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European Society for Paediatric Infectious Diseases/European Society for Paediatric Gastroenterology, Hepatology, and Nutrition Evidence-Based Recommendations for Rotavirus Vaccination in Europe: Executive Summary

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Rotavirus (RV) is the single most common cause of severe, acute gastroenteritis (AGE) in infants and young children worldwide. By the age of 5 years, almost all children will have experienced at least 1 RV infection, with or without evidence of gastroenteritis symptoms. It is estimated that 1 in 5 cases globally will present to a doctor and 1 in 65 will require hospitalisation (1,2). Furthermore, the latest estimates suggest that more than 600,000 children die from RV-related gastroenteritis (RVGE) each year worldwide (3).

In European and other industrialised countries, death from RVGE is comparatively rare, but nevertheless more than 200 deaths may occur in European Union (EU-25) countries each year (2). Rotavirus causes a considerable burden of disease due to the large number of cases that require treatment in hospital, estimated at a minimum of 87,000 in EU-25 countries (1,2). (The number of hospitalisations was calculated using data from 2000–2003, when there were 25 EU member states. As of January 2007, there were 27 member states of the EU.) The burden on health care resources is particularly prominent during the colder months, when the seasonal peak of RV cases coincides with a peak in incidence of other infections such as influenza and respiratory syncytial virus bronchiolitis (4,5). In addition to community-acquired RV, children who are infected with RV while in hospital present a significant burden on health care systems, mainly as a result of an extended hospital stay and closure of wards to new admissions to prevent further transmission of the disease (4–6). Rotavirus-related gastroenteritis therefore puts considerable pressure on medical resources and is disruptive to the everyday life of infected children and their families.

Natural infection with RV reduces the frequency of subsequent RV episodes and protects against clinically significant RV disease (7–11), thus providing the rationale for the development of a vaccine against RVGE. Early studies with live attenuated, oral RV vaccines of animal origin (bovine or rhesus) mimicking a natural human RV infection showed that oral vaccination can also protect against severe RV disease in children (12–17). The combined experience of the natural history of RV infection and empirical findings in vaccine trials led researchers to the realisation that the primary goal for RV vaccination is, and can only be, to protect children against moderate-to-severe RVGE (13).

In 1998, after several safety and efficacy trials (18–20), the live oral rhesus–human reassortant RV vaccine (RotaShield, Wyeth-Lederle Vaccines, New York) became the first licensed vaccine against RVGE to be approved by the US Food and Drug Administration (FDA).

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The rotavirus recommendations have been approved by the European Society for Paediatric Infectious Diseases and the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition.

Conflicts of interest of the working group members are listed at the end of the article.

RotaShield was recommended for universal vaccination of infants (21). However, 9 months after it first became available, RotaShield was withdrawn voluntarily by its manufacturer due to safety concerns over an apparent, albeit rare, association with intussusception among vaccinated children (22–25). All of the recommendations for the use of RotaShield were subsequently withdrawn (24). It was later determined that most of the cases (~80%) of intussusception occurred in infants given the first dose of vaccine at age 90 days or older (25).

Two new live vaccines against RVGE—an oral live attenuated human G1P[8] vaccine (Rotarix, GlaxoSmith-Kline Biologicals, Rixensart, Belgium) and an oral live human–bovine reassortant vaccine (RotaTeq; Sanofi Pasteur MSD, Lyon, France)—were approved by the European Medicines Agency in 2006. Both Rotarix (26–32) and RotaTeq (33–35) have undergone testing for safety and efficacy, including 2 large-scale trials (each in more than 60,000 infants) that were designed specifically to evaluate safety for intussusception (30,35). In brief, both vaccines have shown >90% protective efficacy against severe RVGE, low reactogenicity, and a safety profile for intussusception not significantly different from placebo.

Taking into consideration the issues described below, a group of European experts in the field of paediatrics, infectious diseases, virology, epidemiology, gastroenterology, and public health systematically developed evidence-based recommendations for RV vaccination in Europe. The European Society for Paediatric Infectious Diseases (ESPID) and the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) played an active role in their development. These recommendations have been developed primarily to guide individual physicians regarding RV vaccination, but may also serve as the basis for future national recommendations.

The evidence-based recommendations are based on a systematic review of the literature, addressing the disease burden of RVGE in infants in Europe and all of the available published or publicly presented evidence from clinical trials of Rotarix and RotaTeq. This review was carried out by the Polish Institute for Evidence-Based Medicine. Data are presented as evidence tables, which were systematically reviewed by the expert group. Previous issues that have arisen in RV vaccination history, particularly with regard to the association between RotaShield and intussusception in the United States, were also taken into consideration.

The recommendations for RV vaccination have been developed according to the GRADE methodology (36), assigning a strength to each recommendation. The methodology, along with the evidence tables used as the basis of this technique, are presented in the Appendix of the supplement to the May 2008 issue of the *Journal of Pediatric Gastroenterology and Nutrition*.

