New insights into rotavirus vaccines

Chiara Mameli,* Valentina Fabiano and Gian Vincenzo Zuccotti

Department of Pediatrics; Luigi Sacco Hospital; University of Milan; Milan, Italy

Keywords: intussusception, post-marketing surveillance, rotavirus vaccines, rotavirus, safety

Abbreviations: RV, rotavirus; USA, United States of America; IS, intussusception

Rotavirus vaccines have shown to be effective and well tolerated in clinical trials. However it's crucial to point out that immunization occurs in "real-world" conditions different from ideal clinical trial settings. Thus, the impact of rotavirus vaccines in terms of effectiveness and safety needs to be evaluated in real-world conditions. Post-licensure data regarding vaccine impact, effectiveness and safety under routine use are now available and provide a "real-world view".

Introduction

Rotavirus (RV) infection is the most common cause of severe diarrhea disease in infants and young children worldwide and has a major global impact on childhood morbidity and mortality. Although RV is called a "democratic virus" (because its incidence is similar in developed and developing countries) it kills an inordinate number of children in low-income countries where treatment for diarrhea is less accessible. Every year, RV gastroenteritis is globally estimated to cause approximately 527,000 (475,000–580,000) deaths among children < 5 y old.¹ Most of these deaths (90%) occur in Africa and Asia, in particular 11 countries (India, Nigeria, Congo, Etiopia, China, Pakistan, Afghanistan, Bangladesh, Indonesia, Nigeria, Angola) account for 65% of all RV deaths in childhood.² In industrialized countries the mortality rate per 100,000 child deaths due to RV disease is usually < 10 deaths/100,000.³

Despite the improvement of control measures (clean water initiatives, personal hygiene) and the availability of oral rehydration solutions, RV continues to cause disease morbidity and mortality. Vaccines have been identified as the only control measure and the optimal strategy to decrease the burden associated with severe and fatal diarrhea. Rotavirus vaccination mimics the protective first infection without causing illness, inducing strong and broad heterotypic immunity against future severe rotavirus infections.

The history of the first RV vaccines began ten years after the discovery of RV in 1973. Clinical studies using bovine RV vaccine did not show significant protection and were soon terminated. Few years later, the tetravalent Rotashield® vaccine was licensed and incorporated into the USA infant immunization schedule in 1998. Initial enthusiasm for this new vaccine waned soon: in fact

Rotashield® was withdrawn in 1999 after the discovery of a small but significant increase in intussusception during post-licensure surveillance.⁴ Currently, two RV oral live attenuated vaccines (Rotarix® and Rotateq®) are licensed worldwide. In clinical trials conducted in Europe, North and South America both vaccines have been demonstrated to be 90–100% effective in preventing severe RV gastroenteritis and 74–85% effective in preventing RV infection of any severity. Clinical trials data have shown both vaccines to have acceptable safety profiles not putatively associated with severe adverse events, such as intussusceptions.^{5,6}

However it's important to point out that immunization occurs in "real-world" conditions, which are different from ideal clinical trial settings. Thus, the impact of rotavirus vaccines in terms of effectiveness and safety needs to be evaluated in real-world conditions. Post-licensure data regarding vaccine impact, effectiveness and safety under routine use are now available and provide a "real-world view".

Epidemiological Aspects in Post-Vaccine Era

Epidemiological changes after the introduction of vaccinations have been reported for several pathogens.⁷⁻¹⁰ Decline in morbidity, changing of the age distribution and seasonality, serotype-replacement and herd immunity are the most important effects of the introduction of a vaccine in a population. Moreover, the large-scale introduction of a new vaccine often determines the emergence of epidemiological effects which cannot be detected otherwise.

Impact of Vaccination on the Age-Specific Incidence of the Primary Infections

Epidemiological shift in the age distribution of a disease to older children induced by vaccine immunization programs has been observed for measles, varicella and pertussis.¹¹⁻¹³ Changes of the age distribution of RV have been proposed by different mathematical models. In settings with high vaccine coverage, an increase in the median age of the primary infection was predicted by some authors, probably because of delays in acquisition of primary rotavirus infection.^{14,15} These described short-term fluctuations in age distribution in rotavirus incidence were explained as natural consequences of a vaccination program and did not necessarily indicate waning immunity.

In real-world settings some authors recently reported that the age distribution of children hospitalized for rotavirus

*Correspondence to: Chiara Mameli; Email: mameli.chiara@hsacco.it
Submitted: 02/25/12; Revised: 03/31/12; Accepted: 04/08/12
<http://dx.doi.org/10.4161/hv.20295>

gastroenteritis has shifted toward older children after the introduction of effective vaccines. Clarke et al. showed that the median age of patients was 20 mo in 2007 to 2008 and 23 mo in 2008 to 2009, compared with 11 mo (range 8–14 mo) over the preceding 13 seasons. Almost half of the cases occurred in children older than 2 y, many of whom were likely too old to have been vaccinated.¹⁶ Similar data were reported in Belgium, where Hanquest et al. observed a progressive shift in age distribution after the introduction of vaccination. The proportion of all rotavirus cases reported in children <1 y of age declined from 53% to 26% and an increase (from 30% in 2005–2006 to 40% in 2008) in children aged 12–23 mo of age was observed.¹⁷ In USA Payne et al. reported an increased median age of RV hospitalization from 14 mo in 2006 to 24 mo in 2009.¹⁸ However these data need to be confirmed in larger epidemiologic studies worldwide.

Change in Seasonal Pattern of Rotavirus Disease

The spatiotemporal pattern exhibited by RV differs from that of other acute seasonal infections (e.g.: influenza, measles) for which epidemics tend to begin in major population centers relatively synchronously and spread to less populous areas in correlation with work commutes. Unlike these pathogens, RV infection appears to persist throughout the year even in relatively small populations, possibly through recurring infections in adults.

