Universal Mass Vaccination Against Rotavirus Gastroenteritis

Impact on Hospitalization Rates in Austrian Children

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Background: Since July 2007, rotavirus vaccinations have been subsidized in Austria for all children from the seventh week up to the sixth month of life. Vaccination coverage over the whole period was 72% with an increase to 87% in 2008.

Methods: In a sentinel network including 11 pediatric hospital wards in Austria, data of children up to 15 years of age and hospitalized due to rotavirus gastroenteritis between January 2001 and December 2008 have been collected.

Results: The hospitalization rates of children up to 12 months of age with rotavirus gastroenteritis were 2066×10^{-5} between 2001 and 2006 and decreased to 631×10^{-5} in 2008. For children between 12 and 24 months of age the hospitalization rate decreased from 1822×10^{-5} (2001–2006) to 1456×10^{-5} in 2008. In children aged 2 to less than 5 years, incidence rates were 436×10^{-5} (2001–2006) and 461×10^{-5} in 2008. In older children, the hospitalization rates remained unchanged. In the target population for the RV-vaccine, a decrease of hospitalization rates due to rotavirus gastroenteritis of 74% was observed compared to the era before the introduction of the vaccine. The field effectiveness of the vaccine was estimated between 61% and 98%, depending on assumptions about the vaccination status.

Conclusions: Within 18 months, the universal mass vaccination program against rotavirus led to a substantial decrease in the hospitalization rates of the target cohort of the immunization program in Austria.

Key Words: rotavirus gastroenteritis, immunization program, vaccination

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Rotavirus gastroenteritis (RV-GE) is not only a burden in developing countries, but is also one of the most frequent reasons for pediatric hospital admissions in industrialized countries.[1–4] According to Soriano-Gabarró et al, every year 1 child below 5 years of age per 100,000 dies from RV-GE in Austria, about 1400 per 100,000 children are admitted to hospital; 11,200 home visits are performed by physicians and about 44,900 episodes of acute gastroenteritis occur because of rotavirus infections.[2]

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In Austria, every 60th child below the age of 2 will be admitted to hospital because of RV-GE.[5] Together with cost calculations[6] this accounted for the recommendation of a universal mass vaccination (UMV) against rotavirus in Austrian infants. It was adopted into the Austrian recommendations for childhood immunizations 2006 by the Austrian Advisory Committee on Immunization Practices.[7] However, at the time of the Austrian market launch of Rotarix (GlaxoSmithKline Biologicals, Rixensart, Belgium; market launch May 2006) and Rotateq (Sanofi Pasteur MSD SNC, Lyon, France; market launch September 2006), the oral vaccines had to be privately financed. Since July 2007, oral rotavirus vaccinations have been subsidized in the course of an UMV program for all children between the sixth week and sixth months of life in Austria. From July up to the end of December 2007, Rotateq was the only distributed vaccine. Between January 2008 and December 2008, Rotarix was subsidized.

This investigation aims to show the significant beneficial effects of a UMV strategy against RV-GE by subsidizing the oral vaccines for all Austrian infants at the respective age.

METHODS

Study Design

The Austrian surveillance of RV-GE for hospitalized children was initiated in 1997. It has been shown to be a representative and conclusive sentinel system for monitoring epidemiology.[5] The present analysis focused on all cases of hospitalized RV-GE reported to the surveillance system between January 1, 2001 and December 31, 2008. In this period, the sentinel system consisted of 11 hospitals representing, during this period, between 29% and 34% of all pediatric beds in Austria. In every hospital 1 pediatrician was dedicated to provide the reports on RV-GE twice a year containing the following information[5]: initials, gender, date of birth (we included children up to 15 years of age), date of onset of symptoms, date of admission to hospital, and date of hospital discharge. Starting in 2007, data on the children's vaccination status against RV-GE (no vaccination/1 vaccination or 2/3 vaccinations) were collected. This information should be provided based on the entries into the vaccination card or, if this was not available, by asking the parents.

