Case study: Evaluation of Rotavirus vaccine impact and safety following introduction into the national immunizations programme of Sudan

Background

Rotavirus is one of the most common causes of childhood death and disease worldwide, claiming the lives of nearly 500,000 children a year. Rotavirus is the most common cause of severe diarrhea and vomiting in infants and young children, and is more likely than other causes of diarrhea to lead to dehydration and death. Even where improvements in water, sanitation, and hygiene have dramatically lowered the overall incidence of diarrheal diseases, the toll taken by rotavirus remains.

New rotavirus vaccines have the potential to improve global child survival and health. Two new rotavirus vaccines have demonstrated efficacy of 85-98% against severe rotavirus disease in clinical trials conducted in high and middle income countries of the Americas and Europe, and encouraging effectiveness data is also accumulating from the early introducing rich countries. In resource poor countries, factors such as co-infection with other enteric pathogens, co-morbidities, and malnutrition could adversely affect the performance of these orally administered vaccines. Therefore, efficacy trials of these vaccines were conducted in many countries of Asia and Africa. Results from these trials have demonstrated moderate efficacy (51-64%) that is lower than that in high and middle income countries but nevertheless suggests substantial health benefits from vaccination. After reviewing these clinical trials data in April 2009, WHO recommended inclusion of rotavirus vaccines in all countries worldwide. Countries where diarrheal deaths account for >10% of child mortality are considered high priority for vaccine introduction. Recent sentinel surveillance for diarrheal disease in Sudan has revealed that rotavirus accounts for about 20% of all diarrhea cases among hospitalized children.

Based on a recommendation from their National Immunizations Technical Advisory Group (NITAG), the Federal Ministry of Health (FMoH) of Sudan decided to introduce rotavirus vaccine into their national immunization program. However, since this is an expensive vaccine, the Ministry of Finances (MoF) and the Interagency Coordinating Committee (ICC) requested the MOH to develop a plan to document the impact of this vaccine on diarrhea in Sudan, before providing final approval for vaccine introduction and in order for them to make long term commitment to financing this vaccine. In addition, the FMoH wanted to ensure monitoring the safety of the vaccine post introduction, esp. in view of reports of intussusception with earlier rotavirus vaccines.

Task

The FMOH asked the NITAG and a specially gathered group of experts, to develop a strong plan to evaluate the impact of rotavirus vaccine on diarrhea in Sudan, including various epidemiologic studies as well as studies to evaluate the programmatic impact on EPI and the program of Diarrheal Disease Control (DDC) which had been very successful in Sudan. By the end of the session your group will have to come up with a short list of various studies / assessments that the country will need to conduct to adequately evaluate the impact and safety of the newly introduced rotavirus vaccine.

Composition of the National Immunizations Technical Advisory Group (NITAG)

Sudan NITAG deals with both adult and childhood immunizations. It consists of the following 8 members

- Chairman (University hospital pediatrician with subspecialty in child infectious diseases, and special interest in enteric pathogens)
- Secretary (National Immunizations Director/EPI manager)

Six other members who are:

- a clinical pediatrician with extensive experience in clinical trials
- a virologist who is the national rotavirus specialist
- a clinical epidemiologist with background in both chronic and infectious disease epidemiology in national and international context
- a public health nurse with special experience in health education and adverse events monitoring
- a clinical microbiologist who heads the national reference center for special pathogens
- a pharmacist with the national regulatory authority for drugs and vaccines

The MOH has invited the following experts to help develop the evaluation plan:

- a health economist with experience in rota virus cost effectiveness study
- the chairman of the Pediatric Society of Sudan,
- A surveillance officer from the MOH who is in charge of national surveillance for diarrhea
- A vaccine safety officer

Advice on the group work process

- Choose the chairman. Choose the rapporteur.
- Give each member of the group a role of the different participants at the meeting, and debate the value of the different studies, including cost, feasibility, ease of implementation, existence of background data in order to have before and after information for comparison, etc…. You will need to make some assumptions. The facilitators of the group will try to provide you with more data should you need it.

The meeting should last no longer than 1 hour 20 minutes, after which the MOH has arranged for the chairman of the expert group to give a summary of their advice to the Ministry of Finances who presently is drafting the 5 year financial plan of the country.

References (in separate files)

1. Generic protocol for monitoring impact of rotavirus vaccination on gastroenteritis disease burden and viral strains, WHO, 2008 (www.who.int/vaccines-documents)
2. Bines JE, Patel M, Parashar U. Assessment of postlicensure safety of rotavirus vaccine, with emphasis of intussusception. J Infect Dis 2009;200:S282-90
3. Patel M, Parashar U. Assessing the effectiveness and public health impact of rotavirus vaccines after introduction in immunization programs. J Infect Dis 2009;200:S2919-9.
4. Global rotavirus information and surveillance bulletin, Vol. 3, April 2011

Statistics

Total population	**42,272,000**
Gross national income per capita (PPP international $)	**1,920**
Life expectancy at birth m/f (years)	**59/59**
Under five mortality (per 1 000 live births)	**109**
Birth Cohort	**1,300,000**
Total expenditure on health per capita (Intl $, 2009)	**161**
Total expenditure on health as % of GDP (2009)	**7.3**

Figures are for 2009 unless indicated. Source: Global Health Observatory

Vaccine	Schedule
BCG	birth;
DTwPHibHep	6, 10, 14 weeks;
Measles	9 months;
OPV	6, 10, 14 weeks;
Pneumo_conj	*[From Janaury 2012]*
Rotavirus	*July 2011 (6 and 10 weeks)*
TT	1st contact; +1, +6 month; +1, +1 years;

Global Rotavirus Information and Surveillance Bulletin

Volume 3: April 2011

The World Health Organization (WHO) produces this twice-yearly Global Rotavirus Information and Surveillance Bulletin to share activities and data from the WHO-coordinated surveillance network for rotavirus with partners at the national, regional and global levels.

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Spotlight on Efforts to Improve Data Quality

Access to high-quality surveillance data is of upmost importance for national governments to take appropriate decisions around introduction and use of rotavirus vaccines and to monitor its impact. Thus, WHO has been supporting the national Ministries of Health to further improve the quality of rotavirus surveillance:

1. Ensuring adherence to case definitions at sentinel hospital sites:

- ***Suspected case*:** Any child aged 0-59 months admitted for treatment of acute (i.e. ≤14 days) watery gastroenteritis/diarrhoea to a sentinel hospital conducting surveillance. Excluded are children with bloody diarrhoea and children transferred from another hospital.

- ***Confirmed case:*** A suspected case in whose stool the presence of rotavirus is demonstrated by means of an enzyme immunoassay.

2. Strengthening the laboratory network

- **by purchasing laboratory supplies**

WHO purchased basic laboratory supplies and equipment for needy sentinel hospital laboratories. Additionally, rotavirus test kits of assured quality were supplied to those laboratories.

- **by launching an external quality assurance (EQA) programme**

WHO is working with the Global Reference Laboratory, based at the U.S. Centers for Disease Control and Prevention (CDC), and the Regional Reference Laboratories (RRLs) to launch an EQA programme in 2011. Two rounds of testing are planned, with the first covering the participating RRLs and the second expanding to include the participating national and sentinel site laboratories.

3. Assessing sentinel sites

WHO and CDC have jointly developed a standardized assessment tool for sentinel surveillance sites. Ongoing assessment of sites with feedback of performance and suggestions to improve activities is critical to ensuring high-quality rotavirus surveillance.

Summary of January through June 2010 Rotavirus Surveillance Data

This Bulletin presents surveillance data for January through June 2010, as reported by Member States participating in the WHO-coordinated global surveillance network for rotavirus. Data are collected through sentinel surveillance targeting children < 5 years of age who are hospitalized for treatment of acute gastroenteritis/diarrhoea. Summarized below are the main findings from January through June 2010:

Member States reporting data

- 49 Member States reported rotavirus surveillance data to WHO from 138 sentinel sites
- 34 of 49 (69%) reporting countries were GAVI-eligible

Annual rotavirus detection rates (July 2009 through June 2010):

- Global median (among 38 countries): 36%
- By WHO Region:
  - Highest: South-East Asia Region (46%)
  - Lowest: Region of the Americas (20%); possibly due to rotavirus vaccine introduction in 4/5 countries in this region
- By country:
  - Highest: Democratic Republic of the Congo (65%)
  - Lowest: Suriname (3%); country had not introduced rotavirus vaccine as of Dec 2009
- By age group[1]:
  - Highest: 6-11 months old
  - Lowest: 24-59 months old

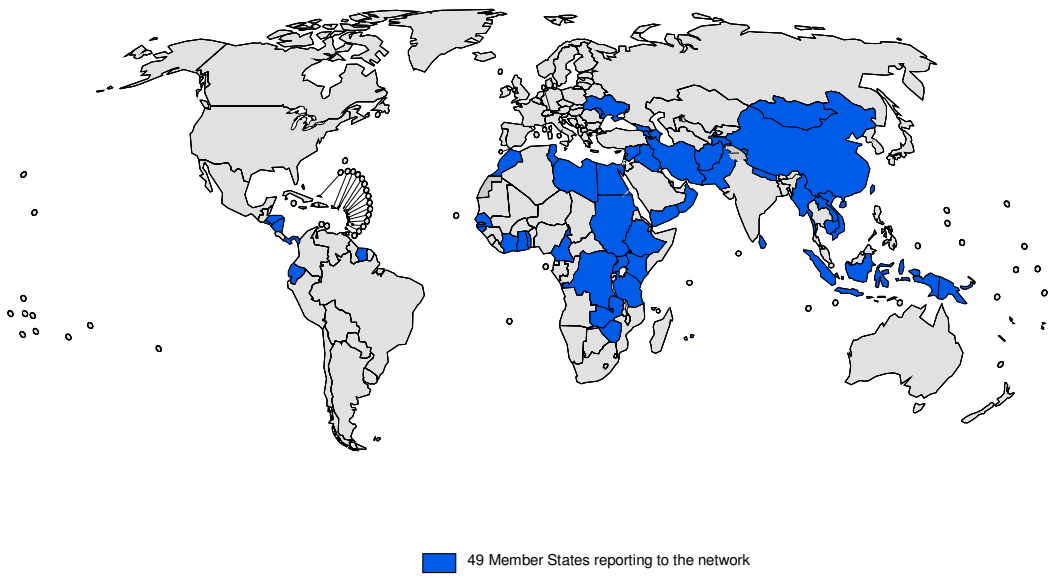
[1] Data available only from the Eastern Mediterranean Region and Western Pacific Region

Annex: January through June 2010 Rotavirus Surveillance Data

The Global Surveillance Network for Rotavirus

In the first semester of 2010, 49 WHO Member States participated in the global surveillance network for rotavirus and reported data to WHO (Figure 1). More than half of these countries (53%) were based in 2 WHO Regions: the African Region and the Eastern Mediterranean Region. Overall, 34 (69%) participating countries were eligible for GAVI funding (Table 1).