Analysis of RV epidemiological data from USA indicates that disease incidence is highly seasonal and spatially structured. Before introduction of vaccine, RV had a winter–spring seasonality and a typical geographic pattern in the USA, with activity beginning in the West during December–January, extending across the country and ending in the Northeast during May–June. Since the widespread use of RV vaccines, this seasonality has shifted and this trend in RV peak activity is no longer consistently observed. A diminished in magnitude compared with seasons before vaccine implementation was reported soon after vaccine introduction.¹⁹

Moreover, Curns et al. recently reported a remarkable and heterogeneous post-vaccination spatiotemporal change in USA: in some areas, peak activity of RV infection occurred approximately 2 to 3 mo later respect to pre-vaccine seasons, whereas in some other areas it occurred earlier.²⁰ These remarkable alterations in rotavirus activity have occurred rapidly following vaccine introduction and provide evidence that the spatiotemporal dynamics of RV activity in USA are likely driven by the rate of accumulation of fully susceptible individuals rather than solely by environmental factors as previously reported by Pitzer and colleagues.¹⁵

In Europe, Braeckman et al. also showed a shift in the onset of the epidemic by 1–2 mo after the introduction of RV vaccination.²¹ Similarly in South-eastern Brazil Sáfadi et al. observed that after vaccine implementation the onset and the peak incidence of RV occurred 3 mo later.²² Prolonged follow-up of season patterns worldwide will clarify this issue; thus, continue monitoring of RV infections is required. Particularly data are needed from tropical areas, where seasonality is less distinct than in

temperate zones and RV occurs year-round. Because of the high burden of RV disease in developing countries and because many of these countries lie in the tropical belt, further analysis of the epidemiological consequences of introducing rotavirus vaccination in these settings are needed.

Indirect Benefit of Vaccination: Herd Immunity

Indirect benefit after vaccinations (herd immunity) occurs as a result of decreased transmission of the infectious agent in the community. It is an attractive way to extend vaccine benefits beyond the directly targeted population and amplify the direct benefits of vaccination among both vaccinated and unvaccinated subjects. The herd immunity refers to the indirect protection of unvaccinated persons, whereby an increase in the prevalence of immunity by the vaccine prevents circulation of infectious agents in susceptible populations. It has already been described for many diseases caused by different pathogens as smallpox, *Hemoflus influenzae type b*, *Bordetella pertussis*, influenza, *Neisseria meningitidis* and more recently for *Streptococcus pneumoniae*.^{23,24}

The presence of herd immunity after RV vaccination was initially excluded because of the high level of secondary spread of RV after infection in both symptomatic and asymptomatic individuals. Some authors suggested its presence using mathematical modeling developed to assess the impact of a vaccination program on the incidence of RV infection and disease. These models were developed using some variables as current knowledge of the natural history of RV disease, transmission within the population and RV age-specific incidence.^{14,25}

Currently heard immunity after RV vaccination has been noted at the population level in USA^{18,26,27} Australia,^{28,30} Austria³¹ and El Salvador.³² Post-licensure data clearly show that RV vaccination not only reduces the rate of infection in the younger vaccinated children but protects older children as well. Moreover a recent study showed a 48.5% decline in the prevalence of RV in adults that coincides with similar declines observed in pediatric population following widespread vaccination: these data strongly suggest an indirect effect of pediatric RV vaccination upon adult rotavirus disease.³³

Herd immunity induced by RV vaccination could be extremely important in developing country settings wherein vaccine efficacy and coverage tend to be lower. It is noteworthy that herd immunity (or protection) in developing settings should translate into much greater benefit as compared with the benefit from direct effectiveness. Considering the lower vaccine efficacy and coverage in these settings, the process of heard immunity could save a consistent number of lives in developing countries over the years. Whereas some studies have documented the indirect effect of the rotavirus vaccine, it is unclear whether we can expect similar indirect effects when the vaccine is introduced into low-income settings. Considering epidemiological differences in industrialized vs. low-income countries (severity of the disease, presence of mixed infections and serotype diversity, median age of onset) and the difference in vaccine effectiveness, it is hard to predict whether the indirect effects seen in industrialized country might also apply in low-income settings.

Selective Pressure and Serotype Replacement

Changes in serotypes or strains of a pathogen can occur naturally due to the background fluctuation or due to the selective pressures from vaccines or antibiotic use. Lesson learnt from *Streptococcus pneumoniae* serotype replacement after the introduction of pneumococcal 7-valent vaccine has showed that vaccines can put new evolutionary pressures on circulating strains, favoring those that are most resistant to the neutralizing activity of vaccination-induced immunity.³⁴ Postmarketing surveillance studies monitoring the impact of vaccine on circulating strains are extremely important to screen for possible vaccine selection pressure and strain replacement.

As regard RV vaccines, whether pressure from the vaccine might alter the distribution of rotavirus strains in circulation is not currently known. A large proportion (19.8%) of P non-typeable RV has been reported by some authors.³⁵ Brazil was the first Latin American country to introduce universal RV vaccination in 2006, resulting in a unique epidemiological scenario. Reports from Brazil have described changes in RV genotype prevalence (predominance of G2P4 strains) following vaccine introduction. The predominance of G2P4 seen raised speculation that this heterotypic strain was being selected by vaccination, however it has not been established whether these observations are a result of vaccine-induced immune pressure or simply reflect natural temporal variations in RV genotype circulation.³⁶⁻³⁸ Moreover a more recent national surveillance including 18 Brazilian states demonstrate the nationwide reemergence of genotype G2P4 from 2005 to 2008, and show that the rate of G2P4 detection is currently decreasing, probably reflecting the natural oscillation of RV genotype distribution.³⁹ In USA, rotavirus strain surveillance showed an overall increased prevalence of G3P8, higher than in pre-vaccine era.^{40,41} These data are consistent with Australian reports that showed that postvaccine strain variation differs on the basis of vaccine usage: G2P4 and G3P8 appeared to occur more often in sites using Rotarix® and RotaTeq®, respectively.⁴² However, these strain changes have occurred in the context of large declines in severe rotavirus disease and we cannot rule out that they are simply the result of naturally occurring changes in RV strain prevalence.

