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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

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Two live vaccines against rotavirus gastroenteritis (RVGE) were approved by the European Medicines Agency in 2006: oral live attenuated human rotavirus (RV) vaccine (RIX4414, Rotarix; GlaxoSmithKline Biologicals, Rixensart, Belgium) and oral live human–bovine reassortant RV vaccine (RotaTeq; Sanofi Pasteur MSD, Lyon, France).

As of October 2007, Rotarix had been licensed in 102 countries with applications submitted to 18 others, and RotaTeq had been licensed in more than 61 countries with applications submitted to 131 others. In at least 5 countries, Rotarix is used in a national immunisation programme (Brazil, El Salvador, Mexico, Panama, and Venezuela), and RotaTeq is used for universal immunisation in the United States (1,2). In Europe, as of February 2007, Austria, Belgium, and Luxembourg had made recommendations for universal RV vaccination.

A group of European experts in the field of paediatrics, infectious diseases, virology, epidemiology, gastroenterology, and public health herein present systematically developed evidence-based recommendations on RV vaccination for the prevention of RV disease 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 the development of these recommendations.

These recommendations pertain to the available RV vaccines—Rotarix and RotaTeq. The official use of the vaccines, as recommended by the European Medicines Agency, is outlined in the summary of product characteristics available for each vaccine (3,4). This is the legally binding document for physicians.

The recommendations have considered the following:

1. The need to vaccinate against RV, as based on country-specific estimates of the disease burden of RVGE among infants (5) and other options for the prevention of RV disease relevant to the European setting (6)
2. Evidence gathered from clinical studies of Rotarix and RotaTeq (final and nonfinal formulations) up to January 30, 2007, including peer-reviewed papers; abstracts (those published between January 30 and August 31, 2007 were also considered if presenting

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

data previously supplied in an unpublished form by vaccine manufacturers); and raw data from these studies obtained through personal communication with authors and manufacturers.

3. Previous issues that have arisen in RV vaccination history, particularly the temporal association between RotaShield and intussusception in the United States

OBJECTIVES

The aims of the recommendations presented are to provide evidence-based advice on the use of RV vaccines in Europe, and provide a framework for RV vaccination at a national level. As such, these recommendations are sufficiently general and flexible for widespread application, taking into account the diversity and complexity of health care systems and practices across Europe.

These recommendations are designed for use primarily by individual physicians. They also should provide policymakers in European countries with the information and tools necessary to assist in decision making regarding vaccination policy (eg, evidence tables) and to develop their own practical guidelines through local or national bodies.

METHODOLOGY

The expert group recommendations were formulated according to systematic evidence-based methodology as proposed by the Grading of Recommendations Assessment, Development and Evaluation working group (7,8). Clinical questions were defined, and each group of questions (efficacy, safety, coadministration) provided the basis for eligibility criteria that guided a systematic review of the literature. This review was performed by independent guideline methodologists at the Polish Institute of Evidence-Based Medicine (Appendix I). Peer-reviewed papers and other data were included, as described above. Independent peer review of available information was performed by the European expert group, and the quality of the evidence was considered (high, medium, low, or very low) according to study design and directness and consistency of results (Table 1) (7). The quality of evidence indicates the extent to which one can be confident that an estimate of effect (or no effect) is correct. Recommendations were developed and graded according to the quality of the evidence during panel meetings of the European expert group (Table 2) (8). The expert group included members of the European paediatric societies, ESPID, and ESPGHAN. Panel meetings also were attended by representatives from the RV vaccine manufacturers, in a supporting role only. The methodology, scope, content, and nature of the recommendations issued reflect the opinions of the authors, and the final document has been approved by ESPID and ESPGHAN.

The methodology used for developing the recommendations, together with the tables of evidence for Rotarix and RotaTeq, are provided in Appendices I, II, and III, respectively.