All reported cases of RV-GE were confirmed routinely by commercially available rotavirus tests. Based on immunochromatographic methods the Vikia Rota-Adeno Test (Bio-Merieux), the Diarlex MB test (Orion Diagnostica), the Rotavirus Test by CerTest Biotec, and the Rota-Strip by Coris Bioconcept were used. Sensitivity and specificity of these test systems is between 96% to 99% and 96% to 100%, respectively.[8,9] In one hospital an enzyme immunoassay called Ridascreen Rotavirus test (r-biopharm) was used (sensitivity 100%, specificity 99.7%).[10]

Study Population

The epidemiology of RV-GE was described focusing on the number of hospitalized cases, the age of the affected children, the season when the disease occurred and the duration of hospitaliza-

tion. The yearly reports were extrapolated for whole Austria by using the official numbers of pediatric beds.[11] Hospitalization rates of RV-GE per 100,000 in different age groups[12] were assessed.

To determine the influence of the UMV on the age distribution of children with RV-GE, focus was laid on the children who suffered from RV-GE between August 2007 and December 2008. The children of the "vaccination period" were subdivided into 3 age groups: (1) children <90 days old, who were too young for complete basic immunization during the observation period, (2) children 90 days to <20 months of age during the observation period, the "target group" for vaccination (children born between May 2007 to September 2008 were fully eligible for vaccination because of their appropriate age between 90 days and 6 months), and (3) children 20 months of age up to 48 months, who were "out of range" for vaccination.

As control group served children admitted out of the range of the "vaccination period." These were analyzed in analogy to the children of the "vaccination period" within the following time intervals: August 2001 to December 2002; August 2003 to December 2004; August 2005 to December 2006. Thus 4 complete rotavirus seasons (highest incidence between October and April) were covered.

Hospital Acquired RV-GE

Cases were assumed as hospital acquired infections (nosocomial) if the onset of the symptoms was at least 24 hours (1 day) after admission to hospital and the diagnosis at time of admission was not any kind of gastroenteritis. Hospital acquired RV-GE could only be evaluated from 10 hospitals, due to missing onset dates from 1 hospital.

Duration of Stay

The duration of stay in hospital due to RV-GE was defined as the time span between the day of admission to hospital and the day of discharge. When evaluating the mean duration of stay in hospital, the hospital acquired cases were excluded from the analysis.

Vaccination Coverage Rate and Field Effectiveness of the Vaccines

The vaccination coverage rate between July 2007 and December 2008 was calculated from the number of distributed doses in the course of the UMV program.

For evaluating the field effectiveness, only children who were between 90 days and 20 months of age (eligible for vaccination in the course of the UMV program) were analyzed. The field effectiveness of the vaccines was calculated according to the equation described by Heinz et al.[13] In brief, field effectiveness was defined as the percentage of prevented cases of hospitalized RV-GE. Let I_v and I_n be the number incident hospitalized cases of RV-GE in the vaccinated and unvaccinated population, respectively, and r be the vaccination rate, then field effectiveness is given by $100[1 - I_v(1 - r)/I_n r]$.

Adverse Events

Vaccine related adverse events were assessed by using the official reporting system of the Austrian Ministry of Health, the Austrian Competent Authority, which is similar to the US "VAERS" (Vaccine Adverse Event Reporting System): Incoming reports are collected, but not validated with respect to their relationship to the vaccination. All the adverse events following rotavirus vaccination over the period between September 2006 and December 2008 were inquired.

RESULTS

Overall Numbers and Hospitalization Rates

From January 1, 2001 to December 31, 2008 10,834 reports on hospitalized cases of RV-GE in children up to 15 years of age were received from 11 hospitals, representing 29% to 34% of all pediatric beds in Austria.

Prevaccination Period (2001–2006)

From 2001 to 2006, the number of reports extrapolated for Austria was between 3379 (year 2002) and 5406 (year 2006), on average 4457 cases per year (±708.9 SD). The highest incidence rate of hospitalization was found in the age group below 12 months (average incidence rate 2065.8×10^{-5}, peak incidence 2412.4×10^{-5} in 2005). In children aged between 12 and 24 months, the hospitalization incidence rate was 1821.9×10^{-5} between 2001 and 2006 (peak incidence 2391.0×10^{-5} in 2006). In children between 2 and less than 5 years of age, the mean annual incidence was 435.5×10^{-5} (peak incidence rate of 633.3×10^{-5} in 2006).