These findings underscore that additional seasons of monitoring are needed to assess the significance of the observed trends in circulating strains and to carefully monitor possible vaccine pressure-induced strain changes and vaccine effectiveness against various RV genotypes. Moreover, the recent emergence of rare/novel or genetically divergent strains was reported and poses an additional threat to long-term vaccine efficacy.⁴³ Thus, continued monitoring is critical to assess whether these rotavirus strains with unusual genotypes become more prevalent following the implementation of RV vaccines or simply reflect natural temporal variations in genotype circulation.

Post-Licensure Effectiveness

Rotavirus vaccine efficacy (a measure in a clinical trial setting of the reduction in the incidence of a disease among people who

have received a vaccine compared with the incidence in unvaccinated people) has ranged from 72–100% in countries with low-mortality rate to 46–72% in countries with high child mortality rates according to the last available WHO report.⁴⁴ These data have clearly shown that the highest protective efficacy against severe rotavirus gastroenteritis is achieved in populations in the lowest mortality stratum for children aged < 5 y.

However, vaccine effectiveness, a measure of the effect in a real life setting that also takes into consideration herd immunity, should be assessed in evaluating immunization programs.

High Income Countries

Data coming from high income countries that implemented childhood RV immunization are in line with pre-licensure studies: effectiveness of up to 100% has been observed in industrialized countries for both vaccines as recently reviewed by Giacchino et al. and O'Ryan et al.^{45,46} The introduction of RV vaccines has rapidly and dramatically reduced the large health burden of rotavirus gastroenteritis in children. A reduction in severe RV disease, hospitalizations, emergency department and outpatient visits for RV gastroenteritis has been reported worldwide. In USA, after the vaccine was introduced in July 2006, there was a 58 to 86% reduction in rotavirus-related hospitalizations over the following three years.^{26,47-51} In Australia Snelling et al. reported a vaccine effectiveness against RV-related hospitalization of 19% demonstrating a lower than expected overall protective effect of RV vaccines against hospitalization during outbreak of RV G2P4 infection.⁵² Nevertheless a striking 89–94% reduction in hospitalizations due to RV gastroenteritis in children under five years of age was observed two years after vaccine introduction by some authors.^{29,53} Similar to data reported in European countries,⁵⁴⁻⁶⁰ No differences in effectiveness between two RV vaccines have been observed. The real-world effectiveness data for both vaccines are consistent with clinical trials estimates and strengthen the argument for the introduction of rotavirus vaccination as an effective means for controlling severe and fatal childhood diarrhea.

Middle and Low Income Countries

A growing body of literature offers convincing evidence of real world vaccine program successes in Latin American settings. Data coming from middle-income countries (Mexico, Brazil, El Salvador and Panama) provide evidence of substantial reductions in both diarrhea deaths and hospitalizations among children. Rotavirus vaccine contributed to a gastroenteritis-associated mortality reduction of 22–41%, a gastroenteritis-associated hospitalization reduction of 17–51% and a RV hospitalization reduction of 59–81% among children younger than five years of age.⁶¹ Few data in low-income settings are currently available. In Nicaragua a lower effectiveness of 46% was seen, similar to the one reported in clinical trial settings. A key unanswered question is why rotavirus vaccines do not work equally well in the developing world, where they offer the greatest potential lifesaving benefits. Experience with previous rotavirus vaccines, as well as

Table 1. Studies assessing vaccine safety after introduction of rotavirus vaccines

Country	Source and methods	Vaccine	Safety data: intussusceptions (IS) risk
USA	Vaccine Adverse Event Reporting System	Rotarix®	Some, but not all, studies suggest that the RotaTaq® and Rotarix® may possibly cause a small increase in the risk of IS.
	Vaccine Safety Datalink ⁷²⁻⁷⁵	Rotateq®	
	Hospital discharge before vs after rotavirus vaccine reintroduction ⁷⁰		No increase in the number of hospital discharges for intussusception among USA infants in 2009
	Health insurance claims ⁷⁶	Rotateq®	No association with an increased risk of IS
Latin America	Mexico	Rotarix®	An increased risk of IS 1 to 7 d after the first dose
	Active surveillance in 16 hospitals ⁶⁸		
	Brasil	Rotarix®	No significant risk after the first dose An increased risk, albeit smaller than that seen after the first dose in Mexico 1 to 7 d after the second dose
	Active surveillance in 53 hospitals ⁶⁸		
Australia	Hospital-based case ascertainment and monthly reports from Pediatricians ⁶⁹	Rotarix®	An increased risk of IS in the weeks following the first dose of both rotavirus vaccine in children aged 1–3 mo.
		Rotateq®	No overall increase in the risk of IS for vaccinated children aged 1 to 9 mo
Worldwide	Spontaneous reported cases ⁷¹	Rotarix®	An increased risk of intussusception 1 to 7 d after the first dose

vaccines against cholera, polio and typhoid fever, has shown that the efficacy of live oral vaccines can be impaired in developing countries. Several host and environmental factors (such as interference by maternal antibodies, high levels of coinfection with other enteropathogens, malnutrition and concurrent administration of oral polio vaccine) could affect the processing of vaccine in the infant bowel and impair an infant's ability to generate an effective immune response. Moreover, in developing countries, some authors highlight the existence of significant diversity of rotavirus strains with unusual type combinations that could influence RV vaccine effectiveness.^{62,63} Recently Gladstone et al. showed that early infection and frequent reinfection in a setting with high viral diversity resulted in lower protection than has been reported elsewhere, providing a possible explanation for the observed lower than expected efficacy of rotavirus vaccine in Asia and Africa.⁶⁴

Safety

Intussusception (IS), a process in which a segment of intestine invaginates into the adjoining intestinal lumen causing obstruction to the blood supply, bowel wall edema, infarction or bowel perforation, is the most critical safety concern of live-attenuated RV vaccines. In fact, after the withdrawal of Rotashield®, debate continues over the association of RV vaccines with this condition. Although the risk of development of intussusception associated with Rotashield® has been estimated to be low (< 1 in 10,000 vaccine recipients), this has had important implications for clinical trials of other RV vaccine candidates. Important lessons have been learnt from this experience: newer RV vaccines now require safety assessment in large clinical trials (more than 60,000 children enrolled) to identify a risk of the magnitude of 1 in 32,000 vaccine recipients and an intensive post-marketing surveillance in order to detect any rare or unexpected vaccine-related adverse events.⁶⁵

Rotavirus vaccines (Rotarix® and Rotateq®) have been shown to be safe in placebo-controlled phase III clinical trials, each

involving over 60,000 infants.^{66,67} Trial data led to licensure of both vaccines and to reintroduction of rotavirus vaccination for infants in many countries. However, considering that their safety outside the clinical trial setting and in situations of routine use in a range of healthcare settings had not been demonstrated, data coming from these settings have been considered urgently needed. Thanks to the effort of the post-marketing surveillance in collaboration with State Health Authorities, new safety data are now available at the population level in different countries and regions (Table 1).