Figure 1: WHO Member States reporting to the global surveillance network for rotavirus – Jan-June 2010.



Source: Data collected from WHO Regions and partners. Date of slide: 11 April 2011

Table 1: Characteristics of the global surveillance network for rotavirus, by WHO Region - Jan-June 2010

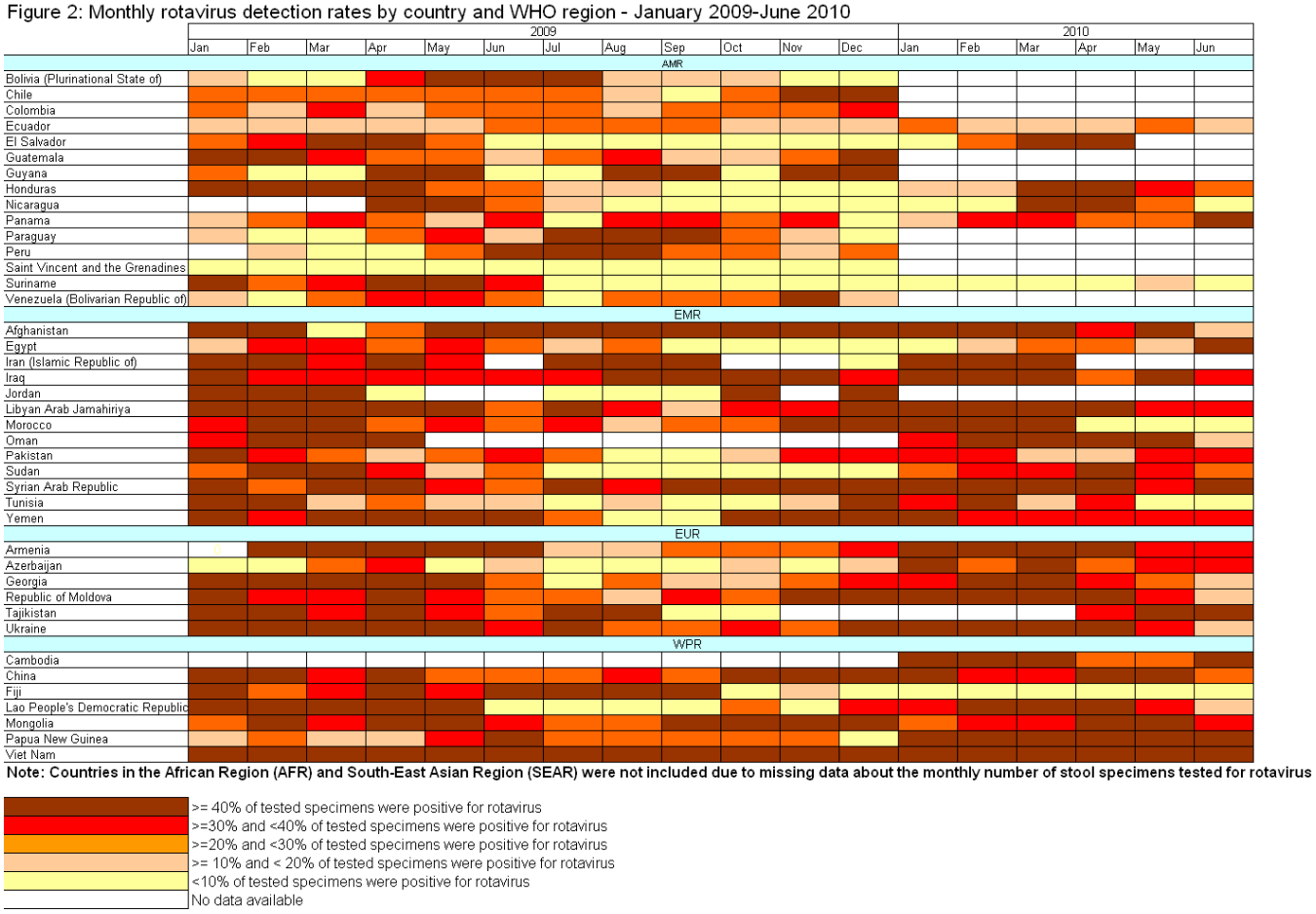
WHO Region*	Total number of countries reporting	Number of GAVI-eligible countries reporting	% of all countries reporting who are GAVI-eligible	Total number of sentinel sites reporting
AFR	14	13	93%	20
AMR	6	2	33%	27
EMR	12	4	33%	56
EUR	6	6	100%	9
SEAR	4	4	100%	7
WPR	7	5	71%	19
Total	49	34	69%	138

*The following countries participated in the global surveillance network for rotavirus from January through June 2010 : Cameroon, Côte d'Ivoire, Democratic Republic of the Congo (the), Ethiopia, Ghana, Guinea-Bissau, Kenya, Mauritius, Senegal, United Republic of Tanzania (the), Togo, Uganda, Zambia and Zimbabwe in the African Region (AFR); Ecuador, El Salvador, Honduras, Nicaragua, Panama and Suriname in the Region of the Americas (AMR); Afghanistan, Egypt, Iran (Islamic Republic of), Iraq, Libyan Arab Jamahiriya, Morocco, Oman, Pakistan, Sudan, Syrian Arab Republic, Tunisia and Yemen in the Eastern Mediterranean Region (EMR); Armenia, Azerbaijan, Georgia, Republic of Moldova, Tajikistan and Ukraine in the European Region (EUR); Indonesia, Myanmar, Nepal and Sri Lanka in the South-East Asian Region (SEAR); Cambodia, China, Fiji, Lao People's Democratic Republic, Mongolia, Papua New Guinea and Viet Nam in the Western Pacific Region (WPR).

Rotavirus Detection

Rotavirus detection rates were calculated as the proportion of tested stool specimens positive for rotavirus. Detection rates were displayed by month, country and WHO Region starting from January 2009 (Figure 2). Nine countries in the Region of the Americas discontinued reporting to WHO during the 1st semester of 2010 compared to 2009.

Figure 2: Monthly rotavirus detection rates by country and WHO region - January 2009-June 2010



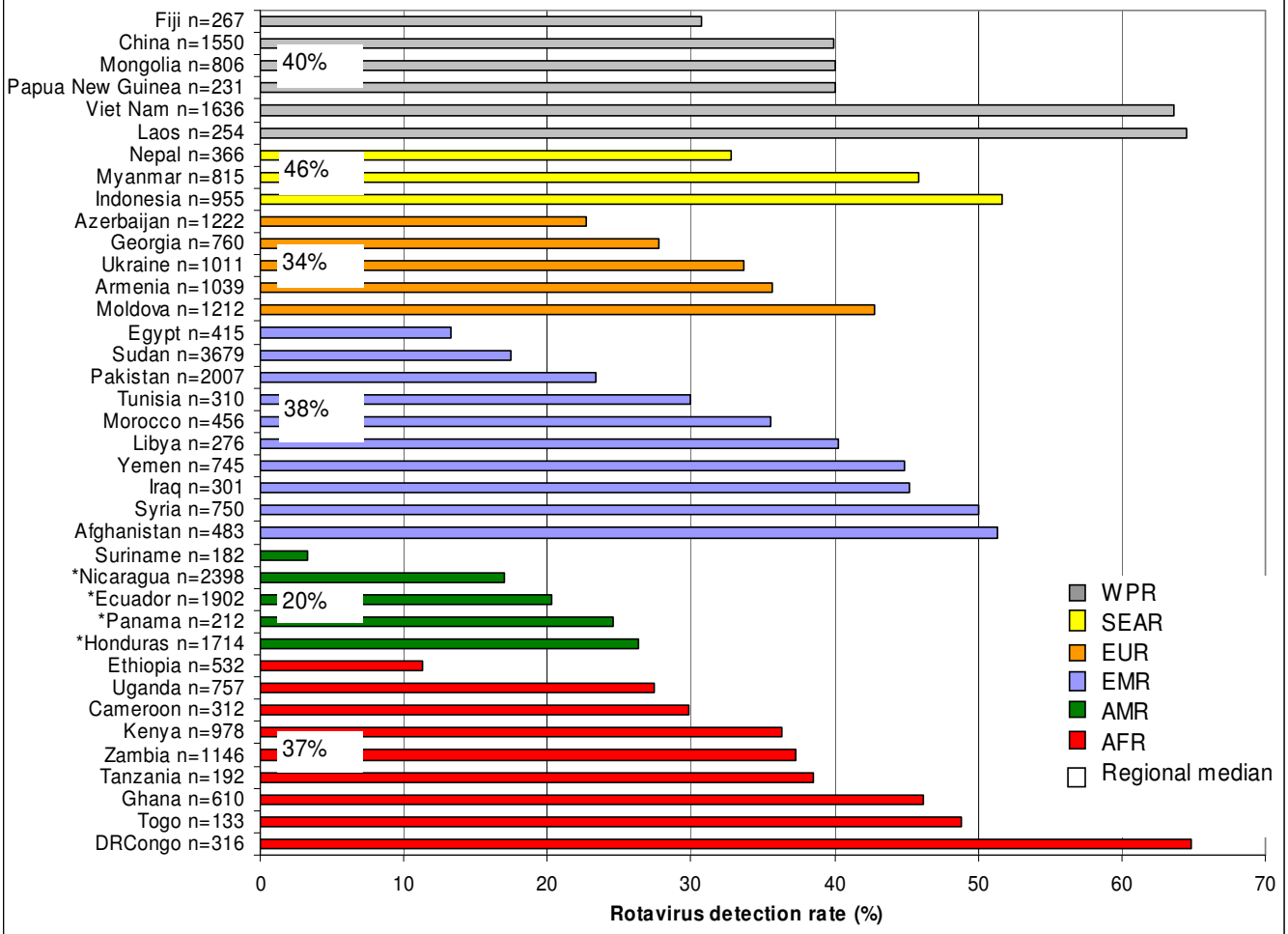
Note: Countries in the African Region (AFR) and South-East Asian Region (SEAR) were not included due to missing data about the monthly number of stool specimens tested for rotavirus

- >= 40% of tested specimens were positive for rotavirus
- >=30% and <40% of tested specimens were positive for rotavirus
- >=20% and <30% of tested specimens were positive for rotavirus
- >= 10% and < 20% of tested specimens were positive for rotavirus
- <10% of tested specimens were positive for rotavirus
- No data available

Annual rotavirus detection rates were also calculated for the period of July 2009 through June 2010. In order to avoid bias due to seasonal variations in rotavirus disease, only countries that reported on the number of stool specimens tested for all 12 months were included in this full-year analysis. Furthermore, countries were only included if at least 100 specimens were tested. A rotavirus detection rate was calculated for each of the 38 countries meeting these two criteria (Figure 3). Regional and global median detection rates were also calculated for all 38 countries. The regional median detection rates ranged from 20% in the Region of the Americas to 46% in the South-East Asian Region The global median detection rate was 36%, with a range of 3-65% among the 38 countries

The 3% detection rate reported by Suriname is an extreme outlier - further evaluation of rotavirus surveillance in the country is needed to identify factors contributing to such a low detection rate since the country had not introduced rotavirus vaccine in their national immunization programme.