RATIONALE FOR RV VACCINATION OF HEALTHY INFANTS IN EUROPE

There are several compelling reasons for adopting RV vaccination of healthy infants in countries across Europe. First, RV universally affects young infants (<5 years of age), and there are no other known risk factors that can predict progression of the disease to severe diarrhoea and dehydration with sufficient sensitivity or specificity to create a selective immunisation programme (9–11). Second, improvements in hand hygiene and sanitation have limited benefits for the prevention of disease, and long-term compliance with these regimens can be a problem (12–17). In addition, other measures for the prevention of RVGE (eg, passive immunisation, probiotics) have limited long-term effectiveness and are not suitable for large-scale use (6). Third, in Europe, oral rehydration solutions and medical management of infants with RVGE is widespread, yet RV still causes considerable morbidity, with at least 87,000 young children hospitalised each year from severe RVGE in 25 EU countries (18,19). Although rare, deaths also still occur from RVGE in previously healthy children. These deaths are not acceptable given the high standard of European health care (18). Finally, natural infection with different RV serotypes reduces the frequency of subsequent RV episodes and protects against clinically significant RV disease in the future (15,20–22). Vaccination early in life, before the first RV infection, should therefore prevent most severe cases of the disease and sequalae in healthy children. Proof of this concept was demonstrated in the early RV vaccine studies of the 1980s in Europe (23,24).

TABLE 1. *Grading the strength of the evidence (7)*

Study quality	Study design	Implication
High	Randomised controlled	Further research is unlikely to change the estimate of effect
Moderate	Randomised controlled (downgraded)/observational (upgraded)	Further research may change the estimate of effect
Low	Observational	Further research is highly likely to change the estimate of effect
Very low	Case reports, expert opinion, reasoning from first principles	Any estimation of effect is uncertain

TABLE 2. *Grading the quality of recommendations*[8]

Grade of recommendation	Clarity of risk–benefit	Methodological strength of supporting evidence	Implications
1A	Clear	RCTs without important limitations	Strong recommendation; can apply to most patients in most circumstances without reservation
1C+	Clear	No RCTs but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies	Strong recommendation; can apply to most patients in most circumstances
1B	Clear	RCTs with important limitations (inconsistent results, methodological flaws)	Strong recommendation; likely to apply to most patients
1C	Clear	Observational studies	Intermediate strength recommendation; may change when stronger evidence is available
2A	Unclear	RCTs without important limitations	Intermediate strength recommendation; best action may differ depending on circumstances or patients' or societal values
2C+	Unclear	No RCTs, but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies	Weak recommendation; best action may differ depending on circumstances or patients' or societal values
2B	Unclear	RCTs with important limitations (inconsistent results, methodological flaws)	Weak recommendation; alternative approaches likely to be better for some patients under some circumstances
2C	Unclear	Observational studies	Very weak recommendation; other alternatives may be equally reasonable

RCT = randomised controlled trial.

BACKGROUND OF RV VACCINATION

The development of RV vaccines and their widespread uptake is considered a matter of global priority by the World Health Organization, the Global Alliance for Vaccines and Immunization, and the Rotavirus Vaccine Program at the Program for Appropriate Technology in Health (25,26).

Candidate RV vaccines have been derived from the attenuation of human strains (live attenuated) in cell culture (27,28) or the reassortment of human strains with bovine strains that replicate poorly in the human host (naturally attenuated) (23,29,30). These live vaccines are administered orally to infants to mimic natural infection.

After standard safety and efficacy trials (31–33) in 1998, the US Food and Drug Administration approved a tetravalent rhesus–human reassortant RV vaccine, RRV-TV (RotaShield; Wyeth-Lederle Vaccines, New York, NY) for use in humans (34,35). The vaccine was endorsed by the Advisory Committee for Immunization Practices and the American Academy of Pediatrics for universal use in infancy (35,36). However, 9 months after it first became available, RotaShield was voluntarily withdrawn by its manufacturer in response to reports of intussusception in infants (ie, an obstruction of the bowel, due to 1 portion becoming telescoped within another), occurring particularly after the first dose of RotaShield (37–39).