Conflicting results are reported by different Authors with substantial variability in the quality of post-marketing surveillance systems (e.g., active surveillance, spontaneous reports, health insurance claims). As a result, the whole data available might be difficult to interpret and might be insufficient to draw any definitive conclusion about the relationship between RV vaccines and IS. A small but clinically significant increased risk of IS following rotavirus vaccine administration was recently reported in Latin America,⁶⁸ Australia⁶⁹ however in USA Zickafoose et colleagues do not support this evidence.⁷⁰

In Latin America, Patel et al. used case-series and case-control methods to assess the association between Rotarix® and IS.⁶⁸ Six hundred and fifteen infants with IS were identified through active surveillance at 69 hospitals (16 in Mexico and 53 in Brazil) and were age-matched with 2,050 infants from the same neighborhood. The infants were observed from 45 d to 245 d of age. An increased risk of IS one to seven days after the first dose of Rotarix® was identified among infants in Mexico with both the case-series method (incidence ratio 5.3; 95% CI: 3.0–9.3) and the case-control method (odds ratio 5.8; 95% CI: 2.6–13.0). No significant risk was found after the first dose among infants in Brazil, but an increased risk by a factor of 1.9 to 2.6 was seen one to seven days after the second dose. In Mexico, a 2-fold risk of IS after vaccination was also noted during the second and third weeks after the second dose. Even if a combined annual excess of IS in Mexico (approximately 1/51,000 infants) and in Brazil (approximately 1/68,000 infants) and five deaths due to IS

were attributable to Rotarix®, this vaccine was found to prevent approximately 80,000 hospitalizations and 1,300 deaths from diarrhea each year in these two countries.

Nevertheless, a link between IS and RV vaccines cannot be certainly assessed considering study results; in fact this study design did not take in consideration the fact that a reduction of cases occurs later in life.

The incidence ratio of IS in Mexico has been found to be similar to those reported by Escolano and colleagues who conducted a case-series analysis of 151 spontaneous reports of intussusception worldwide after administration of Rotarix®.⁷¹ They found that the incidence ratio for the period 3 through 7 d after the first dose was 5.0 times as high as that for the same period after the second dose.

In Australia, a study conducted using two surveillance systems (the Paediatric Enhanced Disease Surveillance hospital-based network and the Australian Paediatric Surveillance Unit) found no overall increase in intussusception following receipt of RV vaccine; nevertheless in infants 1 to < 3 mo of age, there was suggestive evidence of excess intussusception cases 1–7 and 1–21 d following dose 1 (1–7 d: RotaTeq® relative risk (RR) = 5.3, 95% confidence interval [CI] 1.1, 15.4; Rotarix® RR 3.5, 95% CI: 0.7, 10.1; 1–21 d: RotaTeq® RR 3.5, 95% CI: 1.3, 7.6; Rotarix® RR 1.5, 95% CI: 0.4, 3.9).⁶⁹

In USA Zickafoose and his colleagues consulted a nationally-representative database of infants discharged from more than 4,000 hospitals over the decade before the vaccine was re-introduced, and one year shortly after.⁷⁰ They found that from 1997 to 2006, the number of infants hospitalized for IS seemed to drop slightly, from about 42 out of every 100,000 infants to 37 out of 100,000. In 2009, after the rotavirus vaccine was re-introduced, this downward trend has continued: an estimated 33 out of every 100,000 infants were discharged after treatment for IS.

Data coming from this study are not directly comparable to those previously reported: this analysis alone cannot prove or disprove the association between IS and RV vaccine. However the

measured rates of hospital discharges for intussusception in 2009 were well below the estimates that would be expected from the increased risk of IS after RV vaccination found in Latin America studies. More recently Shui et al. did not observe any increased risk of intussusceptions following pentavalent RV vaccination.⁷²

Reasons for the inconsistent results between different studies are unclear. A possible explanation might be the effect modification of the rotavirus vaccine–intussusception association by an environmental or genetic factor that differs between the populations. Moreover because IS is a rare event the possibility of not detecting a low-level risk of IS cannot be excluded.

In the light of these recent data it is crucial to make efforts to strengthen post-marketing surveillance and national and international collaborations using large linked databases. However it is reasonable to conclude that the very low risk of IS reported in these studies must be balanced against the benefits of RV vaccination. Currently, the absolute number of deaths and hospitalizations averted because of vaccination far exceeded the number of IS cases that may have been associated with vaccination, thus Health Authorities continue to strongly recommend routine RV vaccination of infants.

Conclusion

Growing post-licensure studies offer convincing evidence of real world vaccine program successes and straighten the recommendation of the use of RV vaccines as a part of a comprehensive strategy to control diarrheal diseases in both industrialized and developing countries. Long-term surveillance will be needed to assess the effectiveness and safety of RV immunization programs. Moreover epidemiologic surveillance is necessary to determine whether changes in strain ecology will affect the RV vaccine effectiveness.

Acknowledgments

We thank Elena Carcereri De Prati for her precious collaboration.