Figure 3: Annual rotavirus detection rates by country and WHO region - July 2009-June 2010.
The number of stool specimens tested (n=) stated next to the country.



*Countries with rotavirus vaccine in national immunization schedules: Nicaragua and Panama (2006 introductions), Ecuador (2007 introduction) and Honduras (2009 introduction).

Annual rotavirus detection rates for July 2009 through June 2010 were also assessed by age groups in the Eastern Mediterranean and Western Pacific Regions (Table 3); other regions only recently started to report data by age groups or have yet to do so. Among 10 countries in the Eastern Mediterranean Region, the median detection rate was highest among children 6-11 months old (41%) and lowest among children 24-59 months old (31%). Among 5 countries in the Western Pacific Region, the median detection rate was also highest among children 6-11 months old (52%) and lowest among children 24-59 months old (30%).

Table 3: Annual rotavirus detection rates, medians by age group and WHO region - July 2009-June 2010

		Median detection rate (%)				
WHO Region	No.of countries*	0-5months	6-11months	12-23months	24-59months	All children < 5 years of age
EMR	10	36	41	36	31	38
WPR	5	40	52	46	30	40

*Countries meeting the criteria for inclusion in July 2009-June 2010 full-year analysis and reporting surveillance data by age group: Afghanistan, Egypt, Iraq, Libyan Arab Jamahiriya, Morocco, Pakistan, Sudan, Syrian Arab Republic, Tunisia and Yemen in the Eastern Mediterranean Region (EMR); China, Lao People's Democractic Republic, Mongolia, Papua New Guinea and Viet Nam in the Western Pacific Region (WPR).

Acknowledgements

WHO gratefully acknowledges the dedicated efforts of the numerous individuals and organizations involved with compiling this surveillance information, including Ministries of Health, sentinel hospitals, as well as the network of global, regional and national reference laboratories.

WHO Rotavirus Surveillance Websites

http://www.who.int/nuvi/rotavirus/en/index.html
http://www.who.int/nuvi/surveillance/en/

Assessing the Effectiveness and Public Health Impact of Rotavirus Vaccines after Introduction in Immunization Programs

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Two new vaccines against severe rotavirus gastroenteritis that have high efficacy in middle- and high-income countries have recently been licensed in many countries worldwide. Clinical trials in low-income countries in Africa and Asia are ongoing. Experience gained through studies of natural rotavirus infection and the clinical trials for the current and previous rotavirus vaccines indicate that, as countries begin to introduce these newly approved vaccines into routine childhood immunization programs, monitoring their performance in real world settings should be a high priority. Key epidemiological considerations in the postlicensure period include (1) how the vaccine will perform against severe rotavirus disease under routine public health use; (2) how routine vaccination will impact the epidemiology of disease with regard to the burden of severe disease and death, age distribution of cases, seasonality, and serotype distribution; (3) whether vaccination will have a sufficient impact on transmission to reduce disease burden in unvaccinated age groups; and (4) whether vaccine will confer protection through the first 3 years of life, when most severe disease and mortality associated with rotavirus occur. Monitoring of impact with focus on these public health considerations will allow parents, health care providers, and decision makers to appreciate the health benefits of vaccination in reducing the burden of severe rotavirus disease. It will also allow assessment of the effectiveness of rotavirus vaccines in programmatic use and the need for modifying vaccination schedules or vaccine formulations to enhance the performance of immunization. In this article, we review data for the protective efficacy of the 2 new rotavirus vaccines, with emphasis on issues particularly important for consideration as these vaccines are introduced in routine infant immunization programs.

With the licensure and introduction of 2 new rotavirus vaccines (RotaTeq [Merck Vaccines] and Rotarix [GlaxoSmithKline Biologicals]) in routine immunization programs, monitoring their impact on rotavirus-associated morbidity and mortality and demonstrating public health benefits of vaccination are high priorities in many countries worldwide. Prelicensure clinical trials of these vaccines have demonstrated excellent efficacy (85%–98%) against severe rotavirus disease in middle- and high-income countries [1–9]. In developing countries, many factors, such as interference by maternal antibodies, breastfeeding, prevalent viral and bacterial gut infections, and malnutrition, might adversely affect the performance of these vaccines, and trials to evaluate efficacy in these settings are underway [10, 11]. In middle- and high-income countries, variations in use of the vaccine in routine public health practice, compared with clinical trials, could also lead to efficacy that is different from that in clinical trials. In addition, efficacy could vary in areas where the prevalence of strains is different from that in clinical trials [12]. In this article,

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The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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we review key issues that remain to be fully addressed regarding the effectiveness and public health impact of rotavirus vaccines and outline a framework to address these issues as rotavirus vaccines become a component of routine infant immunization programs globally.

KEY ISSUES

Impact on health care use for diarrhea, including herd immunity. In addition to their high demonstrated efficacy against severe rotavirus disease, both Rotarix and RotaTeq substantially reduced overall health care use for diarrhea in clinical trials (Table 1). In the trials, Rotarix reduced the rate of hospitalizations for all-cause gastroenteritis by 42% in Latin America and by 72% in Europe [1, 2]. Similarly, RotaTeq reduced the rate of hospital admissions for all-cause gastroenteritis by 59% in studies conducted primarily in Finland and the United States [3]. These reductions should have a noticeable impact on decreasing childhood morbidity if field effectiveness is similar to efficacy in trials [2].

In addition to the direct benefits for vaccinated infants, it is possible that vaccination of a proportion of the population could reduce overall transmission of rotavirus in the community and, thus, also could lead to a reduction in disease risk among unvaccinated persons who are part of the community (ie, herd immunity). Indeed, early postlicensure data from the United States indicate that the decrease in the prevalence of rotavirus disease after vaccine introduction appears to be greater than that expected based on levels of vaccine coverage, and reductions have also been noted among older infants who are age-ineligible for vaccination, raising the possibility of herd immunity [13].

Impact on the prevalence of rotavirus strains and strain-specific vaccine effectiveness. In the Latin American and Finnish trials of Rotarix, a monovalent P[8]G1 vaccine, cross-protection was observed against the most common circulating strains (G1, G3, G4, and G9) that share P[8] serotype specificity, with efficacy ranging from 82% to 96% against severe rotavirus disease caused by these strains (Table 2) [1, 2, 6, 9]. In Latin America, Rotarix was less effective against G2 strains (vaccine effectiveness, 44%; 95% confidence interval [CI], <0% to 88%), which belong to a different G serotype, P subtype, and genogroup than do the vaccine strain and other globally common strains [1]. In Finland, however, Rotarix did confer good protection against severe disease caused by P[4]G2 strains (vaccine effectiveness, 86%; 95% CI, 24%–98%).

These findings have prompted debate over whether Rotarix vaccine will provide sufficient protection against P[4]G2 strains [14]. The small number of P[4]G2 strains detected among placebo recipients ($n = 7$) with severe disease in the Latin American trials indicates that P[4]G2 was not circulating during the trial period, and thus, the study did not attain power to conclusively assess protection against this strain [6]. In a meta-analysis of phase II and III studies, the efficacy of Rotarix against severe diarrhea caused by the P[4]G2 strain was estimated to be 71% (95% CI, 20%–91%) [15]. More recently, 2 surveillance studies from Brazil, one of the first countries to implement routine childhood vaccination with Rotarix vaccine, have identified P[4]G2 strains in a large proportion of children with severe diarrhea [16, 17]. Although the observed predominance of P[4]G2 strains in this Brazilian community with Rotarix vaccination coverage of ~50% is intriguing, it could represent a natural shift in strains that is unrelated to vaccination. For example, in ongoing hospital-based surveillance in El Salvador, where routine Rotarix vaccination was introduced in 2006, P[4]G2 was also predominant (~80% of total cases were caused by the strain) in 2005–2006, before vaccine introduction [18]. However, P[8]G1 strains became predominant (~90% of total cases were caused by the strains) during the first rotavirus season after vaccine implementation; only 2% of strains were P[4]G2. Similar findings of periodic strain emergence in the absence of vaccination have been extensively documented in other settings and will likely continue to occur during the postlicensure period. Determination of whether emerging strains are related to vaccination will require caution and careful consideration for employing longitudinal surveillance and epidemiologic studies to better assess interaction of the vaccine with strain ecology.

In the Rotavirus Efficacy and Safety Trial (REST) of the pentavalent RotaTeq vaccine, a high level of efficacy was observed against all G1–G4 and G9 serotypes (range, 88%–100%) [2, 3]. Of note, during the study period, relatively few (14%) non-G1 rotavirus strains were in circulation; thus, estimates had wide confidence intervals, and efficacy against non-G1 strains warrants closer attention during the postlicensure period. The pentavalent vaccine conferred 88% (95% CI, <0% to 98%) protection against P[4]G2 strains in Finland and the United States, but data should be cautiously interpreted, because only 8 children in the placebo group were infected with the strain [2, 3]. A recently reported 3-year follow-up of Finnish infants who were part of REST revealed that efficacy against severe rotavirus diarrhea caused by P[4]G2 strains was 82%, compared with >93% efficacy against other strains [19].