Vaccination Period (2007 and 2008)

The UMV started in July 2007. Therefore, the reported cases 2007 could not be attributed entirely to the prevaccination or to the vaccination period and this year was excluded from comparative statistical analyses. In 2008, the extrapolated number of reported cases was 3074. In children below 12 months of age the hospitalization incidence dropped to 630.6×10^{-5} (reduction of 69.5% compared with 2001–2006). In children aged between 12 and 24 months, the incidence decreased to 1456.1×10^{-5} in 2008 (reduction of 20.1% compared with 2001–2006). In children between 2 and less than 5 years of age, the incidence of hospitalized children was 461.4×10^{-5} (increase of 6.0% compared with 2001–2006). In children 5 to below 15 years old, incidence rates remained unchanged during the observation period 2001–2008 with on average 34.4×10^{-5} cases (Fig. 1).

Age Distribution of Hospitalized Children up to 48 Months of Life

In the years 2001 to 2006, 5.3% of the hospital admitted cases occurred in children below 90 days of age, in 2007 the respective percentage was 3.8% and in 2008 4.0% (Fig. 2).

The age group 90 days to 12 months contributed to hospitalizations with 35.3% between 2001 and 2006, 25.3% in 2007, and 14.6% in 2008. Percentage of hospitalized children in the age group 12 to 24 months was 36.2% in the years 2001–2006, 41.8% in 2007, and 44.0% in 2008. Also increases were observed in the age group 2 to 4 years: 23.2% in 2001–2006, 29.1% in 2007, and 37.4% in 2008. In accordance with this shift of the age distribution, the mean age of children hospitalized for RV-GE increased from 1.9 (±2.0 SD) years in 2001–2006, to 2.3 (±2.2 SD) years in 2007, and 2.6 (±2.3 SD) years in 2008.

Effect of UMV and Vaccine Effectiveness

The UMV program between August 2007 and December 2008 resulted – compared with identical time periods in the prevaccination era—in (1) a decrease of 42.0% of hospitalized children below 90 days of age, (2) a decrease of 73.6% for children between 90 days and 20 months and (3) an increase of 8.0% in the age group of children between 20 months and 48 months.

In Austria, the vaccination coverage rate according to the distributed numbers of vaccine doses in the course of the UMV was 59% in the period July 2007 to December 2007 (use of Rotateq). In 2008, an estimated vaccination coverage of 87% was achieved (use of Rotarix). Overall, during this period 77,351 double or triple doses as

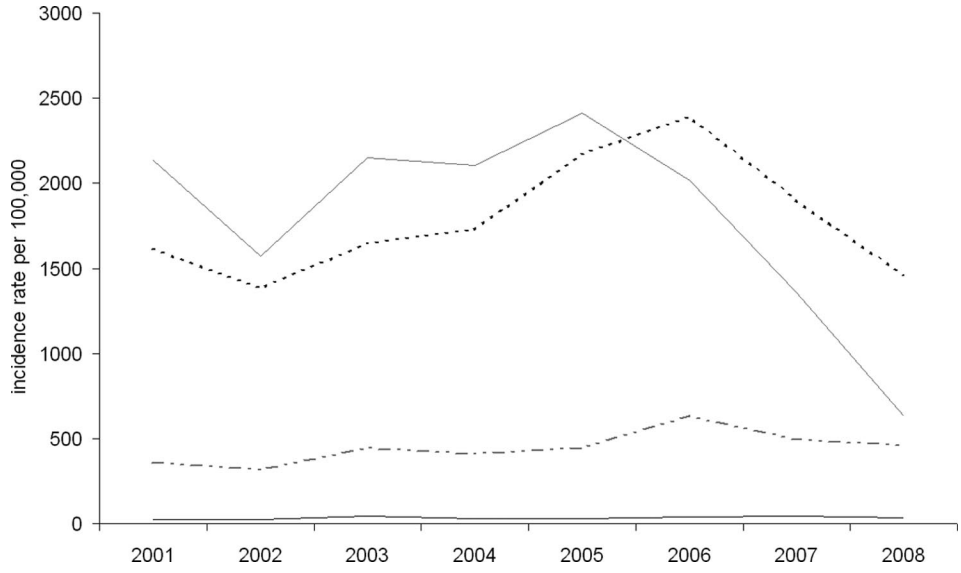

FIGURE 1. Hospitalization rates of RV-GE in children per 100,000 population in the respective age group. The grey line shows incidence rates in children <12 months of age, the black broken line shows incidence rates in children 12 to <24 months of age, the grey broken lines shows incidence rates in children 24 to <60 months of age and the dark grey line shows incidence rates in children 60 months of age to <15 years.