References

- Centers for Disease Control and Prevention (CDC). Rotavirus surveillance—worldwide 2009. *MMWR Morb Mortal Wkly Rep* 2011; 60:514-6; PMID:21527889.
- Tate JE, Burton AH, Boschi-Pinto C, Steele AD, Duque J, Parashar UD; WHO-coordinated Global Rotavirus Surveillance Network. 2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis. *Lancet Infect Dis* 2012; 12:136-41; PMID:22030330; [http://dx.doi.org/10.1016/S1473-3099\(11\)70253-5](http://dx.doi.org/10.1016/S1473-3099(11)70253-5).
- World Health Organization. Decision making and Implementation of Rotavirus Vaccines http://www.who.int/nuvi/rotavirus/decision_implementation/en/index.html. Accessed 22nd January 2012.
- Ward RL, McNeal MM, Steele AD. Why does the world need another rotavirus vaccine? *Ther Clin Risk Manag* 2008; 4:49-63; PMID:18728720.
- O’Ryan M, Linhares AC. Update on Rotarix: an oral human rotavirus vaccine. *Expert Rev Vaccines* 2009; 8:1627-41; PMID:19943758; <http://dx.doi.org/10.1586/erv.09.136>.
- Chandran A, Santosham M. RotaTeq: a three-dose oral pentavalent reassortant rotavirus vaccine. *Expert Rev Vaccines* 2008; 7:1475-80; PMID:19053204; <http://dx.doi.org/10.1586/14760584.7.10.1475>.
- Tsai CJ, Griffin MR, Nuorti JP, Grijalva CG. Changing epidemiology of pneumococcal meningitis after the introduction of pneumococcal conjugate vaccine in the United States. *Clin Infect Dis* 2008; 46:1664-72; PMID:18433334; <http://dx.doi.org/10.1086/587897>.
- Hargreaves RM, Slack MP, Howard AJ, Anderson E, Ramsay ME. Changing patterns of invasive *Haemophilus influenzae* disease in England and Wales after introduction of the Hib vaccination programme. *BMJ* 1996; 312:160-1; PMID:8563536; <http://dx.doi.org/10.1136/bmj.312.7024.160>.
- Zepp F, Heininger U, Mertsola J, Bernatowska E, Guiso N, Roord J, et al. Rationale for pertussis booster vaccination throughout life in Europe. *Lancet Infect Dis* 2011; 11:557-70; PMID:21600850; [http://dx.doi.org/10.1016/S1473-3099\(11\)70007-X](http://dx.doi.org/10.1016/S1473-3099(11)70007-X).
- Tsou TP, Liu CC, Huang JJ, Tsai KJ, Chang HF. Change in hepatitis A epidemiology after vaccinating high risk children in Taiwan, 1995–2008. *Vaccine* 2011; 29:2956-61; PMID:21329774; <http://dx.doi.org/10.1016/j.vaccine.2011.02.001>.
- Goodson JL, Masresha BG, Wannemuehler K, Uzicanin A, Cochi S. Changing epidemiology of measles in Africa. *J Infect Dis* 2011; 204:205-14; PMID:21666163; <http://dx.doi.org/10.1093/infdis/jir129>.
- Guris D, Jumaan AO, Mascola L, Watson BM, Zhang JX, Chaves SS, et al. Changing varicella epidemiology in active surveillance sites—United States, 1995–2005. *J Infect Dis* 2008; 197:71-5; PMID:18419413; <http://dx.doi.org/10.1086/522156>.
- Skoff TH, Cohn AC, Clark TA, Messonnier NE, Martin SW. Early Impact of the US Tdap Vaccination Program on Pertussis Trends. *Arch Pediatr Adolesc Med* 2012; 166:344-9; PMID:22213608; <http://dx.doi.org/10.1001/archpediatrics.2011.1093>.
- de Blasio BF, Kasymbekova K, Flem E. Dynamic model of rotavirus transmission and the impact of rotavirus vaccination in Kyrgyzstan. *Vaccine* 2010; 28:7923-32; PMID:20933563; <http://dx.doi.org/10.1016/j.vaccine.2010.09.070>.
- Pitzer VE, Viboud C, Simonsen L, Steiner C, Panozzo CA, Alonso WJ, et al. Demographic variability, vaccination and the spatiotemporal dynamics of rotavirus epidemics. *Science* 2009; 325:290-4; PMID:19608910; <http://dx.doi.org/10.1126/science.1172330>.