Effectiveness of partial vaccination. Because trials of the currently licensed vaccines were designed to evaluate the full series, few children in the trial received less than a full series of the vaccines. However, some of the burden of severe rotavirus disease may occur among children <6 months of age, before completion of the full series of the vaccine, thus highlighting the importance of evaluating the effectiveness of partial vaccination.

With regard to Rotarix, evidence from the recent European trial suggests that the first dose conferred protection of 90% against rotavirus disease of any severity for cases that occurred between receipt of doses (Table 3) [2]. Few cases of severe

Table 1. Review of Efficacy Data from Clinical Trials of Rotarix and RotaTeq

Vaccine, location	Reference	No. of participants		Vaccine efficacy against severe rotavirus AGE, % (95% CI)		Vaccine efficacy against severe all-cause AGE, % (95% CI)	Comments
		Vaccine arm	Placebo arm	First year	Second year		
Rotarix							
Finland[a]	[9]	245	123	90 (10–100)	83 (7–98)	ND	241 Vaccine recipients and 120 placebo recipients were followed up through the second year
Latin America and Finland[b]	[1]	9009	8858	85 (70–94)	ND	42 (29–53)	During the first season, efficacy was 100% for children with a Vesikari score >19
Latin America[b]	[6]	7205	7081	83 (67–93)	79 (66–87)	39 (29–43)	7175 Vaccine recipients and 7062 placebo recipients were followed up through the second year
Europe[a]	[2]	2572	1302	96 (90–99)	86 (76–92)	72 (53–83)[c]	2554 Vaccine recipients and 1294 placebo recipients were followed up through the second year; efficacy against all-cause AGE admissions was 75% during the first year and 65% during the second year of follow-up
Belem, Brazil[a,d]	[4]	170	149	82 (44–95)	ND	ND	Data presented for the highest titer ($1 \times 10^{5.8}$ FFU)
Brazil, Mexico, and Venezuela[a]	[7]	464	454	86 (63–96)	ND	ND	Data presented for the highest titer ($1 \times 10^{5.8}$ FFU)
RotaTeq							
United States[c]	[5]	218	229	100 (43–100)	ND	ND	Quadrivalent WC3 (G1, G2, G3, P1[8])
United States and Finland[c]	[3]	2834	2839	98 (88–100)	88 (49–99)	59 (52–65)[e]	813 Vaccine recipients and 756 placebo recipients were followed up through the second season
United States, Finland, and Latin America[e]	[8]	28,646	28,488	94 (91–97)	ND[d]	59 (52–65)	No difference in efficacy between the United States and Europe; only 8% of the cohort was from Latin America, and the small sample size precludes assessment of efficacy in this region

NOTE. AGE, acute gastroenteritis; CI, confidence interval; FFU, focus-forming units; ND, not determined.

[a] Severe cases were defined by a score ⩾11 on the 20-point Vesikari scale.

[b] World Health Organization plan B refers to oral rehydration therapy, and plan C refers to intravenous rehydration therapy.

[c] Severe disease was defined as a case requiring hospitalization or a visit to the emergency department that had a severity score >16 on the 24-point Clark scale.

[d] Data were presented jointly with data from 2 other countries in Salinas et al [7].

[e] Data are from the Rotavirus Efficacy and Safety Trial [11], with health care use alone used as an outcome (92% of the cohort was from the United States and Europe, and 8% was from Latin America). Data on efficacy during the second year are not presented for the cohort that was followed up for a total of 2 years ($n = 2502$), and the reported overall efficacy was 97%.

Table 2. Strain-Specific Efficacy of Rotarix and RotaTeq against Severe Rotavirus Gastroenteritis or Hospitalizations and Emergency Department Visits

Vaccine, location [reference], vaccine arm	Total no. of participants	G1		G2		G3		G4		G9	
		No. of infections	VE, % (95%CI)	No. of infections	VE, % (95% CI)	No. of infections	VE, % (95%CI)	No. of infections	VE, % (95%CI)	No. of infections	VE, % (95%CI)
Rotarix[a]											
Latin America and Finland [1]											
Rotarix[b]	9009	3	91 (70–98)	5	45 (<0 to 86)	4	…	…	…	…	…
Placebo	8858	35	…	9	…	30	…	…	…	…	…
Latin America [6]											
Rotarix[c]	7205	9	83 (64–92)	4	44 (<0 to 88)	17	…	…	…	…	…
Placebo	7081	51	…	7	…	94	…	…	…	…	…
Finland [2]											
Rotarix	2572	4	96 (90–99)	2	86 (24–98)	1	94 (53–100)	1	95 (68–100)	13	85 (72–93)
Placebo	1302	57	…	7	…	8	…	11	…	44	…
RotaTeq[d]											
United States and Finland [3]											
RotaTeq	28,646	16	95 (92–97)	1	88 (<0 to 98)	1	93 (49–99)	2	89 (52–98)	0	100 (67–100)
Placebo	28,488	328	…	8	…	15	…	18	…	13	…

NOTE. CI, confidence interval; VE, vaccine efficacy.

[a] Efficacy against severe rotavirus gastroenteritis with a Vesikari score ⩾11.
[b] Pooled efficacy for G3, G4, and G9 was 87% (95% CI, 63%–97%).
[c] Pooled efficacy for G3, G4, and G9 was 82% (95% CI, 70%–90%).
[d] Efficacy against hospitalizations and emergency department visits.

Table 3. Review of Efficacy Data on Subpopulations from Clinical Trials of Rotarix and RotaTeq

Vaccine, outcome measure	Reference	Efficacy, % (95% CI)	Comments
Rotarix			
Partial series efficacy: dose 1 (n = 2572)	[2]	90 (9–100)	Efficacy against episodes of rotavirus AGE of any severity between dose 1 and 2
Nutritional status	[26]	…	Efficacy against severe disease;[a] study conducted in Brazil and Venezuela using WHO growth charts (weight-for-age) to assess nutritional status
Malnourished	…	100 (40–100)	…
Well nourished	…	81 (51–94)	…
OPV	[23]	88 (64–97)	Efficacy against severe disease;[b] 6 countries in Latin America; OPV given with both doses of Rotarix (n = 4376) or placebo (n = 2192)
HIV infection or AIDS	…	…	Trial that includes children with HIV infection or AIDS is ongoing
Low SES setting	[28]	83 (62–93)	Efficacy against severe disease;[a] impoverished population in South Africa during 2 seasons when G1 was detected in 54% of stool samples; results from Malawi pending
RotaTeq			
Partial series efficacy	[20]	…	Analysis based on episodes of severe rotavirus disease occurring immediately after the dose to the next dose (ie, dose 1–2 and dose 2–3)[c]
Dose 1 (n = 5764)	…	29 (<0 to 73)	…
Dose 2 (n = 2805)	…	80 (8–96)	…
Partial series efficacy	[21]	…	Analysis based on episodes of severe rotavirus disease occurring 14 days after vaccination to next dose (ie, dose 1–2 and dose 2–3)[c]
Dose 1 (n = 29,422)	…	82 (39–97)	…
Dose 2 (n = 29,497)	…	84 (54–96)	…
Coadministration with parenteral vaccines	[25]	90 (26–100)	Subset of REST assessing rotavirus AGE of any severity
Premature infant	[27]	96 (76–100)	Subset of REST assessing efficacy in infants aged 25–36 gestational weeks[c]
OPV	[24]	…	Immunogenicity study in which OPV given with RotaTeq or staggered 2 weeks after RotaTeq was conducted, but no efficacy data exist
HIV infection or AIDS	…	…	Trial that includes children with HIV infection or AIDS is ongoing
Low SES setting	…	…	Trials in Asia and Africa are ongoing

NOTE. AGE, acute gastroenteritis; HIV, human immunodeficiency virus; OPV, oral poliovirus vaccine; REST, Rotavirus Efficacy and Safety Trial; SES, socioeconomic status.

[a] Severe disease was defined as a score ⩾11 on the 20-point Vesikari scale.

[b] Severe disease was defined as diarrhea requiring hospitalization and/or rehydration therapy in a medical facility.

[c] Efficacy against hospitalizations and emergency department visits.

rotavirus disease precluded firm assessment of efficacy against this outcome.

With regard to RotaTeq, an initial subanalysis of REST suggested that a partial vaccine series was unlikely to protect against severe rotavirus gastroenteritis, with an efficacy of 29% after dose 1 and 80% after dose 2 (Table 3) [20]. However, because this analysis included children immediately after vaccination and because not all children in the cohort were included in the follow-up analysis, the authors recently reanalyzed the data for partial dose efficacy. In this reanalysis, they included the entire study cohort that was monitored for hospitalizations and emergency department visits to assess for breakthrough rotavirus events leading to a hospital visit between doses (ie, from 14 days after the administered dose to the following dose). In this analysis, the first dose conferred 82% protection against rotavirus hospitalization and emergency department visits, and the second dose conferred 84% protection [21].

Duration of protection. To have an optimal public health impact, rotavirus vaccines would need to provide protection against severe disease in children ⩽2 years of age in developing

countries and in children ⩽3 years of age in industrialized countries. With regard to Rotarix, recently published data on efficacy in the large clinical cohorts suggest that, although efficacy decreased slightly in Latin America (from 83% to 79%) and Europe (from 96% to 86%) during the second season of follow-up, overall vaccine protection was sustained at a reasonable level in children ⩽2 years of age (Table 1) [2, 6].

With regard to RotaTeq, a subset of the cohort involved in the clinical efficacy analysis and the cohort involved in health care use in REST were followed up through the second rotavirus season after vaccination. In the cohort involved in the clinical efficacy analysis, overall efficacy was high during both years; however, protection was decreased by 10% during the second season (88%), compared with the first season (98%), which suggests that a waning effect with time may occur [3]. From the cohort involved in the health care use analysis in REST, a smaller cohort of 2502 children were followed up for 2 years, and although data on efficacy against hospitalization during the second season have not been published, overall efficacy in this cohort (97%; 95% CI, 82%–100%) was similar to that in the cohort with 1 year of follow-up (94%; 95% CI, 91%–97%); this finding indicates that there was a sustained level of protection [8]. A recently completed extension of REST demonstrated a sustained reduction in the number of hospitalizations for rotavirus disease for 3 years after vaccination [19].

