Paediatrica Indonesiana

VOLUME 52 January • 2012 NUMBER 1

Original Article

Surveillance of rotavirus diarrhea

Titis Widowati[1], Achirul Bakrie[2], Hera Nirwati[3] , Yati Soenarto[1]

Abstract

Background Rotavirus is a major cause of severe diarrhea and dehydration in children worldwide. Data on the burden of disease in Indonesia is limited.

Objective To provide an epidemiological profile of rotavirus infection among children hospitalized for diarrhea in Mohammad Hoesin Hospital, Palembang.

Methods In January - December 2006, a prospective, hospital-based surveillance was carried out in children aged less than five years, presenting with diarrhea. Stool samples were examined for rotavirus using enzyme immunoassay (EIA). G- and P-typing were performed on specimens confirmed to be positive by EIA.

Results A total of 513 fecal specimens from 534 children were tested for rotavirus. Rotavirus was detected in 64% of the specimens, mostly of the G9 type (62.5%). Incidence of rotavirus diarrhea was highest in the 6 month to 2 years age group (60.4%). Children with rotavirus diarrhea were more likely to present with dehydration, compared to those with non-rotavirus diarrhea (94% vs 70%, respectively, P=0.03).

Conclusion Rotavirus was the most common pathogen found in children with diarrhea. Rotavirus was detected in 64% of pediatric diarrheal specimens tested in our study. This finding warrants the use of a large-scale program to prevent disease, such as vaccination against rotavirus. **[Paediatr Indones. 2012;52:22-7]**.

Keywords: *rotavirus, diarrhea, dehydration, G9 strain*

Rotavirus is the most common cause of severe diarrhea in infants and young children in both industrialized and developing countries. The severity of rotavirus diarrhea, in particular, is associated with life-threathening dehydration. In developing countries where diarrhea is estimated to cause 2 million deaths per year, more than 600,000 children under five years of age die annually from rotavirus infection. This figure represents about 5% of all deaths in children younger than five years.[1-3]

Indonesia is one of the countries with greatest number of rotavirus related deaths which accounted for 9,970 per 100,000 children under 5 years age in 2008 (2% of the worldwide total) according to the results of systematic reviews and meta-analysis research on the estimation of worldwide rotavirus associated mortality in children younger than 5 years.[4]

While most deaths are in children from developing countries, industrialized nations also have a substantial disease burden. More than

From the Department of Child Health, Gadjah Mada University Medical School, DR Sardjito Hospital, Yogyakarta[1], and Sriwijaya University, Mohammad Hoesin Hospital, Palembang[2], and the Department of Microbiology, Gadjah Mada University Medical School, Yogyakarta[3], Indonesia.

Reprint requests to: Titis Widowati, Department of Child Health, Medical School, Gadjah Mada University, DR Sardjito Hospital, Yogyakarta, Jl Kesehatan no 1, Sekip Utara, Yogyakarta, 55821, Indonesia. Tel. +62-274-587333. Fax. +62-274-583745. E-mail: *titis_widowati@yahoo.com*

90% of children have been reported to be infected with rotavirus by the age of 3 years, regardless of nationality, level of hygiene, sanitation or access to clean water.[5,6]

Good hygiene practice and oral rehydration programs have not controlled the disease, and vaccination seems to be the only option to prevent rotavirus infection. Vaccines have been estimated to prevent 80% of severe disease. In addition to studying vaccine safety and efficacy, the decision on whether to introduce rotavirus vaccine into the state immunization program should be supported by information on disease burden, health benefits, and impact on governmental budgets.[7,8]

In Indonesia, studies on rotavirus have been conducted since 1978. Past research revealed that rotavirus was responsible for 25%-50% of pediatric hospitalizations for diarrhea in both industrialized and developing countries.[9] To date, only a few studies on rotavirus strain prevalence in Indonesia have been done. Our study, conducted in Palembang, Sumatra, Indonesia, was performed to further elucidate the prevalence of rotavirus infection and characterize infecting strains.

Methods

Children under 5 years of age who were hospitalized for acute diarrhea in January to December 2006 were enrolled into our study. Diarrhea was defined as passing watery and/or bloody stools, as well as mucous stool.

The diagnosis of diarrhea was made by the admitting physician. The study coordinator or research assistant then evaluated subjects for eligibility. Informed consent was obtained from parents of all eligible subjects. Data on demographic, clinical and laboratory characteristics were completed by a trained study assistant. All patients received the standard treatment protocol, regardless of their enrollment status.