16. Clark HF, Lawley D, Matthijssens J, DiNubile MJ, Hodinka RL. Sustained decline in cases of rotavirus gastroenteritis presenting to the Children's Hospital of Philadelphia in the new rotavirus vaccine era. *Pediatr Infect Dis J* 2010; 29:699-702; PMID:20661099; <http://dx.doi.org/10.1097/INF.0b013e3181d73524>.
17. Hanquet G, Ducoffre G, Vergison A, Neels P, Sabbe M, Van Damme P, et al. Impact of rotavirus vaccination on laboratory confirmed cases in Belgium. *Vaccine* 2011; 29:4698-703; PMID:21571023; <http://dx.doi.org/10.1016/j.vaccine.2011.04.098>.
18. Payne DC, Staat MA, Edwards KM, Szilagyi PG, Weinberg GA, Hall CB, et al.; New Vaccine Surveillance Network (NVSN). Direct and indirect effects of rotavirus vaccination upon childhood hospitalizations in 3 US Counties, 2006-2009. *Clin Infect Dis* 2011; 53:245-53; PMID:21705316; <http://dx.doi.org/10.1093/cid/cir307>.
19. Tate JE, Panozzo CA, Payne DC, Patel MM, Cortese MM, Fowlkes AL, et al. Decline and change in seasonality of US rotavirus activity after the introduction of rotavirus vaccine. *Pediatrics* 2009; 124:465-71; PMID:19581260; <http://dx.doi.org/10.1542/peds.2008-3528>.
20. Curns AT, Panozzo CA, Tate JE, Payne DC, Patel MM, Cortese MM, et al. Remarkable postvaccination spatio-temporal changes in United States rotavirus activity. *Pediatr Infect Dis J* 2011; 30:54-5; PMID:21183841; <http://dx.doi.org/10.1097/INF.0b013e3181feda9>.
21. Braeckman T, Van Herck K, Raes M, Vergison A, Sabbe M, Van Damme P. Rotavirus vaccines in Belgium: policy and impact. *Pediatr Infect Dis J* 2011; 30:21-4; PMID:21183836; <http://dx.doi.org/10.1097/INF.0b013e3181feca51>.
22. Sáfadi MA, Berezin EN, Munford V, Almeida FJ, de Moraes JC, Pinheiro CF, et al. Hospital-based surveillance to evaluate the impact of rotavirus vaccination in São Paulo, Brazil. *Pediatr Infect Dis J* 2010; 29:1019-22; PMID:20543761.
23. Fine PE. Herd immunity: history, theory, practice. *Epidemiol Rev* 1993; 15:265-302; PMID:8174658.
24. Kim TH, Johnstone J, Loeb M. Vaccine herd effect. *Scand J Infect Dis* 2011; 43:683-9; PMID:21604922.
25. Van Effelterre T, Soriano-Gabarró M, Debrus S, Claire Newbern E, Gray J. A mathematical model of the indirect effects of rotavirus vaccination. *Epidemiol Infect* 2010; 138:884-97; PMID:20028612; <http://dx.doi.org/10.1017/S0950268809991245>.
26. Tate JE, Cortese MM, Payne DC, Curns AT, Yen C, Esposito DH, et al. Uptake, impact and effectiveness of rotavirus vaccination in the United States: review of the first 3 years of postlicensure data. *Pediatr Infect Dis J* 2011; 30:56-60; PMID:21183842; <http://dx.doi.org/10.1097/INF.0b013e3181fedc0>.
27. Lopman BA, Curns AT, Yen C, Parashar UD. Infant rotavirus vaccination may provide indirect protection to older children and adults in the United States. *J Infect Dis* 2011; 204:980-6; PMID:21878425; <http://dx.doi.org/10.1093/infdis/jir492>.
28. Buttery JP, Lambert SB, Grimwood K, Nissen MD, Field EJ, Macartney KK, et al. Reduction in rotavirus-associated acute gastroenteritis following introduction of rotavirus vaccine into Australia's National Childhood vaccine schedule. *Pediatr Infect Dis J* 2011; 30:25-9; PMID:21183837; <http://dx.doi.org/10.1097/INF.0b013e3181fedee>.
29. Clarke MF, Davidson GP, Gold MS, Marshall HS. Direct and indirect impact on rotavirus positive and all-cause gastroenteritis hospitalisations in South Australian children following the introduction of rotavirus vaccination. *Vaccine* 2011; 29:4663-7; PMID:21575665; <http://dx.doi.org/10.1016/j.vaccine.2011.04.109>.
30. Macartney KK, Porwal M, Dalton D, Cripps T, Maldigri T, Isaacs D, et al. Decline in rotavirus hospitalisations following introduction of Australia's national rotavirus immunisation programme. *J Paediatr Child Health* 2011; 47:266-70; PMID:21244557; <http://dx.doi.org/10.1111/j.1440-754.2010.01953.x>.
31. Paulke-Korinek M, Kundi M, Rendi-Wagner P, de Martin A, Eder G, Schmidle-Loss B, et al. Herd immunity after two years of the universal mass vaccination program against rotavirus gastroenteritis in Austria. *Vaccine* 2011; 29:2791-6; PMID:21320539; <http://dx.doi.org/10.1016/j.vaccine.2011.01.104>.
32. Yen C, Armero Guardado JA, Alberto P, Rodriguez Araujo DS, Mena C, Cuellar E, et al. Decline in rotavirus hospitalizations and health care visits for childhood diarrhea following rotavirus vaccination in El Salvador. *Pediatr Infect Dis J* 2011; 30:6-10; PMID:21048524; <http://dx.doi.org/10.1097/INF.0b013e3181fefa05>.
33. Anderson E, Shippee D, Weinrobe M, Davila M, Katz B, Lee S, et al. Pediatric Rotavirus Vaccination Reduces Prevalence in Adults Infectious Diseases Society of America (IDSA) 49th Annual Meeting: Abstract LB-26. Presented October 22, 2011.
34. Weinberger DM, Malley R, Lipsitch M. Serotype replacement in disease after pneumococcal vaccination. *Lancet* 2011; 378:1962-73; PMID:21492929; [http://dx.doi.org/10.1016/S0140-6736\(10\)62225-8](http://dx.doi.org/10.1016/S0140-6736(10)62225-8).
35. Zuccotti G, Meneghin F, Dilillo D, Romanò L, Bottone R, Mantegazza C, et al. Epidemiological and clinical features of rotavirus among children younger than 5 years of age hospitalized with acute gastroenteritis in northern Italy. *BMC Infect Dis* 2010; 10:218; PMID:20649961; <http://dx.doi.org/10.1186/1471-2334-10-218>.
36. Gurgel RQ, Correia JB, Cuevas LE. Effect of rotavirus vaccination on circulating virus strains. *Lancet* 2008; 371:301-2; PMID:18294994; [http://dx.doi.org/10.1016/S0140-6736\(08\)60164-6](http://dx.doi.org/10.1016/S0140-6736(08)60164-6).
37. Gurgel RQ, Cuevas LE, Vieira SCF, Barros VC, Fontes PB, Salustino EF, et al. Predominance of rotavirus P[4] G2 in a vaccinated population, Brazil. *Emerg Infect Dis* 2007; 13:1571-3; PMID:18258011.