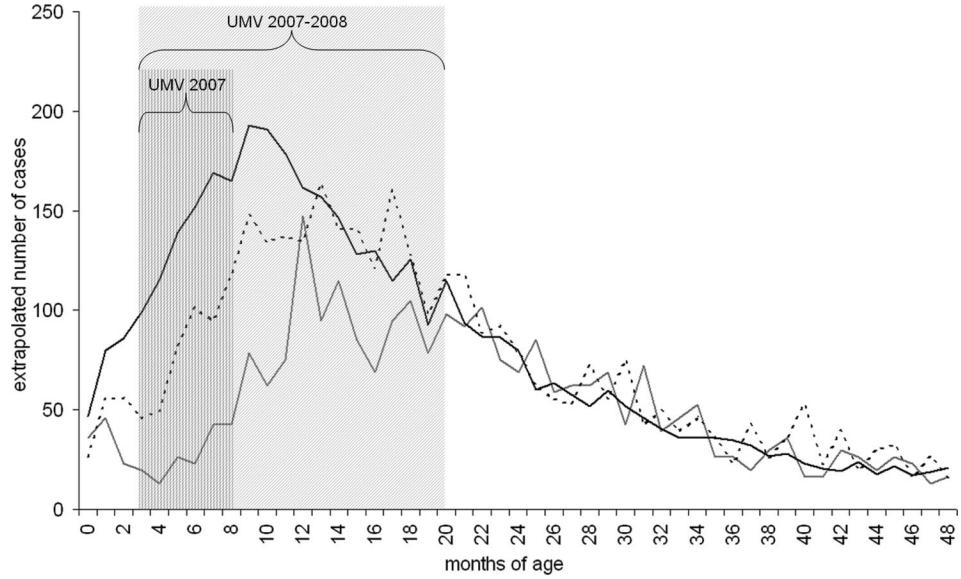

FIGURE 2. Extrapolated number of hospitalized children with RV-GE per months of age and per year. The black line shows the extrapolated number of cases in the period 2001 to 2006. The black broken line shows the extrapolated number of cases in 2007 and the grey line shows the extrapolated number of cases in 2008. The brackets in the upper area of the figure show the population that fell into the UMV program according to their age in 2007 (UMV 2007) and in 2007 and 2008 (UMV 2007–2008) and therefore could most benefit from the vaccination program.

required for the respective vaccines were administered in 108,000 eligible children. Hence, the overall vaccination rate is estimated as 72%.

During the target period August 2007 to December 2008 102 children in the age group 90 days to 20 months were reported with RV-GE. Among them the vaccination status was reported in 39 children: 33 (84.6%) were unvaccinated. Six children had received at least 1 dose of Rotateq or Rotarix. Assuming that children with unknown vaccination status were actually unvaccinated, field effectiveness was calculated as $100[1 - 6\times 28/(96 \times 72)] = 97.5\%$. Furthermore, assuming that the proportion of unvaccinated children was 84.6% (observed in those with known vaccination status), field effectiveness was calculated as: $100[1 - 15.7 \times 28/(86.3 \times 72)] = 92.8\%$. As a third scenario, it was assumed that among the 63 children with unknown vaccination status actually 72% were vaccinated (according to the overall vaccination rate 2007/

2008) the field effectiveness amounted to: $100[1 - 51.36 \times 28/(50.64 \times 72)] = 60.6\%$.

Stay in Hospital

When comparing the duration of hospitalization in the period from August 2007 to December 2008 with the period from August 2005 to December 2006, the difference was significant in children below the age of 90 days (2005/2006: mean: 6.0 days, SD $\pm$ 6.42; 2007/2008: mean: 3.5 days, SD $\pm$ 2.59; $P = 0.022$) and in children between the age of 90 days and below 20 months of life (2005/2006: mean: 4.2 days, SD $\pm$ 3.14; 2007/2008: mean: 3.5 days, SD $\pm$ 2.63; $P < 0.001$). There was no change in the duration of hospitalization for the age group 20 to below 48 months (2005/2006: mean: 3.3 days, SD $\pm$ 3.13; 2007/2008: mean: 3.1 days, SD $\pm$ 1.81; $P = 0.188$).