After a subject enrolled, a ward nurse collected a stool sample within the first 48 hours of hospital admission. Specimens were stored in a dedicated refrigerator at 4^{o}C. Study assistants filled forms on stool sample collections. All stool samples and forms were then sent to Bio Farma Laboratory, Bandung, for rotavirus identification. All stool samples were tested for the presence of group A rotavirus by EIA using IDEIA^{TM} Rotavirus (Dako Cytomation, Ltd., Cambridgeshire, UK) at the Bio Farma Laboratory. G- and P-typing were performed on specimens confirmed to be positive by EIA in the Microbiology Laboratory, Gadjah Mada University Medical School, Yogyakarta. Rotavirus RNA specimens were analyzed to determine the VP4 and VP7 genotypes using the method described by Gentsch *et al.*[10]

All data were entered into a pre-designed data set by a data entry operator in the hospital and sent to Gadjah Mada University Medical School for analysis. Ethical approval was issued by the Ethics Review Committee, Gadjah Mada University Medical School, Yogyakarta. Written informed consent was obtained from all subjects' parents.

Results

In the 12 month study period, a total of 534 children under 5 years of age who were admitted and hospitalized at Mohammad Hoesin Hospital, Palembang with acute diarrhea, were enrolled. From these subjects, 513 stool specimens were tested. There were more boys (59%) than girls (41%) enrolled. Overall, rotavirus was detected in 64% of the specimens tested. The detection rate for rotavirus was higher for males than for females, 65% vs. 62%, respectively, although the difference was not statistically significant (P=0.48) (**Figure 1**).

We plotted the total number of diarrhea cases, number of specimens tested and number of rotavirus-positive cases by month (January – December 2006). Rotavirus diarrhea occurred year-round, with the highest rate occurring between June and August (**Figure 2**).

Figure 3 shows the distribution of rotavirus diarrhea by age groups. Eighty-five percent of rotavirus diarrhea cases occurred before the age of 2 years, with the highest incidence occurring in subjects aged 6 months to 2 years. We found 5% of rotavirus cases in subjects $\leq$ 3 months old, and 51% of rotavirus cases were hospitalized by the age 1 year.

The major signs and symptoms observed in children with rotavirus diarrhea were dehydration,