Prelicensure studies had identified a weak signal for an association between RotaShield and intussusception (35,40). In light of these findings, the possibility of intussusception as an adverse effect of vaccination was included on the RotaShield package insert and the Advisory Committee for Immunization Practices recommended postlicensure studies should be carried out (35). The Vaccine Adverse Event Reporting System regularly monitored cases of intussusception occurring among RotaShield recipients (41). In response to 15 reports of intussusception, the Centers for Disease Control and Prevention and the American Academy of Pediatrics recommended that physicians suspend use of the vaccine, pending a case-control investigation (42). This investigation was carried out in more than 19 states and assessed the potential association between RotaShield and intussusception among infants of at least 1 to 12 months of age (37). The study concluded that there was an increased risk for intussusception 3 to 14 days after the first dose of RotaShield (adjusted odds ratio [OR] 21.7; 95% confidence interval [CI] 9.6–48.9), interpreted to be a result of a unique property of rhesus RV (37). Most (80%) of the cases of intussusception occurred in infants who were 90 days of age or older at the time of the first dose (43). An early study estimated the risk for intussusception after the first dose of RotaShield to be 1 in 4300 vaccinated infants, but later a consensus revised the figure to 1 in 10,000 (23,44). A recent reappraisal has suggested that the risk for intussusception with RotaShield was lower, at between 1 in 10,000 and 1 in 32,000 vaccinated infants (45,46).

Wyeth-Lederle Vaccines voluntarily withdrew RotaShield from the market in October 1999, and all of the recommendations for its use were subsequently retracted

(38,39). The license for RotaShield has since been passed on to another company, BIOVIRx (26,34), although at present it remains uncertain whether RotaShield will re-enter the market.

Candidate RV (human and human–bovine reassortant) vaccines in development at the time that RotaShield was withdrawn were reassessed in light of these findings. Live attenuated human vaccine strains were regarded to be safer for intussusception because wild-type human RVs were not known to cause this adverse event, hence the rationale—from a safety perspective—for the inclusion of an attenuated human strain in the vaccine. Bovine-RV–derived candidate vaccine strains were known to replicate poorly in the human host and be less reactogenic (for fever) than those derived from rhesus RV strains, and therefore also were regarded to be less likely to be associated with serious adverse events (34,37,47).

RV VACCINES LICENSED FOR USE IN EUROPE

Technical descriptions of RV vaccines licensed for use in Europe, Rotarix and RotaTeq, have been compiled based on the vaccines' summaries of product characteristics, which are approved by European regulatory authorities (3,4).

Rotarix

Rotarix is based on an RV of entirely human origin. The vaccine contains the RIX4414 strain of the human RV G1P[8] Wa strain. The RIX4414 strain was developed further by GlaxoSmithKline Biologicals from RV strain 89–12, which was originally derived from a wild-type isolate collected from a young boy in Cincinnati, OH (Table 3) (27). RV strain 89–12 was cloned and passaged 10 times in Vero cells to develop the RIX4414 vaccine strain (28), which expresses the outer capsid protein G1 and the attachment protein P[8].

Technical Description

Rotarix is administered to infants in 2 oral doses. Each dose contains not less than $10^{6.0}$ median cell culture–infective dose ($CCID_{50}$) (4). It is supplied as a lyophilised white solid that must be reconstituted with 1 mL of liquid diluent (supplied) before use. Excipients contained in the vaccine are sucrose, dextran, sorbitol, amino acids, and Dulbecco modified eagle medium. The diluent contains calcium carbonate, xanthan gum, and sterile water. Rotarix should be stored in a refrigerator at 2° to 8°C in its original packaging to protect it from light. The shelf life of the lyophilised vaccine is 3 years, and the reconstituted vaccine should be given promptly by oral administration, although the reconstituted vaccine has been shown to be stable when stored at ambient temperature (18°–25°C) for 24 hours (4).