In Austria, between 2001 and 2006, RV-GE led to a cumulative number of days in hospital of 17,750 per year. The extrapolated cumulative number of days of hospitalization in 2007 and 2008 was 13,260 and 9710, respectively.

Infections Acquired in Hospital

The relationship between the reported start of gastroenteritis symptoms and admission to hospital could be assessed in 69.8% of all cases. On average, 4.8% (95% confidence interval: 3.7%–6.1%) of RV-GE cases between 2001 and 2006 (extrapolated 190 cases [SD $\pm$ 50.30] per year) were hospital acquired (onset of the symptoms at least 24 hours after admission to hospital). In 2008, the percentage of hospital acquired cases was 3.2% (extrapolated: 70 cases) and significantly lower than in the period 2001 to 2006.

Adverse Events Following Immunization

The incidence of severe adverse events per administered dose of vaccination as reported by the Austrian VAERS was 3.6×10^{-5} and the rate of total reported adverse events was 6.5×10^{-5}, respectively. For Rotateq the incidence of reported adverse events was 10.7×10^{-5} in relation to the administered doses and for Rotarix 3.0×10^{-5}, respectively (Table 1).

DISCUSSION

In large clinical trials, the high efficacy of the 2 launched Rotavirus vaccines has been described[14,15]: the human vaccine Rotarix had a vaccine efficacy against severe RV-GE between 71.4% and 93.4% and against RV-GE of any severity between 60.6% and 87.7%.[16] Rotateq has shown an efficacy of 98.0% against severe RV-GE and an efficacy between 48.1% and 82.7% against RV-GE of any severity.[14]

A UMV program has been introduced in several Latin American Countries,[17] in Australia[18] as well as in the United States.[3] In the United States, Rotateq had been used since February 2006,[19] and in 2008 they already observed first effects of the UMV in terms of a delayed onset of the rotavirus season of about 2 to 4 months.[20]

In Belgium and Luxembourg, the vaccination against RV-GE has been recommended.[21]

Our prospective investigation is the first report of a European Community country to define the effects of the UMV against RV-GE on the hospitalization rates. RV-GE cases occurring in the period from August 2007 to December 2008 were compared with 3 identical time periods of the prevaccination era in 3 different age groups:

1. In children younger than 90 days, who received due to their age at most one vaccination, a remarkable decrease of 42% of hospitalized cases was observed compared with the prevaccination period. This decrease may be explained by either an effect of partial protection from a first RV vaccination, or by fewer contact-infections as older siblings and playmates are vaccinated.
2. In children older than 90 days and younger than 20 months of age between August 2007 and December 2008 (eligible for vaccination in the course of the UMV) the number of cases drastically decreased by 74% compared with the prevaccination era.
3. In children between the age of 20 and 48 months a slight increase of 8% could be observed, showing no effect of the UMV in this age group and indicating there was no generally reduced rotavirus activity in the years 2007 and 2008 in Austria.
4. In our surveillance study, only hospitalized cases are monitored, therefore it must be borne in mind that incidence of RV-GE is underestimated in older children because in this group RV-GE is usually less severe and these children are hospitalized less frequently.
5. Our results are comparable to findings from the United States, where the number of performed rotavirus tests decreased about 37%, indicating overall a lower frequency of gastroenteritis cases, and the number of Rotavirus positive tests was only 79% and lower in 2008 compared with the prevaccination period.[20] However, in the United States decreasing rates of RV-GE were also observed for older children in whom the vaccination was not longer applicable.[20]
6. Comparing the number of hospital days of children with RV-GE in Austria between 2001 and 2006 with the year 2008 there was a decrease of 45%. Taking into consideration the costs that accumulate due to RV-GE related hospitalizations,[1,2] and adding the indirect costs that result from these hospital admissions, the UMV is suggested to be cost-effective.[22,23]
7. Although it has been shown that rotavirus vaccines are effective when administered concomitantly with a hexavalent vaccine,[24,25] this should not lead to a delay of the first dose of RV-vaccination: our data indicate that RV-GE occurs in a considerable proportion before the time the first hexavalent vaccine is administered, which emphasizes to start with RV-vaccination already in the seventh week of life.
8. In large clinical trials, it has been shown that both rotavirus vaccines have an excellent safety profile and the American ACIP clearly states that the 2 vaccines are comparable in this respect.[3,14,15,26] Discussions about rotavirus vaccinations being