38. Leite JP, Carvalho-Costa FA, Linhares AC. Group A rotavirus genotypes and the ongoing Brazilian experience: a review. *Mem Inst Oswaldo Cruz* 2008; 103:745-53; PMID:19148411; <http://dx.doi.org/10.1590/S0074-02762008000800001>.
39. Carvalho-Costa FA, Volotão Ede M, de Assis RM, Fialho AM, de Andrade Jda S, Rocha LN, et al. Laboratory-based rotavirus surveillance during the introduction of a vaccination program, Brazil, 2005-2009. *Pediatr Infect Dis J* 2011; 30:35-41; PMID:21048523; <http://dx.doi.org/10.1097/INF.0b013e3181fed5f>.
40. Hull JJ, Teel EN, Kerin TK, Freeman MM, Esona MD, Gentsch JR, et al.; National Rotavirus Strain Surveillance System. United States rotavirus strain surveillance from 2005 to 2008: genotype prevalence before and after vaccine introduction. *Pediatr Infect Dis J* 2011; 30:42-7; PMID:21183839; <http://dx.doi.org/10.1097/INF.0b013e3181fed78>.
41. Desai SN, Vázquez M. Update on rotavirus trends and the importance of surveillance. *Pediatr Infect Dis J* 2010; 29:1130-2; PMID:21099653; <http://dx.doi.org/10.1097/INF.0b013e3181ff1eeb>.
42. Kirkwood CD, Boniface K, Barnes GL, Bishop RF. Distribution of rotavirus genotypes after introduction of rotavirus vaccines, Rotarix® and RotaTeq®, into the National Immunization Program of Australia. *Pediatr Infect Dis J* 2011; 30:48-53; PMID:21183840; <http://dx.doi.org/10.1097/INF.0b013e3181fed90>.
43. Weinberg GA, Payne DC, Teel EN, Mijatovic-Rustempasic S, Bowen MD, Wikswo M, et al. First reports of human rotavirus G8P[4] gastroenteritis in the United States. *J Clin Microbiol* 2012; 50:1118-21; PMID:22170918; <http://dx.doi.org/10.1128/JCM.05743-11>.
44. World Health Organization. Rotavirus vaccines: an update. *Weekly Epidemiological Record (WER)* 18 December 2009; 84:50; http://www.who.int/wer/2009/wer8451_52.pdf. Accessed 19 February 2012.
45. Giaquinto C, Dominiak-Felden G, Van Damme P, Myint TT, Maldonado YA, Spoulou V, et al. Summary of effectiveness and impact of rotavirus vaccination with the oral pentavalent rotavirus vaccine: a systematic review of the experience in industrialized countries. *Hum Vaccin* 2011; 7:734-48; PMID:21734466; <http://dx.doi.org/10.4161/hv.7.7.15511>.
46. O'Ryan M, Lucero Y, Linhares AC. Rotarix®: vaccine performance 6 years postlicensure. *Expert Rev Vaccines* 2011; 10:1645-59; PMID:22085167; <http://dx.doi.org/10.1586/erv.11.152>.
47. Tate JE, Mutuc JD, Panozzo CA, Payne DC, Cortese MM, Cortes JE, et al. Sustained decline in rotavirus detections in the United States following the introduction of rotavirus vaccine in 2006. *Pediatr Infect Dis J* 2011; 30:30-4; PMID:21183838; <http://dx.doi.org/10.1097/INF.0b013e3181ffecb>.
48. Staat MA, Payne DC, Donauer S, Weinberg GA, Edwards KM, Szilagyi PG, et al.; New Vaccine Surveillance Network (NVSN). Effectiveness of pentavalent rotavirus vaccine against severe disease. *Pediatrics* 2011; 128:267-75; PMID:21768317; <http://dx.doi.org/10.1542/peds.2010-3722>.
49. Boom JA, Tate JE, Sahni LC, Rench MA, Hull JJ, Gentsch JR, et al. Effectiveness of pentavalent rotavirus vaccine in a large urban population in the United States. *Pediatrics* 2010; 125:199-207; PMID:20083525; <http://dx.doi.org/10.1542/peds.2009-1021>.
50. Guh AY, Hadler JL. Use of the state immunization information system to assess rotavirus vaccine effectiveness in Connecticut 2006-2008. *Vaccine* 2011; 29:6155-8; PMID:21723356; <http://dx.doi.org/10.1016/j.vaccine.2011.06.066>.
51. Boom JA, Tate JE, Sahni LC, Rench MA, Quayle O, Mijatovic-Rustempasic S, et al. Sustained protection from pentavalent rotavirus vaccination during the second year of life at a large, urban United States pediatric hospital. *Pediatr Infect Dis J* 2010; 29:1133-5; PMID:20634776; <http://dx.doi.org/10.1097/INF.0b013e3181ed18ab>.
52. Snelling TL, Andrews RM, Kirkwood CD, Culveron S, Carapetis JR. Case-control evaluation of the effectiveness of the G1P[8] human rotavirus vaccine during an outbreak of rotavirus G2P[4] infection in central Australia. *Clin Infect Dis* 2011; 52:191-9; PMID:21288843; <http://dx.doi.org/10.1093/cid/ciq101>.
53. Field EJ, Vally H, Grimwood K, Lambert SB. Pentavalent rotavirus vaccine and prevention of gastroenteritis hospitalizations in Australia. *Pediatrics* 2010; 126:506-12; PMID:20732946; <http://dx.doi.org/10.1542/peds.2010-0443>.
54. Paulke-Korinek M, Rendi-Wagner P, Kundi M, Kronik R, Kollaritsch H. Universal mass vaccination against rotavirus gastroenteritis: impact on hospitalization rates in austrian children. *Pediatr Infect Dis J* 2010; 29:319-23; PMID:19935446.
55. Raes M, Strens D, Vergison A, Verghote M, Standaert B. Reduction in pediatric rotavirus-related hospitalizations after universal rotavirus vaccination in Belgium. *Pediatr Infect Dis J* 2011; 30:120-5; PMID:21436757; <http://dx.doi.org/10.1097/INF.0b013e318214b811>.
56. Braeckman T, Van Herck K, Raes M, Vergison A, Sabbe M, Van Damme P. Rotavirus vaccines in Belgium: policy and impact. *Pediatr Infect Dis J* 2011; 30:21-4; PMID:21183836; <http://dx.doi.org/10.1097/INF.0b013e3181feca51>.
57. Castilla J, Beristain X, Martínez-Artola V, Navascués A, García Cenoz M, Alvarez N, et al. Effectiveness of rotavirus vaccines in preventing cases and hospitalizations due to rotavirus gastroenteritis in Navarre, Spain. *Vaccine* 2012; 30:539-43; PMID:22128660; <http://dx.doi.org/10.1016/j.vaccine.2011.11.071>.
58. Martínón-Torres F, Bouzón Alejandro M, Redondo Collazo L, Sánchez Lastres JM, Pérttega Díaz S, Seoane Pillado MT, et al.; ROTACOST research team. Effectiveness of rotavirus vaccination in Spain. *Hum Vaccin* 2011; 7:757-61; PMID:21521947; <http://dx.doi.org/10.4161/hv.7.7.15576>.