RotaTeq

RotaTeq is a human–bovine reassortant vaccine developed from an original Wistar calf 3 (WC3) strain of bovine RV. The vaccine contains 5 live reassortant RV strains. Four reassortant RVs express 1 of the human outer capsid proteins, VP7 of G1, G2, G3, and G4 derived from the human RV parent strains and the attachment protein VP4, P7[5] from the bovine RV parent strain (Table 3). The fifth reassortant RV expresses the outer capsid protein G6, from the bovine RV parent strain, and the attachment protein VP4, P[8] derived from the human parent strain (3).

Technical Description

RotaTeq is given to infants as 3 oral doses. Each dose contains a viral titre of not less than 2 to 2.8×10^6 infectious units (IUs) of each viral strain (3). It is supplied in a 2-mL liquid formulation. Vaccine excipients include sucrose, sodium citrate, sodium dihydrogen phosphate monohydrate, sodium hydroxide, polysorbate

TABLE 3. *Profiles of RV vaccines licensed for use in Europe*

Vaccine	Category of vaccine and dosage	RV parent strain	Vaccine composition	G and P types	Status of vaccine	Manufacturer/ distributor
Rotarix	Human RV 2 doses	Human RV 89–12 strain	G1 strain (RIX4414)	G1P[8]	Large phase III field trials completed; licensed in several countries (including Latin America and European Union)	GlaxoSmithKline Biologicals
RotaTeq	Human–bovine reassortant RV 3 doses	Bovine RV strain Wistar calf 3 (WC3) and human RV strains WI79, Sc2, WI78, and BrB	WI79 × WC3 Sc2 × WC3 WI78 × WC3 BrB × WC3 WI79 × WC3	G1P[5] G2P[5] G3P[5] G4P[5] G6P[8]	Large phase III field trials completed; licensed in US, European Union, and countries in Latin America and Asia	Sanofi Pasteur MSD

80, culture media (containing inorganic salts, amino acids, and vitamins), and purified water. RotaTeq should be stored in a refrigerator at 2° to 8°C in the original carton to protect it from exposure to light. The shelf life of the vaccine is 2 years and the vaccine should be administered promptly after removal from the refrigerator (3).

EVIDENCE FOR RV VACCINATION OF HEALTHY INFANTS

The following sections on efficacy, safety, and coadministration of RV vaccines in healthy infants are derived from the evidence tables presented in Appendices II and III. Data have been analysed from international studies including European infants.

The safety and efficacy of Rotarix and RotaTeq for the prevention of RVGE in healthy infants have been evaluated in 11 randomised controlled trials (RCTs) involving more than 146,000 infants worldwide. This includes 7 RCTs for Rotarix (28,48–53) and 3 RCTs for RotaTeq (47,54,55).

Vaccine Efficacy

In all of the studies, the case definition for RV has been detection of RV antigen in stools by enzyme-linked immunosorbent assay along with clinical criteria (≥3 loose stools per 24-hour period and/or forceful vomiting, depending on vaccine used). Serotype identification was carried out via polymerase chain reaction on enzyme-linked immunosorbent assay–positive samples. The efficacy of the RV vaccines was evaluated against the following endpoints in healthy infants: any RVGE (Rotarix and RotaTeq), severe RVGE (Rotarix and RotaTeq), RVGE requiring an office visit (RotaTeq) or medical attention (Rotarix), RVGE requiring hospitalisation (Rotarix and RotaTeq) or an emergency department visit (RotaTeq), and RVGE caused by different RV serotypes (G1P[8], G2P[4], G3P[8], G4P[8], G9P[8]; Rotarix and RotaTeq).

The percentages quoted in the following sections are point estimates of vaccine efficacy determined from according to protocol populations of vaccine trials; further information, together with the confidence intervals, can be found in the evidence tables in Appendices II and III, Table 1.

Any RVGE

European data indicate that efficacy against RVGE of any severity over 2 years after vaccination ranges from 68% to 79% (49,56).