TABLE 1. Reported Adverse Events Following Rotavirus Immunization Recorded at the Austrian Competent Authority Between September 2006 and December 2008

Total: 18 adverse events (10 severe, 8 non-severe)	12 adverse events after Rotateq (112,240 administered doses), 5 adverse events after Rotarix (164,500 administered doses), In 1 case type of vaccination not known
14 adverse: matching the product information	Diarrhea, vomiting, abdominal pain, restlessness
4 adverse events not listed in the product information	Hyperventilation in a premature infant with congestive cardiomyopathia Candidacies combined with general and drinking weakness during application of concomitant medication Apnoea and anaemia in pre-existing infection with staphylococci Sloppy infant with apathy

associated with intussusceptions as well as Kawasaki syndrome have been raised,[27,28] but detailed analyses have not verified these speculations so far.[3] In Austria, no Kawasaki syndrome or invaginations/intussusceptions has been reported to be timely associated with RV-vaccinations so far. According to the Austrian Competent Authority, the rate of severe adverse events was 4×10^{-5} indicating that both vaccines were well tolerated. Seventy-eight percent of all reported adverse events were those observed in clinical trials.[3,14,15,26]

9. In the course of the Austrian UMV, the vaccine showed field effectiveness against hospitalization between 61% and 98%, supporting the results of the clinical efficacy trials with both vaccines.[3,14,15]

CONCLUSION

The rotavirus UMV program in Austria has caused an impressive decrease in the incidence rates of hospitalizations from RV-GE in the vaccinated population, even within less than 2 years after initiation. Field effectiveness of the rotavirus vaccines against hospitalization reached between 61% and 98% and admission rates to hospital were cut by nearly 75% in children eligible for the UMV. The data show the importance of an early start of immunization in the seventh week of life, and also emphasizes that the mass vaccination program substantially reduces the burden caused by rotavirus infection.