Coadministration with oral poliovirus vaccine (OPV). The concern of gut interference between OPV and oral rotavirus vaccine was initially evaluated in a Rotarix trial involving 450 South African infants [22]. In this trial, no impact on seroconversion against rotavirus was noted at 6 months of age among infants who received Rotarix concomitantly with either OPV or inactivated poliovirus vaccine at 6 and 10 weeks or 10 and 14 weeks of age, respectively. After the first dose at 6 weeks of age, rotavirus IgA seroconversion rates were ~60% lower among infants who received Rotarix concomitantly with OPV than among infants who did not receive OPV; however, after the second dose at 10 weeks of age, seroconversion (anti-rotavirus IgA antibodies) rates were similar in both groups. In a phase III clinical trial in 6 Latin American countries in which 2 doses of Rotarix were administered concomitantly with OPV, Rotarix conferred 88% protection against hospitalization for rotavirus gastroenteritis (Table 3) [23]. This finding was comparable to the efficacy in the large trial in 11 Latin American countries in which OPV and rotavirus vaccines were administered sequentially with a 2-week interval.

Concomitant administration of RotaTeq with OPV did not interfere with titers against polioviruses 1, 2, or 3. The geometric mean titers for anti-rotavirus IgA were 50% lower in the group that received RotaTeq and OPV concomitantly than in the group that received OPV 2 weeks after receipt of RotaTeq [24]. However, the seroconversion rates were high in both groups (93% and 98%, respectively). Trials on the efficacy of RotaTeq coadministered with OPV have not been conducted; however, when administered with other parenteral vaccines, efficacy was 90% against severe rotavirus disease [25].

Studies involving vulnerable groups. Rotarix has also been demonstrated to have equal efficacy against severe rotavirus gastroenteritis in Venezuelan and Brazilian infants considered to be well nourished (vaccine effectiveness, 73%), compared with malnourished infants (vaccine effectiveness, 74%), when using World Health Organization (WHO) growth charts for weight-for-age to assess nutritional status (Table 3) [26]. Studies are currently ongoing in Africa to assess the safety and efficacy of Rotarix in human immunodeficiency virus (HIV)–infected infants.

In a subset of REST, RotaTeq reduced rates of hospitalization for rotavirus gastroenteritis by 96% among premature infants (born at 25–36 gestational weeks of age) [27]. No published data exist on efficacy in malnourished infants. Studies to assess the safety and efficacy of RotaTeq that include HIV-infected infants are ongoing in Africa.

Vaccine performance in developing countries. The first study to assess the efficacy of Rotarix in Africa (South Africa and Malawi) has been completed. An interim analysis of data for the South African cohort indicates a potentially promising future for this vaccine if similar results are obtained in other developing countries in Asia and Africa. In South Africa, 2 doses of the vaccine offered 77% protection against severe rotavirus gastroenteritis during the first year of life [28]. P[8]G1 comprised 54%–56% of the circulating strains in the study population. In contrast, efficacy was only 49% in the low-income country of Malawi [28]. The efficacy of RotaTeq in low socioeconomic settings in Asia and Africa is currently being assessed in clinical trials, and completion is anticipated in 2009.

MONITORING THE IMPACT AND EFFECTIVENESS OF ROTAVIRUS VACCINES AFTER INTRODUCTION

With the licensure and introduction of the 2 new rotavirus vaccines in routine immunization programs, the WHO has highlighted the need for monitoring the impact of these vaccines on rotavirus-associated morbidity and mortality and for assessing the public health benefits of vaccination (Table 4). In this section, we summarize a framework for monitoring the impact of rotavirus vaccines once they are introduced in routine immunization schedules. Additional details are outlined in a recently published WHO generic protocol for monitoring the impact of rotavirus vaccination [29].

Assessment of vaccine impact by monitoring trends in gastroenteritis and rotavirus disease burden. Vaccine impact can be monitored by assessing trends in gastroenteritis and rotavirus disease burden and correlating decreases in disease incidence with vaccination coverage rates. Because the efficacy of rotavirus vaccines is greatest against severe rotavirus disease,

Table 4. Objectives and Rationale for Assessing Postlicensure Performance of Rotavirus Vaccines

Objective	Rationale
Demonstrate effectiveness in real world setting of routine use	•Alternative vaccination patterns may be encountered, such as administration of only a partial series or delays in the vaccination schedule •Vaccine will be coadministered with oral poliovirus vaccine, which might result in interference •Efficacy against unusual strains not included in vaccine formulations may vary •The duration of protection could be less in field settings; because as many as 40% of children may develop disease during the second and third year of life, protection through 24–30 months of life would be necessary to maximize the public health impact •Vaccine quality may vary; for example, cold-chain could be compromised, thus impairing vaccine potency, and antigenicity may vary by formulation •Rotavirus vaccine trials were conducted in middle- and high-income countries and not in developing countries with the highest burden of severe rotavirus disease
Establish epidemiological patterns of rotavirus disease after vaccine implementation	•Age distribution of rotavirus disease could change, with increasing risk of severe disease among school-age children and adults •Assessment of herd immunity (ie, reduction in incidence of disease among nonvaccinated populations because of indirect benefits)
Demonstrate impact on morbidity and mortality	Demonstration of absolute reductions in the incidence of severe childhood gastroenteritis through rotavirus vaccination and creation of demand for rotavirus vaccines by demonstrating direct public health benefits of vaccination
Strain surveillance	•Monitor for possible emergence of unusual rotavirus strains that may escape protection from vaccines •Allow for serotype-specific measures of vaccine effectiveness
Encourage in-country and regional vaccine introduction	Poor performance of previous rotavirus vaccine and other oral vaccines (eg, oral poliovirus and cholera vaccines) in developing countries may hinder the acceptance of newer rotavirus vaccines

the impact of vaccination will be greatest on severe outcomes, such as hospitalization. Furthermore, because rotavirus disease accounts for 30%–50% of all hospitalizations of young children with acute gastroenteritis, the impact of vaccination might be visible even if only data on hospitalization for all-cause gastroenteritis are available, especially in settings where rotavirus disease is seasonal. Depending on the availability of data, in addition to assessment of hospitalizations, countries may want to assess visits to outpatient clinics and emergency departments for gastroenteritis.

Consideration of how the epidemiology of rotavirus disease might change in the era after initiation of vaccination will also be crucial when monitoring disease trends. The reduction in the prevalence of severe disease should be proportional to the vaccination coverage rates in the region and will be seen primarily in infants <1 year of age during the first year of vaccine introduction, in infants <2 years of age during the second year of the program, and in incrementally increasing age groups during successive years. However, the possibility exists that rotavirus vaccines may interrupt transmission and, thus, protect not only children <5 years of age, the age group targeted for vaccine (direct effects), but also other age groups (indirect effects or herd immunity), such as school-age children and adults, in whom rotavirus disease has been reported to occur but remains to be well studied [30–33].

Two general sources of data would meet the objectives of monitoring disease trends in the context of assessing vaccine impact: (1) primary data sources, such as an active gastroenteritis surveillance system, or (2) secondary data sources, such as national data on hospitalizations for gastroenteritis. Although these data are often incomplete and nonspecific, consideration of factors, such as monitoring data from several years before and after vaccine introduction, comparing rates in vaccinated age groups with those in unvaccinated age groups, assessing changes in seasonal patterns (eg, delays in onset of rotavirus season), and monitoring for changing age patterns of illness, may allow for a reasonable assessment of potential vaccine impact.

Active surveillance systems. Primary data sources relevant to the demonstration of rotavirus vaccine impact would involve an active surveillance system at sentinel hospitals where children <5 years of age who have diarrhea are systematically tested for rotavirus disease [34]. Ideally, surveillance would be initiated at least 1–2 years before vaccine introduction to ensure baseline rates of hospitalization for rotavirus disease. Such an active surveillance system would allow monitoring of vaccine impact by assessing the reduction in the rate of hospitalization for rotavirus disease in conjunction with vaccine coverage rates, as demonstrated for other vaccine-preventable diseases [35–37].

Secondary data sources. Regions and countries may have existing data sources on all-cause gastroenteritis, such as hospital discharge and national mortality data, which could be useful for establishing diarrhea disease burden and trends after vaccine introduction. If interpreted with caution, this approach of using existing data sources to monitor trends in rotavirus and all-cause gastroenteritis disease burden may be useful in

assessing vaccine impact in a region with known vaccination coverage.

Assessing vaccine effectiveness with use of a case-control design. The ideal measure of vaccine impact is demonstrating a reduction in rotavirus disease incidence in the vaccinated population. However, from an operational perspective, monitoring secular trends in all-cause gastroenteritis– and rotavirus-associated health outcomes to demonstrate the impact of vaccination can be challenging because of the need for baseline data before implementation of vaccination and difficulties in interpretation of trends because of natural year-to-year variation in disease incidence. Furthermore, a high level of vaccine coverage may need to be achieved before impact may be visible through these ecological methods. Therefore, in the early phases of introduction of rotavirus vaccine in a country, the field performance of a vaccine might be better assessed by conducting specialized epidemiological methods, such as case-control studies [38–40].

With use of a case-control method, vaccine effectiveness can be estimated by comparing the prevalence of vaccination among patients with rotavirus disease with that among control subjects without disease. Interpretation of vaccine effectiveness data in conjunction with vaccination coverage rates would also provide indirect estimates of vaccine impact on rotavirus disease burden. Advantages of the case-control design include efficiency in terms of cost and time to conduct the study and the opportunity to address other parameters of interest (eg, efficacy by severity of disease, effectiveness of partial vaccination, effectiveness against specific rotavirus strains, duration of protection, and potential interference from concomitant OPV administration) and to identify potential risk factors for poor vaccine performance (eg, breastfeeding and low socioeconomic status). Case-control studies might also be used to assess the impact of rotavirus vaccination on reduction in mortality, an outcome that will not be addressed in ongoing clinical trials in low-income countries.

The study is ideally implemented when coverage is 20%–80%, because the sample size is substantially higher outside this range of coverage and could pose practical challenges for the use of this method [29]. In regions with well-established immunization programs, we have noted that vaccine uptake in the age-eligible group can reach a high, steady state soon after vaccine introduction (1–2 years) [41]. In addition, the logistics of a case-control study can be complex; therefore, it is important to plan the study at the beginning of or before implementation of a vaccination program.