59. Gagneur A, Nowak E, Lemaitre T, Segura JF, Delaperrière N, Abalea L, et al.; IVANHOE investigators. Impact of rotavirus vaccination on hospitalizations for rotavirus diarrhea: the IVANHOE study. *Vaccine* 2011; 29:3753-9; PMID:21443962; <http://dx.doi.org/10.1016/j.vaccine.2011.03.035>.
60. Uhlig U, Kostev K, Schuster V, Uhlig HH. Rotavirus vaccination in Germany: analysis of nationwide surveillance data 2006 to 2010. *Pediatr Infect Dis J* 2011; 30:244-7; PMID:21817956; <http://dx.doi.org/10.1097/INF.0b013e31822d1408>.
61. Desai R, de Oliveira LH, Parashar UD, Lopman B, Tate JE, Patel MM. Reduction in morbidity and mortality from childhood diarrhoeal disease after species A rotavirus vaccine introduction in Latin America—a review. *Mem Inst Oswaldo Cruz* 2011; 106:907-11; PMID:22241109.
62. Bonkougou IJ, Damanka S, Sanou I, Tiendrébéogo F, Coulibaly SO, Bon F, et al. Genotype diversity of group A rotavirus strains in children with acute diarrhea in urban Burkina Faso, 2008–2010. *J Med Virol* 2011; 83:1485-90; PMID:21678452; <http://dx.doi.org/10.1002/jmv.22137>.
63. Nokes DJ, Peenze I, Netshifhefhe L, Abwao J, De Beer MC, Seheri M, et al. Rotavirus genetic diversity, disease association and temporal change in hospitalized rural Kenyan children. *J Infect Dis* 2010; 202:180-6; PMID:20684700; <http://dx.doi.org/10.1086/653566>.
64. Gladstone BP, Ramani S, Mukhopadhyaya I, Muliylil J, Sarkar R, Rehman AM, et al. Protective effect of natural rotavirus infection in an Indian birth cohort. *N Engl J Med* 2011; 365:337-46; PMID:21793745; <http://dx.doi.org/10.1056/NEJMoa1006261>.
65. World Health Organization. Post-marketing surveillance of rotavirus vaccine safety. http://whqlibdoc.who.int/hq/2009/WHO_IVB_09.01_eng.pdf. Accessed 28 January 2012.
66. Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR, Abate H, Breuer T, Clemens SC, et al.; Human Rotavirus Vaccine Study Group. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med* 2006; 354:11-22; PMID:16394298; <http://dx.doi.org/10.1056/NEJMoa052434>.
67. Vesikari T, Matson DO, Dennehy P, Van Damme P, Santosham M, Rodriguez Z, et al.; Rotavirus Efficacy and Safety Trial (REST) Study Team. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med* 2006; 354:23-33; PMID:16394299; <http://dx.doi.org/10.1056/NEJMoa052664>.
68. Patel MM, López-Collada VR, Bulhões MM, De Oliveira LH, Bautista Márquez A, Flannery B, et al. Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. *N Engl J Med* 2011; 364:2283-92; PMID:21675888; <http://dx.doi.org/10.1056/NEJMoa1012952>.
69. Buttery JP, Danchin MH, Lee KJ, Carlin JB, McIntyre PB, Elliott EJ, et al.; PAEDS/APSU Study Group. Intussusception following rotavirus vaccine administration: post-marketing surveillance in the National Immunization Program in Australia. *Vaccine* 2011; 29:3061-6; PMID:21316503; <http://dx.doi.org/10.1016/j.vaccine.2011.01.088>.
70. Zickafoose JS, Benneyworth BD, Riebschleger MP, Espinosa CM, Davis MM. Hospitalizations for intussusception before and after the reintroduction of rotavirus vaccine in the United States. *Arch Pediatr Adolesc Med* 2012; 166:350-5; PMID:22213609; <http://dx.doi.org/10.1001/archpediatrics.2011.1501>.
71. Escolano S, Farrington CP, Hill C, Tubert-Bitter P. Intussusception after rotavirus vaccination—spontaneous reports. *N Engl J Med* 2001; 365:2139.
72. Shui IM, Baggs J, Patel M, Parashar UD, Rett M, Belongia EA, et al. Risk of intussusception following administration of a pentavalent rotavirus vaccine in US infants. *JAMA* 2012; 307:598-604; PMID:22318281; <http://dx.doi.org/10.1001/jama.2012.97>.
73. Centers for Disease Control and Prevention. http://www.cdc.gov/vaccinesafety/vaccines/rotateq_intussusception.html. Accessed 30 January 2012.
74. Belongia EA, Irving SA, Shui IM, Kulldorff M, Lewis E, Yin R, et al.; Vaccine Safety Datalink Investigation Group. Real-time surveillance to assess risk of intussusception and other adverse events after pentavalent, bovine-derived rotavirus vaccine. *Pediatr Infect Dis J* 2010; 29:1-5; PMID:19907356; <http://dx.doi.org/10.1097/INF.0b013e3181af8605>.
75. Geier DA, King PG, Sykes LK, Geier MR. The temporal relationship between RotaTeq immunization and intussusception adverse events in the Vaccine Adverse Event Reporting System (VAERS). *Med Sci Monit* 2012; 18:12-7; PMID:22293889.
76. Loughlin J, Mast TC, Doherty MC, Wang FT, Wong J, Seeger JD. Postmarketing evaluation of the short-term safety of the pentavalent rotavirus vaccine. *Pediatr Infect Dis J* 2012; 31:292-6; PMID:22173146; <http://dx.doi.org/10.1097/INF.0b013e3182421390>.