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REFERENCES

1. Glass RI, Parashar UD, Bresee JS, et al. Rotavirus vaccines: current prospects and future challenges. *Lancet*. 2006;368:323–332.
2. Soriano-Gabarro M, Mrukowicz J, Vesikari T, et al. Burden of rotavirus disease in European Union countries. *Pediatr Infect Dis J*. 2006;25(suppl 1):S7–S11.
3. Cortese M, Parashar U. Centers for Disease Control and Prevention. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR*. 2009;58(RR-2):1–25.
4. Frühwirth M, Heininger U, Ehlken B, et al. International variation in disease burden of rotavirus gastroenteritis in children with community-and nosocomially acquired infection. *Pediatr Infect Dis J*. 2001;20:784–791.
5. Rendi-Wagner P, Kundi M, Mikolasek A, et al. Active hospital-based surveillance of rotavirus diarrhea in Austrian children, period 1997 to 2003. *Wien Klin Wochenschr*. 2006;118:280–285.
6. Frühwirth M, Berger K, Ehlken B, et al. Economic impact of community- and nosocomially acquired rotavirus gastroenteritis in Austria. *Pediatr Infect Dis J*. 2001;20:184–188.
7. Obester Sanitätsrat. Österreichischer Impfplan 2006; October 18, 2005. Available at: http://www.schule.at/dl/s0148eb4.pdf. Accessed December 16, 2008.
8. Wilhelmi I, Colomina J, Martín-Rodrigo D, et al. New immunochromatographic method for rapid detection of rotaviruses in stool samples compared with standard enzyme immunoassay and latex agglutination techniques. *Eur J Clin Microbiol Infect Dis*. 2001;20:741–743.
9. Crehalet H, Vandenesch F, Freydiere AM. Rapid detection of rotavirus in children: comparison of Vikia Rota-Adeno and Diarlex MB, two immunochromatographic tests. 16th ECCMID Nice-Avril 2006, P634. Available at: http://www.biomerieux-diagnostics.com/upload/VIKIA_Rota_Adeno_PosterAMFNice6_2006.pdf. Accessed September 14, 2009.
10. Eing BR, May G, Baumeister HG, et al. Evaluation of two enzyme immunoassays for detection of human rotaviruses in fecal specimens. *J Clin Microbiol*. 2001;39:4532–4534.
11. Kux K. *Handbuch für die Sanitätsberufe Österreichs*. 2nd Version. Vienna, Austria: Dieter Göschl Ges.mbH; 2006.
12. Statistik Austria. *Demographisches Jahrbuch 2007*. Wien, Austria: Statistik Austria, Bundesanstalt Statistik Österreich; November 2008. Available at: http://www.statistik.at/web_de/dynamic/statistiken/bevoelkerung/bevoelkerungsstruktur/bevoelkerung_nach_alter_geschlecht/publdetail?id=684&listid=684&detail=490. Accessed April 7, 2009.
13. Heinz FX, Holzmann H, Essl A, et al. Field effectiveness of vaccination against tick-borne encephalitis. *Vaccine*. 2007;25:7559–7567.
14. Vesikari T, Matson DO, Dennehy P, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med*. 2006;354:23–33.
15. Ruiz-Palacios GM, Perez-Schael I, Velazquez FR. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med*. 2006;354:11–22.
16. De Vos B, Han HH, Bouckenooghe A, et al. Live attenuated human rotavirus vaccine, RIX4414, provides clinical protection in infants against rotavirus strains with and without shared G and P genotypes. Integrated analysis of randomized controlled trials. *Pediatr Infect Dis J*. 2009;28:261–266.
17. De Oliveira L, Danovaro-Holliday M, Matus C, et al. Rotavirus vaccine introduction in the Americas: progress and lessons learned. *Expert Rev Vaccines*. 2008;7:345–353.
18. Australian Government, Department of Health and Ageing. National Immunisation Program (NIP) Schedule. April 8, 2008. Available at: http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/ Content/nips. Accessed March 28, 2009.
19. Parashar UD, Alexander JP, Glass R. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR*. 2006;55(RR12):1–13.
20. Centers for Disease Control and Prevention. Delayed onset and diminished magnitude of rotavirus activity–United States, November 2007-May 2008. *MMWR*. 2008;57:697–700.
21. EUVAC.NET. A Surveillance Community Network for Vaccine Preventable Infectious Diseases. 2008. Available at: http://www.euvac.net/graphics/euvac/vaccination/vaccination.html. Accessed December 12, 2008.
22. Gossens LM, Standaert B, Hartwig N, et al. Conclusion on the cost-effectiveness of rotavirus vaccination highly dependent on assumptions. *Vaccine*. 2009;27:2531–2532.
23. Panatto D, Amicizia D, Ansaldi F, et al. Burden of rotavirus disease and cost-effectiveness of universal vaccination in the Province of Genoa (Northern Italy). *Vaccine*. 2009;27:3450–3453.
24. Vesikari T, Karvonen A, Prymula R, et al. Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study. *Lancet*. 2007;370:1757–1763.
25. Ciarlet M, He S, Lai S, et al. Concomitant use of the 3-dose oral pentavalent rotavirus vaccine with a 3-dose primary vaccination course of a diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated polio-Haemophilus influenzae type b vaccine: immunogenicity and reactogenicity. *Pediatr Infect Dis J*. 2009;28:177–181.
26. Linhares AC, Velazquez FR, Perez-Schael I, et al. Efficacy and safety of an oral live attenuated human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in Latin American infants: a randomised, double-blind, placebo-controlled phase III study. *Lancet*. 2008;371:1181–1189.
27. Paul Ehrlich Institut. Informationen des Paul-Ehrlich-Instituts zu Meldungen von Kawasaki-Syndrom in zeitlichem Zusammenhang mit der Rotavirus-Impfung 2009. February 2, 2009. Available at: http://www.pei.de/cln_115/nn_158134/DE/infos/fachkreise/am-infos-ablage/sik/2009–02–01-kawasaki-syndrom.html. Accessed March 13, 2009.
28. Geier DA, King PG, Sykes LK, et al. RotaTeq vaccine adverse events and policy considerations. *Med Sci Monit*. 2008;14:PH9–PH16.