem and, in any case, is usually not diagnosed by the time of RV vaccination.

11.12.4 Short Gut Syndrome and Intestinal Failure

The RV vaccine may cause substantial symptoms in children with short bowel, but given the severity of the wild-type RV infection, they should nevertheless be vaccinated under close observation.

11.13 Non-live RV Vaccines

The need and rationale for the development of non-live RV vaccines as alternatives to live oral RV vaccines are based on efficacy and safety concerns. IS remains a serious safety concern, although the magnitude of the problem is regarded as tolerable. Also, the possibility of contamination by adventitious agents such as PCV is associated with live vaccines. As for efficacy, all live RV vaccines have shown a relatively (in comparison with developed countries) low efficacy in developing countries for reasons that may not be easily remedied. Parenteral immunization may induce a higher level of protection against RV disease bypassing the intestinal obstacles.

The most advanced non-live RV vaccine is trivalent subunit P2-VP8 vaccine, originated

from NIH and endorsed by PATH. This vaccine contains VP8 proteins from rotavirus P-types P(4), P(6), and P(8). The vaccine has been tested against challenge by Rotarix vaccine and has now progressed to an efficacy trial in Africa.

A most straightforward approach is development of inactivated whole virion RV vaccine (IRV). There are several investigative IRVs in the pipeline.

Rotavirus VLP vaccines have been tested over the years preclinically. The simplest one is VP6 alone.

In addition, VLP vaccines may contain RV structural proteins VP2, VP4, and VP7, to eventually form VP2/4/6/7 VLPs. None have been tested in humans as yet.

Rotavirus VP6 alone forms tubular structures or spheres under appropriate conditions, and particulate forms of VP6 are strong immunogens. VP6 is also the simplest possible RV candidate vaccine consisting of only a single protein, which is considered a group antigen common to all group A rotaviruses. A whole new scenario might be a combined immunization against RV and norovirus GE using a RV VP6–norovirus VLP vaccine (see ▶ Chap. 25).

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