Severe RVGE

The severity of RV disease in clinical trials of each vaccine was assessed using different clinical scales (Vesikari vs Clark), and the definition of severity was influenced by the scale applied (≥11/20 vs ≥16/24, respectively) (57,58). To date, no studies have been published that bridge the differences between these 2 scales.

European data indicate that efficacy against severe RVGE over 2 years after vaccination ranges from 90% to 98% (49,56).

Hospitalisations and Emergency Department Visits for RVGE

Efficacy against RVGE hospitalisations during the first year ranges from 85% to 100% (49,52). For Rotarix, European data indicate that efficacy against hospitalisations up through the end of the second season after the second dose of vaccine is 96% (49). For RVGE emergency department visits and hospitalisations in Europe, efficacy up to 2 years after the third dose of RotaTeq was 94% and 96%, respectively (56).

Medical Attention for RVGE

RV vaccination was shown to reduce the need for any medical attention owing to RVGE (49,55). Data available for Rotarix from Europe indicate that efficacy against medical attention (from visit to doctor to hospitalisation) is 84% for up through the end of the second season of follow-up (49). For RotaTeq, European data indicate that efficacy against office visits is 87% for up to 2 years of follow-up (56).

Efficacy Against the Most Prevalent Circulating Serotypes

Efficacy has been established for both vaccines against clinically important outcomes for the most prevalent circulating serotypes (G1P[8], G3P[8], G4P[8], G9P[8], and G2P[4]) (49,55,56). However, the point estimate with both vaccines is less precise for G2[P4] than the other common serotypes (49,55,56). Efficacy data and confidence intervals are presented in the evidence tables (Appendices II and III, Table 2).

Vaccine Safety

The evidence summarised below refers to the final vaccine formulations, as detailed in the evidence tables (Appendices II and III, Table 3).

Reactogenicity

When considering reactogenicity in these studies, the endpoints measured are fever, vomiting, diarrhoea, and irritability. Reactogenicity data show good consistency of results, no contradictory results, and completeness of follow-up. For Rotarix, no difference versus placebo was observed in the incidence of diarrhoea, fever or severe fever, vomiting or severe vomiting, and irritability or

severe irritability, within 14 days of vaccination with any dose (28,48,50,53). For RotaTeq, no significant difference was observed in the incidence of fever or severe fever and irritability or severe irritability. A slight increase in the incidence of diarrhoea and vomiting (on average, 1 in 77 vaccinated infants, within 7 days after dose 1) was observed with RotaTeq, but these symptoms were mild and did not require treatment (54,55,59).

Both vaccines are well tolerated with a low reactogenicity profile when given alone. When coadministered with other common injectable childhood vaccines, they do not cause clinically significant increases in reactogenicity (50,51,53,60,61).

Intussusception

Two trials were specifically designed to address the question of the effect of RV vaccination on risk for intussusception (52,55). For both vaccines, the risk for intussusception was no greater than that observed in placebo recipients. For Rotarix, up to 31 days after each dose of vaccine, 6 cases of intussusception were reported in 31,673 vaccine recipients versus 7 cases in 31,552 placebo recipients (relative risk [RR] 0.9, 0.3–2.4). In a subset of infants, up to 1 year after each dose of Rotarix, 4 cases of intussusception were reported among vaccine recipients and 14 in placebo recipients (RR 0.3, 0.1–0.8). For RotaTeq, up to 42 days after each dose of vaccine, 6 cases of intussusception were reported among 28,038 vaccine recipients versus 5 cases in 27,965 placebo recipients (RR 1.2, 0.3–5.0). Up to 1 year after each dose of RotaTeq, 12 cases of intussusception were reported among vaccine recipients and 15 in placebo recipients (RR 0.8, 0.3–1.8) (55,62). Other smaller trials have also evaluated this endpoint (28,47,50,51,53,54,63–67). Although isolated occurrences of intussusception have been detected, no conclusion can be based upon them.