The ESPID/ESPGHAN evidence-based recommendations for RV vaccination in Europe are summarised below. (The official use of both RV vaccines [Rotarix and RotaTeq], as recommended by the European Medicines Agency, is outlined in the Summary of Product Characteristics [SPC] for each vaccine (37,38). The SPC is the legally binding document for physicians.)

Recommendation 1: It is recommended that RV vaccination should be offered to all healthy infants in Europe (high-quality data; net benefit; strong recommendation; 1A).

Recommendation 2: Both RV vaccines licensed for use in Europe can be administered separately or concomitantly with inactivated, injectable childhood vaccines. Rotavirus vaccination can be integrated into the majority of European vaccination schedules (high-quality data; net benefit; strong recommendation; 1C+).

Recommendation 3: In European countries where oral poliovirus vaccine is still in use, concomitant administration with RV vaccine is not suggested (low-quality data; no clear net benefit; weak strength recommendation; 2B).

Recommendation 4: It is recommended that the first dose of RV vaccine should be given between the age of 6 and 12 weeks, and the full schedule (Rotarix 2 doses; RotaTeq 3 doses) should be completed by the age of 6 months (high-quality data; net benefit; strong recommendation; 1A).

Recommendation 5: It is suggested that for some special populations of infants—premature infants or those with HIV infection—RV vaccination may be considered at calendar age according to recommendations for healthy infants, at the discretion of the physician (low-quality data; less certain of the magnitude of benefit; very weak strength recommendation; 2C).

Recommendation 6: For infants with severe immunodeficiency, RV vaccination is not recommended (low-quality data; no clear net benefit; strong recommendation; 1C).

Recommendation 7: It is recommended that continued monitoring for serious adverse events should be in place for RV vaccination (high-quality data; net benefit; strong recommendation; 1C+).

The full version of the ESPID/ESPGHAN evidence-based recommendations for RV vaccination in Europe, together with articles on RV and options for the prevention of RVGE, are contained in Volume 46, Supplement 2, of the *Journal of Pediatric Gastroenterology and Nutrition*.

Conflicts of Interest of the Working Group

Prof Vesikari has received honoraria for consultancy services and lectures from Chiron, Merck, GlaxoSmith-Kline (GSK), MedImmune, and Wyeth; he has been the

principal investigator in clinical trials for RotaShield (Wyeth-Lederle Vaccines), RotaTeq (Merck), and Rotarix (GlaxoSmithKline Biologicals). Prof Van Damme has been the principal investigator in vaccine studies for Merck, Sanofi Pasteur, Sanofi Pasteur MSD, GSK Biologicals, Wyeth, and Berna Biotech, from which the University of Antwerp obtains unrestricted educational grants; the University of Antwerp received travel support grants and honoraria from Sanofi Pasteur MSD, Merck, and GSK Biologicals. Dr Giaquinto has been the principal investigator in epidemiological studies supported by Sanofi Pasteur MSD and GSK Biologicals; he has also received honoraria for consultancy services from GSK Biologicals and Sanofi Pasteur MSD. Dr Gray is the principal investigator and coordinator of a European RV strain surveillance programme supported jointly by Sanofi Pasteur MSD and GSK, and principal investigator of a burden of disease study funded by Sanofi Pasteur MSD; for both of these activities, Dr Gray is funded entirely by the Health Protection Agency (HPA), and he has received travel grants and honoraria for consultancy services from Sanofi Pasteur MSD. Dr Mrukowicz has received honoraria for consultancy services and lectures from GSK, MSD, Wyeth, Nutricia Poland, Nestlé Poland, Sanofi Pasteur Poland, and Pfizer, research grants from Nutricia and Wyeth, and financial support for scientific congresses from Nestlé Poland and GSK. Prof Dagan has been a scientific consultant to and a principal investigator in studies supported by Aventis Pasteur, Berna Biotech, GSK, MedImmune, Merck, Novartis, and Wyeth-Lederle Vaccines. Prof Guarino is a member of the Italian Rotavirus Advocacy Committee, and members of his group have received travel grants to attend meetings from companies active in the field of gastroenterology; he received research grants from Milupa, Dicofarm, and GSK. Prof Szajewska has received lecture fees and/or honoraria for consultancy services from Nestlé, Nutricia Poland, Numico, Mead Johnson Nutritionals Poland, Mead Johnson International, Biocodex France, Danone, Crotex, Merck, Biomed Lublin, Biomed Kraków, and GSK; she has received research grants or donations from Dicofarm Italy, Nutricia Research Foundation, and Biomed Lublin, and sponsorship to attend meetings from Nestlé Poland, Danone, and GSK. Prof Usonis has been the principal investigator in studies supported by GSK, Novartis, and Wyeth-Lederle Vaccines; he has been a scientific consultant to Aventis Pasteur, Baxter, GSK, Merck, and Wyeth-Lederle Vaccines and has received sponsorship from these companies to attend scientific meetings.

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