Assessment of the impact of vaccination on rotavirus strains. Two questions with regard to the impact of vaccination on rotavirus strains warrant close scrutiny [12, 14, 18]. Will strain-specific variations in efficacy occur? Will vaccination exert a selective pressure resulting in antigenic shifts or drifts of public health concern? Information on the prevalence of circulating rotavirus strains will be important for assessing the likely impact of vaccine, for understanding reasons for any observed reduction in vaccine effectiveness, and for monitoring possible changes in strains as a result of vaccination. For example, rare human strains and reassortants between wild-type and vaccine strains may become more common in humans after vaccine introduction [12]. In addition to assessing the prevalence of different strains before and after vaccine implementation, evaluating strain-specific disease incidence over several seasons and strain-specific vaccine effectiveness through epidemiological studies will allow full assessment of the public health impact of vaccination. Examination of strains among children who become infected despite receiving vaccination and monitoring for emergence of unusual reassortants of common strains will also help with understanding of mechanisms of immunity against rotavirus and viral evolution.

Because of known secular trends and regional differences in strain variation even before vaccine introduction, strain surveillance data should be cautiously interpreted with regard to determining the association between vaccination and any observed changes in the circulating strains in the vaccinated community. Perhaps a better measure of public health impact of vaccination on strain prevalence might be through a case-control evaluation of vaccine effectiveness against specific strains.

SUMMARY

In summary, clinical trials of rotavirus vaccines in middle- and high-income countries have demonstrated high efficacy against severe rotavirus disease, including a substantial reduction in the incidence of severe gastroenteritis caused by any pathogen. Two important topics will be studied over the next several years: (1) the efficacy of the vaccines in low-income settings and (2) performance of the vaccines under routine field settings. As countries begin to introduce rotavirus vaccines in routine childhood immunization programs, opportunities will exist to address many unanswered scientific questions about vaccine performance in different settings and to demonstrate the real world impact and value of these vaccines to parents, physicians, and policy makers, thereby generating key evidence to sustain vaccine use.

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SUPPLEMENT ARTICLE

Assessment of Postlicensure Safety of Rotavirus Vaccines, with Emphasis on Intussusception

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The global implementation of rotavirus vaccines will result in a major step toward limiting the disease burden of rotavirus infection. However, as history has shown with the experience of Rotashield (Wyeth Lederle Vaccines), the introduction of a new vaccine should occur in parallel with a postmarketing surveillance strategy to detect any unexpected or rare adverse events. Two new rotavirus vaccines (Rotarix [GSK Biologicals] and RotaTeq [Merck]) have been found to be safe and effective in large clinical trials involving >60,000 infants in the Americas and Europe. However, given that intussusception is an extremely rare event, some risk could be detected as the vaccine is administered to a larger number of infants. In response to a recommendation of the World Health Organization Global Advisory Committee for Vaccine Safety, a standardized approach to the postmarketing surveillance of rotavirus vaccine safety has been developed. We review the principal safety issues requiring further evaluation in postlicensure use of rotavirus vaccines. For intussusception, we also discuss challenges and approaches to monitoring.

The first oral rotavirus vaccine (Rotashield; Wyeth Lederle Vaccines) was licensed in the United States in October 1998, heralding a major step toward the reduction in severe rotavirus disease [1–3]. However, 9 months later, the Rotashield immunization program was suspended because of an unexpected association with intussusception [4, 5]. In October 1999, the US Advisory Committee on Immunization Practices [4, 6] withdrew its recommendation for Rotashield, and the manufacturer voluntarily withdrew the vaccine from the US market. The abrupt demise of Rotashield delayed the introduction of potentially lifesaving rotavirus vaccines for children in the developing world. Clinical trials of new rotavirus vaccines were now required to demonstrate safety for an adverse event occurring in <1 in 10,000–32,000 vaccine recipients. Two new rotavirus vaccines (Rotarix [GSK Biologicals] and RotaTeq [Merck]) have been found to be safe and effective in large clinical trials of >60,000 infants in the Americas and Europe [7, 8]. These vaccines have been licensed in >80 countries and have been introduced into the routine infant immunization schedule in several countries of the Americas and Europe and in Australia. However, given that intussusception is an extremely rare event, some risk could be detected as the vaccine is administered to a larger number of infants after licensure. We review the principal safety issues requiring further evaluation in postlicensure use of rotavirus vaccines. For intussusception, we also discuss challenges and approaches to monitoring.

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INTUSSUSCEPTION

What Is Intussusception?

Intussusception is the invagination of a segment of the intestine within a more distal segment. It is the most

common cause of bowel obstruction in infants, usually occurring between 4 and 10 months of age [9]. In most infants, the intussusception involves the ileum invaginating through the ileocaecal valve into the caecum. As the bowel intussuscepts, it pulls along its blood supply. If the intussusception is not relieved, the vascular supply of the bowel may be compromised, resulting in intestinal ischemia and possibly perforation. Untreated intussusception may be fatal.

Clinical Features and Diagnosis

The clinical presentation of infants with intussusception reflects the underlying pathophysiology. Intestinal obstruction causes abdominal pain, vomiting, and abdominal distension. Obstruction to the venous or arterial supply of the effected intestine results in rectal bleeding, sometimes described as "red currant jelly" stool. An abdominal mass, representing the intussusception, may be palpated on clinical examination. The diagnosis of intussusception is confirmed by the demonstration of intestinal invagination during surgery, air- or liquid-contrast enema, or ultrasound examination (Figure 1). Because transient invaginations are observed during dynamic procedures, such as ultrasound or endoscopy, the diagnosis of intussusception requires an assessment of the extent of invagination and evidence of obstruction or failure of spontaneous resolution. With recognition that access to radiological facilities may be limited in some regions, a clinical case definition for the diagnosis of acute intussusception in infants and children was developed by the Brighton Collaboration [10]. This definition provides a clinical approach to diagnosis of intussusception that is suitable for use in a range of health care settings and has been validated in developed and developing countries [11]. Uncomplicated intussusception is treated by air-contrast or hydrostatic enema under radiological or ultrasound guidance or by surgery. Treatment practices appear to vary by region; surgical treatment percentages range from 12% to 88% in large studies worldwide (Table 1). Approximately 10% of infants require intestinal resection as a result of intestine ischemia or perforation [9].

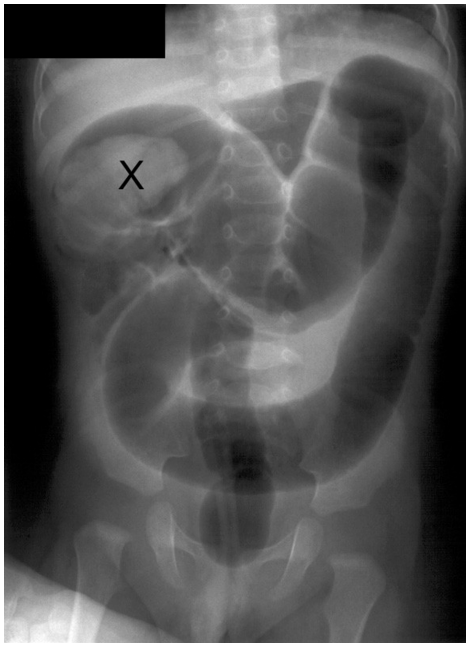

Figure 1. Air-contrast enema showing the apex of an ileocolic intussusception at the hepatic flexure of the colon.

Epidemiology

Despite being an important cause of intestinal obstruction in infants, intussusception is relatively uncommon. The incidence is reported to be <100 cases per 100,000 infants aged <1 year in most developed countries, and a consistent but unexplained decrease in the number of cases has been observed over the past decade [18, 20, 24, 25]. The incidence of intussusception varies among global regions (Table 1). A slightly higher incidence is reported in the United Kingdom, Australia, Hong Kong, Taiwan, and Denmark (66–88.2 cases per 100,000 infants aged <1 year) [17, 19, 26–29], and a slightly lower incidence is reported in Panama, Venezuela, Switzerland, and some states in the United States (30–38.1 cases per 100,000 infants aged <1 year). The incidence of intussusception in Vietnam is reported to be >300 cases per 100,000 infants, 9-fold higher than that reported among infants in the United States [13]. It is not known whether genetic, cultural, dietary, or environmental factors may place infants in some regions at a higher risk for development of intussusception. Interestingly, no microbiological, dietary or environmental risk factors explained the marked difference in incidence of intussusception in a parallel case-controlled study involving infants in Vietnam and Australia [13].

The incidence of intussusception varies substantially by age during the first 6 months of life. The expected intussusception hospitalization rate among US infants is low from birth to age 8 weeks (2–5 hospitalizations per 100,000 infants) but increases almost 10-fold during the next 2 months, peaking at age 26–29 weeks (62 hospitalizations per 100,000 infants) before decreasing again by age 1 year (~26 hospitalizations per 100,000 infants) (Figure 2) [24]. Interesting differences in age-specific incidence were observed by race/ethnicity. For infants who were aged <16 weeks, intussusception rates did not vary meaningfully by race/ethnicity. This was in sharp contrast to the group aged 21–44 weeks, in which non-Hispanic white infants had substantially lower rates of intussusception, compared with non-Hispanic black infants and Hispanic infants.

Etiology

In older children and adults, intussusception is frequently associated with a pathological "lead point," such as a polyp or tumor. In contrast, the cause of intussusception in the majority

of infants is not known [9]. The presence of mesenteric lymphadenitis observed in association with intussusception has led to the search for a possible infectious agent. A wide range of viruses, bacteria, and parasites have been identified in patients with intussusception [9]. The development of intussusception in infants who received Rotashield raised the question of whether wild-type rotavirus infection was associated with intussusception [30]. Wild-type rotavirus has variably been identified in stool samples from patients with intussusception (incidence range, 3%–49%) [13, 31–33], and changes in the thickness and characteristics of the intestinal wall have been detected on ultrasound in infants with acute rotavirus infection [34]. However, controlled studies do not suggest a significant association between wild-type rotavirus infection and intussusception [13, 35]. On the other hand, adenovirus was identified in the stool samples from more than one-third of infants with intussusception in a case-controlled study involving Vietnamese and Australian infants with intussusception [13]. Interestingly, the predominant adenovirus detected in infants with intussusception was serotype C, a respiratory adenovirus [36]. Adenovirus has also been identified in the mesenteric lymph nodes of patients with intussusception, consistent with the hypothesis that a mesenteric lymphoid tissue reaction in response to an infection, such as infection with adenovirus, may affect mucosal thickness or function of the distal small intestine, contributing to the development of intussusception [37, 38].