Initial postmarketing surveillance for RotaTeq from the United States showed that ''the number of intussusception cases reported to date does not exceed the number expected based on background rates of 18 to 43 [cases] per 100,000 [children] per year for an unvaccinated population of children ages 6 to 35 weeks'' (68). Consistent with this report, updated data (March 2006–August 2007) shows the incidence of intussusception to be 160 cases per 9.1 million doses of vaccine distributed, which is considerably lower than the expected background rate of intussusception (69). Although this figure is reassuring, the exact numbers of doses administered and children vaccinated with RotaTeq are not known at this stage, thus continued surveillance is warranted. The Centers for Disease Control and Prevention continue to support vaccination with RotaTeq in the United States. Rotarix is not marketed in the United States, therefore similar data are not yet available. Active surveillance with Rotarix has been implemented in Mexico, and findings are likely to be available soon.

Other Adverse Events

There was no statistically significant increased risk for death or other serious adverse events noted with either vaccine compared with placebo.

Shedding and Transmission

There is evidence of vaccine virus shedding for both RV vaccines during early clinical trials. For Rotarix, there have been only a few cases of documented transmission to contacts. The rate of transmission is unknown, and no cases have developed symptoms of RVGE (50). There are no documented cases of transmission of RotaTeq, although in 2 instances the vaccine virus was detected in the stools of placebo recipients (70). Owing to the nature of the attenuated RV vaccine strains, shedding and transmission is not considered a significant safety concern.

Vaccine Coadministration

Two endpoints were considered: the percentage of infants above commonly accepted cutoff values, and the geometric mean titres/geometric mean concentrations.

Inactivated Vaccines

The manufacturers recommend that the RV vaccines be given in the first 6 months of life. The issue of coadministration of RV vaccines (Rotarix and RotaTeq) with commonly used paediatric vaccines has been evaluated in 7 RCT studies involving approximately 9500 infants (50,51,53,60,61,71–75). Both Rotarix and RotaTeq can be coadministered with diphtheria-tetanus–acellular pertussis, diphtheria-tetanus–whole cell pertussis (specific data are available for Rotarix only), *Haemophilus influenzae* type B vaccine, inactivated polio vaccine, hepatitis B vaccine, and pneumococcal conjugate vaccine, with no observed immune interference for any measured entity; Rotarix also can be given together with meningococcal C conjugate vaccine. Results are not yet available for coadministration of RotaTeq with meningococcal vaccines.

Oral Poliovirus Vaccine

Concomitant administration of 2 oral attenuated vaccines may result in interference with the immune response to 1 or both vaccines. Administration of RV vaccines at the same time as oral poliovirus vaccine (OPV) is under investigation. Data from a South African study showed that concomitant administration of Rotarix and OPV did not interfere with the immune response to

OPV (for all 3 strains), and did not significantly interfere with the immune response to Rotarix after a full course (2 doses) of RV vaccine given at 10 and 14 weeks of age (60,61). Data from a study performed in Latin America showed that concomitant administration of RotaTeq and OPV did not interfere with the immune response to OPV (for all 3 strains), and did not significantly interfere with the immune response to RotaTeq after a full course (3 doses) of RV vaccine administered at 8, 16, and 24 weeks of age (75).

In large-scale clinical trials of Rotarix, efficacy data were obtained when RV vaccine was given 2 weeks apart from OPV (52); OPV was not used in clinical efficacy trials of RotaTeq (47,54,55,70,74). At present, data are not sufficient to support coadministration with OPV; however, collection of efficacy data for concomitant administration of both oral vaccines is ongoing. There were no studies available during the period covered by the literature review to evaluate the safety (eg, intussusception) of RV vaccines when coadministered with OPV.

EVIDENCE FOR RV VACCINATION OF BREAST-FED INFANTS AND INFANTS WITH UNDERLYING CONDITIONS

Data on the efficacy, safety, and reactogenicity of RV vaccine in infants with underlying conditions are scarce.

Breast-fed Infants

RCTs have shown that both RV vaccines licensed for use in Europe can be administered to infants who are being breast-fed without affecting the efficacy of the vaccines. Normal breast-feeding activity was not altered for infants participating in large-scale clinical investigations of both vaccines (52,53,55).

Human Immunodeficiency Virus-infected Infants

One study by Fontana et al (76) suggests that RVGE is no more severe in human immunodeficiency virus (HIV)–infected infants than in immunocompetent infants. However, case reports have described severe diarrhoea in HIV-infected European infants. HIV-infected infants are, therefore, a target for RV infection, and diarrhoea in these infants may be severe (77). Studies in HIV-infected infants are ongoing for Rotarix and planned for RotaTeq.

Premature Infants

Evidence indicates that RotaTeq can be safely given to otherwise healthy premature infants older than 32 weeks of gestation (median, 34 weeks of gestation) (78) if administered according to schedule at the infants' calendar age. Studies examining administration of Rotarix in premature infants are ongoing.

EVIDENCE-BASED RECOMMENDATIONS

The ESPID/ESPGHAN evidence-based recommendations for RV vaccination in Europe are presented below and summarised in the executive summary presented in the May 2008 issue of the *Journal of Pediatric Gastroenterology and Nutrition*.

Healthy Infants: Routine Administration

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

Remarks

RV is a universal disease with a high burden in European countries. There are 2 licensed RV vaccines in Europe (Rotarix and RotaTeq), both of which can be used to control and prevent severe RVGE. RCTs have shown that both of these RV vaccines are highly effective, have a good safety profile, and are well tolerated in infants to prevent RVGE, severe RVGE, and hospital admission.

Concomitant Administration

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

Remarks

Given the highly populated landscape of the childhood vaccination calendar, new vaccines introduced must integrate well into the existing schedule. It has been shown that RV vaccines can be coadministered with most commonly used, injectable childhood vaccines given in the first 6 months of life without affecting efficacy or safety.

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

Remarks

There were insufficient clinical efficacy and safety (eg, intussusception) data available to support a recommendation for concomitant administration of RV vaccines with OPV. Given that in the European setting vaccine safety is prioritised over efficacy, the expert group adopted a conservative approach while formulating this recommendation.

Dosing Schedule

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

Remarks

There were insufficient data available to describe the risk for intussusception when the first dose of RV vaccine is given to infants older than 3 months. Taken alongside the facts that the risk for RotaShield-associated intussusception was observed in infants who received the first dose of vaccine after 3 months of age, and that the peak natural incidence of intussusception occurs at 4 to 9 months of age (79–81), it is advisable that the first dose of RV vaccine be given before the age of 3 months, and the complete course (Rotarix 2 doses; RotaTeq 3 doses) be completed by 6 months of age (this schedule was used in almost all clinical trials of these vaccines). Catch-up vaccination with the first dose of RV vaccine given to infants older than 3 months and any dose given to infants older than 6 months is therefore not recommended.

Evidence for efficacy of the available RV vaccines is limited to a full schedule. However, incomplete dosing of RV vaccines is likely to result in at least some efficacy against RV endpoints.

There were no data available concerning a mixed schedule (Rotarix first followed by RotaTeq or vice versa); therefore, no recommendation can be issued with regard to interchangeability of these vaccines.

Vaccination of Infants With Underlying Conditions

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).*

Remarks

Prelicensure clinical trials have been performed in healthy infants and have not investigated the possibility of using RV vaccines in infants with underlying conditions (eg, chronic diseases, malformations of the gastrointestinal tract, food intolerance, following abdominal surgery). Therefore, because of insufficient evidence at present, no specific recommendation can be made for RV vaccination of infants with underlying conditions. However, because it is expected that infants with HIV infection undergo progressive immune impairment, RV vaccination could be indicated in HIV-infected infants. Supportive data are required. Preliminary evidence of RotaTeq efficacy and tolerance in otherwise healthy premature infants was discussed earlier in the article.