Intussusception and Rotashield Vaccine

In prelicensure trials, 5 of 10,054 Rotashield vaccine recipients (~0.5 per 1000) developed intussusception, compared with 1 of 4633 control individuals (~0.2 per 1000) [39]. Three of the 5 cases of intussusception occurred in the week after vaccination. However, the rate of intussusception was not statistically different in the vaccine recipients, compared with control individuals, and the cases occurred after receipt of the second and third doses of vaccine, at an age when the background rate of intussusception is increasing rapidly. Rotashield was licensed, but the package insert included intussusception as a potential adverse event.

Initial data presented to the US Advisory Committee on Immunization Practices in October 1999 estimated the population-attributable risk of intussusception following Rotashield vaccination to be 1 in 2500–3300 (relative risk, 1.6–1.8 in the first year of life), or an additional 1200–1600 cases per year of intussusception if the Rotashield immunization program was fully implemented [5, 6]. The risk estimate was reduced to 1 in 4670–9474 after analysis of case-series and case-control studies [5, 40]. However, no increase in intussusception-related hospitalizations were noted in ecological studies, and it has been suggested that the risk may have been as low as 1 in 32,000 vaccinees [40, 41].

Although the magnitude of risk of intussusception following Rotashield vaccination remains controversial, the temporal relationship between the receipt of the vaccine and the development of intussusception in affected infants is acknowledged. Cases of intussusception clustered at 3–14 days following vaccination with the first dose of the vaccine (odds ratio, 21.7) [5]. Some have suggested that the age of the infant at the time of administration of the first dose of Rotashield appeared to influence the risk of intussusception [42, 43]. Of cases of intussusception reported following Rotashield vaccination, 80% occurred in infants who received dose 1 at age >3 months, whereas only 38% of the first doses had been given to this age group [43]. However, firm conclusions about an age-dependent

Table 1. Literature Review of Population-Based Studies Examining National or Regional Rates of Hospitalization for Intussusception among Children Aged <12 Months

Study authors [reference]	Year(s)	Country or region	Rate of hospitalizations for intussusception per 100,000 children per year	Percentage surgically treated
Abate et al [12]	2002	Latin America	51.0	84
Bines et al [13]	2003	Vietnam	302.0	12–20
Buettcher et al [14]	2003–2006	Switzerland	38.1	23
Chen et al [15]	1998–2002	New Zealand	65.1	…
Ho et al [16]	1999–2001	Taiwan	68.4	31
Gay et al [17]	1994	United Kingdom	66.0	…
Justice et al [18]	2000	Australia	81.0	…
Fischer et al [19]	2001	Denmark	68.8	…
Nelson et al [20]	1997–1999	Hong Kong	88.2	23
O'Ryan et al [21]	2000–2001	Chile	51.0	78
Perez-Schael et al [22]	1998–2001	Venezuela	35.0	88
Saez-Llorens et al [23]	1998–2002	Panama	30.0	68
Tate et al [24]	2001–2004	United States	33.6	51

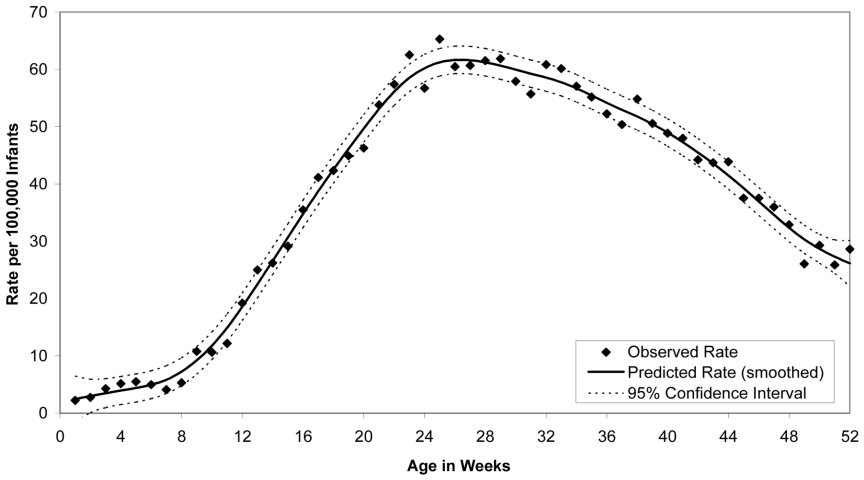

Figure 2. Intussusception hospitalization rates per 100,000 infants aged <12 months, by week of age, United States, 1993–2004. Reproduced with permission from *Pediatrics,* Vol. 121, Pages e1125–32, Copyright © 2008 by the AAP.

risk could not be made, because of the sparse data for certain age groups [42, 44, 45]. After reviewing all the available evidence, the World Health Organization (WHO) Global Advisory Committee on Vaccine Safety concluded that the risk for Rotashield-associated intussusception was high in infants vaccinated after age 60 days and that insufficient evidence was available to conclude that the use of Rotashield at age <60 days was associated with a lower risk. The Global Advisory Committee on Vaccine Safety noted, however, that the possibility of an age-dependent risk for intussusception should be taken into account in assessment of future rotavirus vaccines. In part on the basis of these considerations, the currently licensed rotavirus vaccines have developed clear recommendations, restricting the administration of the first dose of vaccine to infants aged >6 weeks and <12 weeks (RotaTeq) and infants aged >6 weeks and ⩽20 weeks (Rotarix).

The pathophysiological mechanism for the association between Rotashield and intussusception is not well understood. Early clinical trials suggested that Rotashield was reactogenic with fever, irritability, and decreased appetite and activity, which were reported in a higher proportion of infants who received vaccine, compared with control infants who did not receive vaccine [46]. This was attributed to a reaction to the rhesus component of the vaccine. Subsequent analysis of adverse events reported during the period of Rotashield availability suggested that fever, bloody stool, diarrhea, abdominal pain, and dehydration were part of a spectrum of gastrointestinal illness related to vaccination [47, 48]

Intussusception and New Rotavirus Vaccines

After the withdrawal of Rotashield, the future development of rotavirus vaccine hinged on the answer to the question: Was intussusception an adverse event specifically related to Rotashield, or would intussusception also occur following administration of other rotavirus vaccines? Although Rotashield and the new Rotarix and RotaTeq are all live attenuated rotavirus vaccines, their intrinsic biological characteristics and reactogenicity profiles are quite different. Rotashield and RotaTeq are both multivalent human-animal rotavirus reassortant vaccines; Rotashield is based on a rhesus rotavirus strain, and RotaTeq is based on a bovine rotavirus strain. Rotarix is a monovalent, attenuated human rotavirus strain–based vaccine. In prelicensure trials, neither RotaTeq nor Rotarix was observed to be particularly reactogenic, especially when compared for rates of fever, vomiting, and diarrhea that were reported among infants who received Rotashield. Furthermore, the Rotashield vaccine strain replicated well in the infant gut and was shed in >80% of vaccine recipients after the first dose. In contrast, RotaTeq replicates poorly and is shed in only ~10% of first-dose recipients. With Rotarix, shedding by enzyme-linked immunosorbent assay (ELISA) occurs in ~50% of infants after dose 1 in the first 2 weeks after vaccination, and live virus can be detected in approximately one-half of the infants who demonstrate shedding by ELISA.

Despite these biological differences between the different rotavirus vaccine strains, it was not possible to determine the risk of intussusception with each vaccine on theoretical considerations alone. Both vaccines have been required to assess safety in large clinical trials involving >60,000 infants, powered to assess an intussusception risk of a magnitude similar to that seen for Rotashield [49, 50]. No significant association between receipt of vaccine and intussusception was identified in these large clinical trials. Rotarix and RotaTeq have been licensed in >80 countries.

Rationale for Postlicensure Monitoring for Intussusception

Although prelicensure trials did not demonstrate an association of the new rotavirus vaccines with intussusception, efforts to monitor safety postlicensure must continue for several reasons. First, even though each of the clinical trials evaluated a large number of infants, they were powered only to exclude a risk of intussusception similar in magnitude to that of Rotashield (eg, the RotaTeq trial was powered to exclude a risk of >10-fold during the 42-day period after vaccination) [51]. To evaluate a risk of smaller magnitude with any specific dose of vaccine will require careful follow-up of hundreds of thousands of infants during routine vaccine use. Second, the incidence and epidemiology of intussusception varies across different geographical settings, and the safety of rotavirus vaccines in different regions and across a wide range of health care settings has not yet been demonstrated. Finally, in the clinical trials, both vaccines were administered according to a very strict vaccination schedule, with the first dose given at age 6–14 weeks. The incidence of intussusception varies substantially during the first 6 months of life, and the safety of these vaccines when given outside the administration schedule examined in the clinical trials has not been evaluated.

Goals and Approaches for Postlicensure Monitoring for Intussusception

The WHO Global Advisory Committee on Vaccine Safety has recommended a standardized approach to postmarketing surveillance in countries planning to introduce and implement rotavirus vaccines [52]. In response to this recommendation, the document *Post-marketing Surveillance of Rotavirus Vaccine Safety* was developed by the WHO [53]. This document provides guidelines for routine postmarketing surveillance to assess the safety of rotavirus vaccines and can be adapted at the country level, according to existing surveillance systems, health care infrastructure, and resources [54]. A key goal is to enhance the quality of safety data at a regional level so that the safety of rotavirus vaccines can be established and compared across regions.

Surveillance systems require clear case definitions to assist in the identification and reporting of potential adverse events. The Brighton Collaboration has developed a number of standardized case definitions for the detection of vaccination-related adverse events and to assist in the comparability of data collected from different surveillance systems [55]. Ideally the baseline incidence of intussusception should be known for sites prior to the introduction of rotavirus vaccines. A generic protocol from the WHO has been developed to assist in the defining the epidemiology and baseline incidence of intussusception in countries where these data do not currently exist [56].

Passive surveillance. The association between Rotashield vaccine and intussusception was first detected by a passive surveillance system, the US Vaccine Adverse Events Reporting System [57]. Such passive surveillance systems aim to detect a "signal" (ie, when the number of reported events exceed the number expected to occur by chance) of an association with an adverse event. Interpretation of data on intussusception from passive reporting systems requires data on 3 key parameters: (1) completeness of reporting of intussusception events after vaccination, (2) background rates of natural intussusception, and (3) number of rotavirus vaccine doses administered. The completeness of reporting of adverse events tends to be highest for events occurring soon after vaccination (eg, 1–2 weeks). This may result in an apparent clustering of events close to vaccination that may not necessarily indicate a signal or a true association with vaccination. Intussusception provides specific challenges in the interpretation of passive surveillance data. Baseline expected intussusception rates are known to vary up to 10-fold by week of age during the first 6 months of life. This is also the time when rotavirus vaccines are administered. Therefore, intussusception rates among vaccine recipients should be stratified according to age (ideally by week of age) to allow comparison with expected intussusception rates among the unvaccinated population of that age. Finally, calculation of the intussusception rate among vaccine recipients requires the estimation of the number of doses of vaccine administered in the target population. Unfortunately, often data are available only on the number of doses sold by the manufacturer, and the reporting completeness of adverse events to passive surveillance systems is not known. In this scenario, sensitivity analyses incorporating various assumptions for these parameters should be conducted to allow interpretation of passive surveillance data. However, even with these techniques, passive surveillance has limitations, and investigation of a signal generated by passive surveillance requires more-sophisticated methods.

Active surveillance and epidemiological studies. Active surveillance of intussusception cases with verification of diagnoses through review of clinical features and with diagnostic evaluation of potential cases remains the reference standard for detection of intussusception cases. Once intussusception cases are identified through active surveillance, the association with rotavirus vaccination can be assessed through various methods.

In traditional cohort-based evaluations, the rate of intussusception among vaccinated infants is compared with the rate among unvaccinated infants during specific time periods after vaccination. To adjust for potential differences in characteristics of vaccinated and unvaccinated children, multivariate analyses can be conducted to include potential confounders (eg, age, socioeconomic status, and feeding practices). Because intussusception is uncommon, follow-up data on large numbers of children are needed to assess a low level of risk. Generally, such data are available only through large administrative data sets

that capture information on vaccination and medical outcomes for an enrolled population, such as the US Vaccine Safety Datalink.

If platforms such as the Vaccine Safety Datalink and the substantive resources needed to establish a cohort study are not available, the risk of intussusception could be assessed using case-control or case-series methodology. Indeed, when the passive Vaccine Adverse Events Reporting System identified a signal of a possible association between Rotashield and intussusception, a nationwide case-control study was conducted to confirm this association. Both case control and case series are case-based methods that begin with identification of children with intussusception, as opposed to cohort methods, in which vaccinated and unvaccinated children are followed up over time to determine whether they develop intussusception. A key advantage of the case-based methods is that a smaller sample size is required to identify an association, compared with a traditional cohort-based study. However, case-control studies are particularly challenging because of the importance in identifying appropriate controls and their vaccination status. If the controls are not representative of the source population from which the cases arise, the study may be prone to bias.

In the absence of an existing database platform or the resources needed to conduct a cohort study and to avoid the potential biases of case-control study that result from the choice of controls, the relatively novel self-controlled case-series (SCCS) method could be used. The SCCS relies only on identification of intussusception cases, and no controls are needed. An important caveat is that the surveillance system used to identify intussusception cases for the SCCS analysis should not preferentially identify cases on the basis of vaccination status. Thus, data from passive surveillance systems for monitoring adverse events cannot be used, because they are likely to be biased toward cases occurring shortly after vaccination. To assess risk with vaccination, the incidence of intussusception in the "risk" windows close to vaccination (eg, 0–7 days or 0–21 days after vaccination) is compared with the incidence in "control" windows. Because incidence is compared for different time periods after vaccination for the same case, the SCCS approach automatically controls for fixed individual-level confounders (eg, socioeconomic status and race/ethnicity) that might affect risk assessment. Furthermore, because no controls are needed, several potential biases in selection of controls are avoided, and fewer subjects need to be studied, which reduces the resources required.

Three key issues in assessment of the risk of intussusception by the SCCS method deserve special attention. First, because the background rate of intussusception varies substantially during the first few months of life, it is important to adjust for the difference in background rates for the "risk" and "control" periods for each case. Therefore, data on the relative incidence of intussusception among unvaccinated children at the same ages are required. Second, data from clinical trials of the Rotarix vaccine suggest the possibility of a reduced rate of intussusception among vaccinated infants, compared with placebo recipients, when they were followed up for a period of 1 year after vaccination [58]. If vaccine alters the overall risk of developing intussusception in the first year of life, then the fundamental assumption of the SCCS method (ie, that the incidence in the "control" period is unchanged from baseline in the absence of vaccination) would be violated, and a falsely elevated risk estimate could be derived. Until additional data are obtained, a second approach, such as the case-control or the cohort approach, should support the SCCS method. Finally, in light of the public awareness of intussusception as a potential association with a rotavirus vaccine, there may be a "diagnostic bias" in which there is increased vigilance in diagnosis and treatment of intussusception soon after vaccination (eg, within 7 days), compared with the current practice for unvaccinated children. This phenomenon might falsely increase risk in the windows of time closest to vaccination and would call for cautious interpretation of elevated risks of smaller magnitude (eg, relative risk of 2–4) during these windows.

OTHER POTENTIAL SAFETY ISSUES

Extraintestinal spread of rotavirus infection. Wild-type rotavirus infection is not confined to the gut. Rotavirus has been identified in lymph nodes, liver, lung, myocardium, and the central nervous system of patients with acute rotavirus gastroenteritis [59]. Noninfectious rotavirus proteins (antigens) and infectious particles have been identified in serum samples from a large proportion of children hospitalized with severe gastroenteritis [59–61]. In one study, 22 of 33 children with acute gastroenteritis who had rotavirus detected in stool samples also had rotavirus antigen detected in their serum samples [60]. Rotavirus double-stranded RNA was detected by reverse-transcriptase polymerase chain reaction in 3 of the 6 antigen-positive serum samples, suggesting that infectious particles may also be present in the serum of patients with acute rotavirus gastroenteritis [59, 60, 62]. The transmission of rotavirus infection via serum of a rotavirus-infected animal has been demonstrated in gnotobiotic piglets [63]. The ability of a rotavirus to be associated with antigenemia or viremia may vary with specific characteristics of the rotavirus. G1 rotavirus strains appear to have a unique tropism for blood [64]. No data on viremia after vaccination have been reported.

Central nervous system infection, including seizures, meningitis, and encephalitis, have been reported following wild-type rotavirus infection [65–70]. The same rotavirus strain was identified in paired faecal and cerebrospinal fluid samples obtained from children presenting with acute gastroenteritis, meningitis, and seizures [71]. However, these reports are rare and

are likely to be associated with high rates of viral shedding or with specific serotypes, such as G1 [70, 71]. To date, there have been no reports of central nervous system disease associated with rotavirus vaccines.

Concerns regarding other potential rare adverse events following rotavirus vaccination have been raised; however, these can be investigated further only by large-scale phase IV clinical trials or with postmarketing surveillance after vaccine implementation. In the phase III trial of the Rotarix vaccine, an excess of pneumonia-related deaths were observed in vaccine recipients (16 vaccine vs 6 placebo recipients) [7]. It is difficult to interpret this unexpected finding, because it was not consistent across studies and there was no significant difference in other potential pneumonia-related outcomes such as hospitalization or in pneumonia-related deaths in the 31 days immediately following vaccination. In response to a small number of reports of Kawasaki disease following vaccination with RotaTeq, the US Food and Drug Administration amended the product information for the United States to capture any cases. However, a causal relationship between RotaTeq and Kawasaki disease has not been established [72]. Because rotavirus contains peptide sequences similar to T cell epitopes in the islet autoantigens glutamic acid decarboxylase and tyrosine phosphatase, there have been concerns that acute rotavirus infection may trigger or exacerbate islet cell autoimmunity, leading to the development of diabetes in genetically susceptible children [73]. However, conflicting results from studies investigating this hypothesis have been presented, and it is considered more likely that the development of type 1 diabetes results from a complex series of environmental and genetic factors [73–75]. The risk of celiac disease is reported to be higher in children with a history of repeated rotavirus infection in infancy and early childhood. It has been suggested that the disturbance in intestinal permeability associated with rotavirus infection may facilitate the deamination of cereal proteins into more immunogenic epitopes, resulting in celiac disease in genetically susceptible individuals [76]. Postmarketing surveillance is likely to be an effective method for further investigation of a potential association between vaccination and these rare but not confirmed observations linked with wild-type rotavirus infection.

Furthermore, to understand fully the risks and benefits of vaccination, it is of value also to understand the long-term risk of these adverse events beyond the risk window after vaccination that is being monitored (ie, >30 days after vaccination). If natural rotavirus infection is associated with conditions such as seizures, celiac disease, or diabetes, then vaccination could conceivably protect against these conditions, and evidence of such protection would help interpret the full risk profile and health benefits of the vaccines.

Shedding and transmission of vaccine virus strains. The potential of vaccine strains to infect human intestinal cells and to shed the vaccine virus in the stool varies according to the specific characteristics of the vaccine strain [77]. The Rotarix vaccine is a monovalent vaccine derived from the human rotavirus strain G1P[8]. It replicates well within the intestine, and live virus can be detected in >25% of patients after only 1 dose of vaccine [78]. RotaTeq vaccine is a pentavalent human-bovine reassortant vaccine that does not replicate well in the human intestine and is shed infrequently (incidence of virus in stool, <10%) in the stool [78]. As a result, higher aggregate vaccine titers are required to achieve protection. Because both Rotarix and Rotateq are live attenuated vaccines, the safety of these vaccines for immunocompromised patients or for immunodeficient household contacts requires consideration. Unfortunately, there are no clinical data to confirm the safety of rotavirus vaccines for patients with immunodeficiency. However, available evidence does not indicate that wild-type rotavirus infection is more severe in HIV-infected infants than in HIV-uninfected infants, suggesting that the risk from attenuated vaccine virus may be minimal, if any [79]. Studies addressing the safety of rotavirus vaccines for infants with HIV infection are currently in progress and will further guide immunization recommendations.

CONCLUSIONS

The global implementation of rotavirus vaccines will result in a major step toward limiting the disease burden of rotavirus infection. However, as history has shown with the experience of Rotashield, the introduction of a new vaccine should occur in parallel with a postmarketing surveillance strategy to detect any unexpected or rare adverse events not identified prelicensure. Despite the large clinical trials that each involved >60,000 infants and the growing experience after implementation of rotavirus vaccines in some countries, the safety of rotavirus vaccines should be further evaluated outside the clinical trial setting in a range of health care environments. In response to a recommendation of the WHO Global Advisory Committee on Vaccine Safety, a standardized approach to the postmarketing surveillance of rotavirus vaccine safety has been developed.

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