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

Remarks

Given the absence of specific data, this recommendation has been reached by extrapolation of evidence from other live vaccines.

Continued Safety Surveillance

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

Remarks

For both vaccines, short- and long-term (1-year) data show no increased risk for intussusception after vaccination. However, in light of the link between RotaShield and intussusception, particular emphasis should be placed on this outcome for continued surveillance (82). These data should evaluate intussusception and vaccination in a real-life setting. It is hoped that these results will confirm the lack of an association between intussusception and RV vaccines that was observed in prelicensure trials of both vaccines in healthy infants (45,46).

Given that intussusception is the most common cause of intestinal obstruction in young infants, cases will naturally occur within the time frame of RV vaccination (82). Surveillance systems will, therefore, need to distinguish between those cases temporally linked by chance with RV vaccination, and those that may have occurred as a direct result of the vaccine.

CONCLUSIONS

The recent approval of Rotarix and RotaTeq by European authorities has revived the need for European recommendations pertaining to RV vaccination. The recommendations presented here advise individual physicians on the evidence-based use of RV vaccination in Europe and provide a framework for use of the vaccine at a national level.

European countries will need to decide which vaccination policy to adopt—universal vaccination of all infants or optional vaccination. It should be noted that all infants and young children are at risk for being infected with RV and—in the absence of risk factors to predict progression to severe disease, hospitalisation, and death—an at-risk–based vaccination programme is not an option for RV

vaccines. Universal vaccination of all infants has the potential to effectively reduce the burden of RVGE in Europe.

Conflicts of Interest of Working Group Members

T.V. has received honoraria for consultancy services and lectures from Chiron, Merck, GlaxoSmithKline, MedImmune, and Wyeth. He has been the principal investigator in clinical trials for RotaShield (Wyeth-Lederle Vaccines), RotaTeq (Merck), and Rotarix (GlaxoSmithKline Biologicals). P.V.D. has been the principal investigator of vaccine studies for Merck, Sanofi Pasteur, Sanofi Pasteur MSD, GlaxoSmithKline Biologicals, Wyeth, and Berna Biotech, a Crucell company, for 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 GlaxoSmithKline Biologicals. C.G. has been principal investigator in epidemiological studies supported by Sanofi Pasteur MSD and GlaxoSmithKline Biologicals. He also has received honoraria for consultancy services and educational and research grants from Abbott, Bristol-Myers Squibb, Gilead, GlaxoSmithKline Biologicals, Sanofi Pasteur MSD, and Tibotec. J.G. is principal investigator and coordinator of a European rotavirus strain surveillance programme supported jointly by Sanofi Pasteur MSD and GlaxoSmithKline. He also is principal investigator of a burden of disease study funded by Sanofi Pasteur MSD. For both of these activities, he is funded entirely by the Health Protection Agency. He also has received travel grants and honoraria for consultancy services from Sanofi Pasteur MSD. J.M. has received honoraria for consultancy services and lectures from GlaxoSmithKline, 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 GlaxoSmithKline. R.D. has been a scientific consultant for and a principal investigator of studies supported by Aventis Pasteur, Berna Biotech, GlaxoSmithKline, MedImmune, Merck, Novartis, and Wyeth-Lederle Vaccines. He has also received compensation for speaking engagements from GlaxoSmithKline, Wyeth, Sanofi Pasteur, and Novartis. A.G. is a member of the Italian Rotavirus Advocacy Committee; members of his group have received travel grants to attend meetings from companies active in the field of gastroenterology, and he received research grants from Milupa, Dicofarm, and GlaxoSmithKline. H.S. 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 GlaxoSmithKline. 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 GlaxoSmithKline. V.U. has been the principal investigator for studies supported by GlaxoSmithKline, Novartis, and Wyeth-Lederle Vaccines. He also has been a scientific consultant for Aventis Pasteur, Baxter, GlaxoSmithKline, Merck, and Wyeth-Lederle Vaccines, and has received sponsorship from these companies to attend scientific meetings.

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