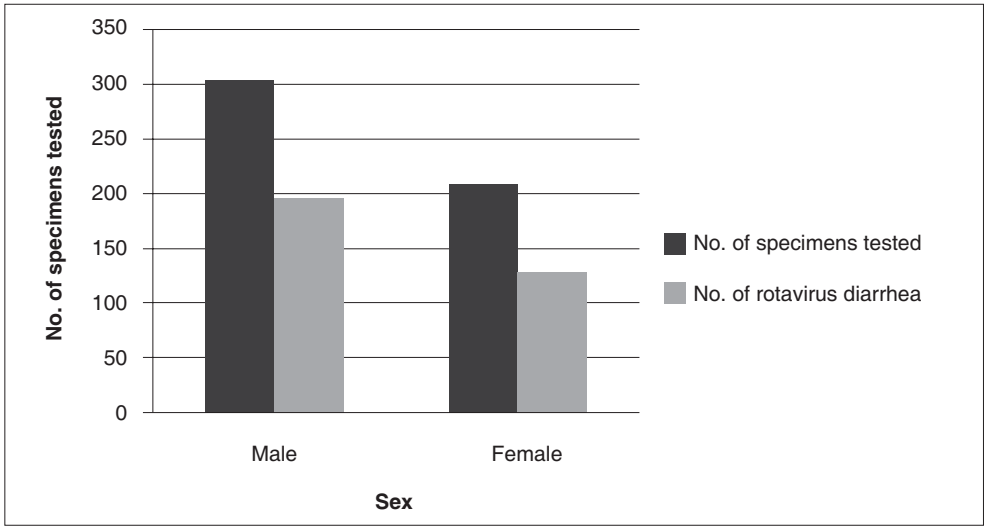

Figure 1. Rotavirus infection by gender

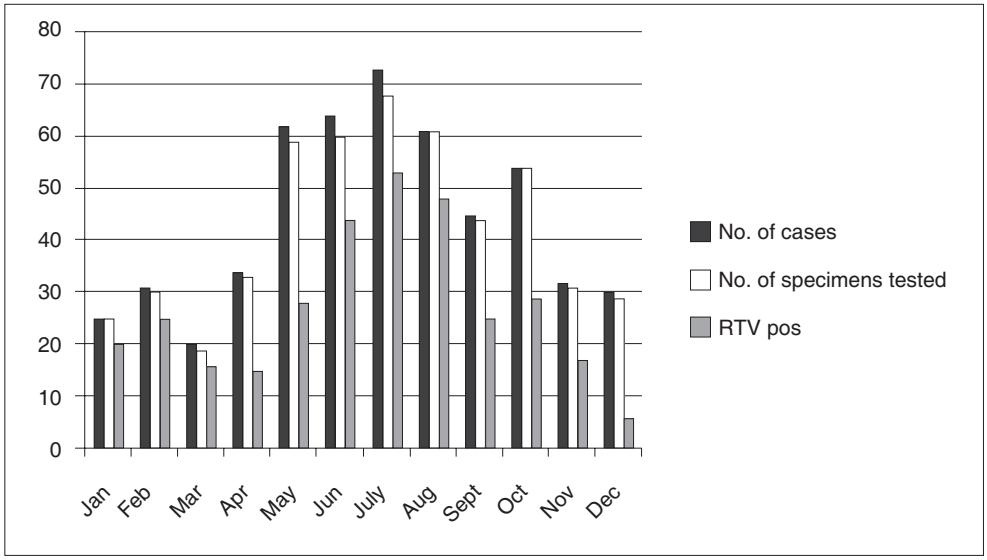

Figure 2. Number of subjects with diarrhea, number of specimens tested and number of rotavirus-positive (RTV pos) cases by month (January – December 2006)

vomiting, mucous stool and fever (**Table 1**). Dehydration occurred more frequently in children with rotavirus diarrhea compared to those with non-rotavirus diarrhea, 94% vs. 89%, respectively. However, vomiting occurred at higher frequency in the rotavirus group, 88% vs. 70%, respectively. Conversely, children with rotavirus diarrhea were less likely to have bloody stools than those with non-rotavirus diarrhea (3% vs. 9%, respectively). Dehydration was the main reason for hospitalization in children with rotavirus diarrhea. Moderate dehydration occurred more frequently than severe dehydration (77% vs. 17%) in rotavirus-positive subjects (**Figure 4**).

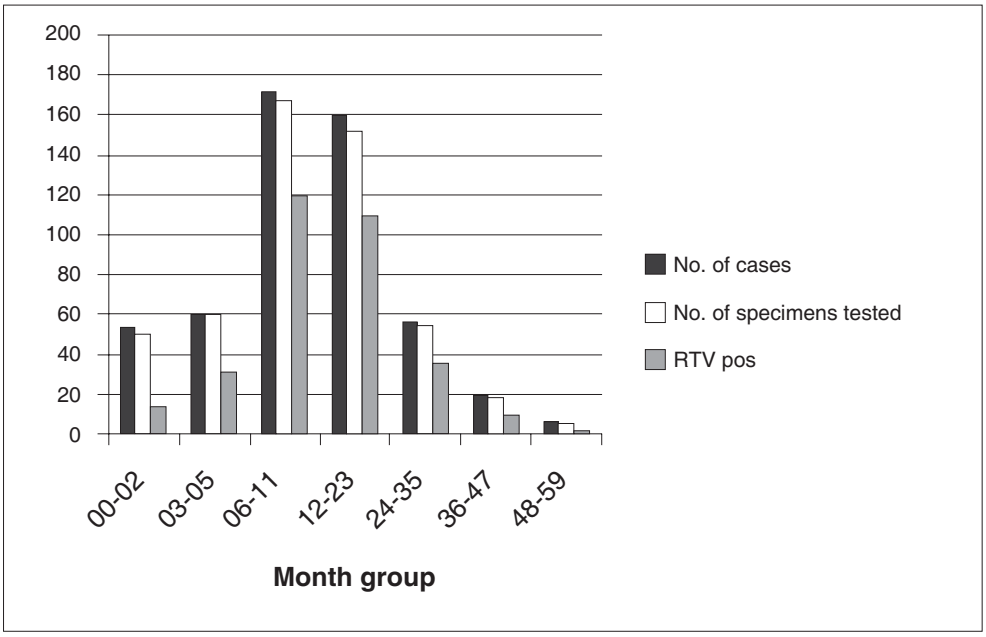

Figure 3. Age distribution of rotavirus (RTV) diarrhea

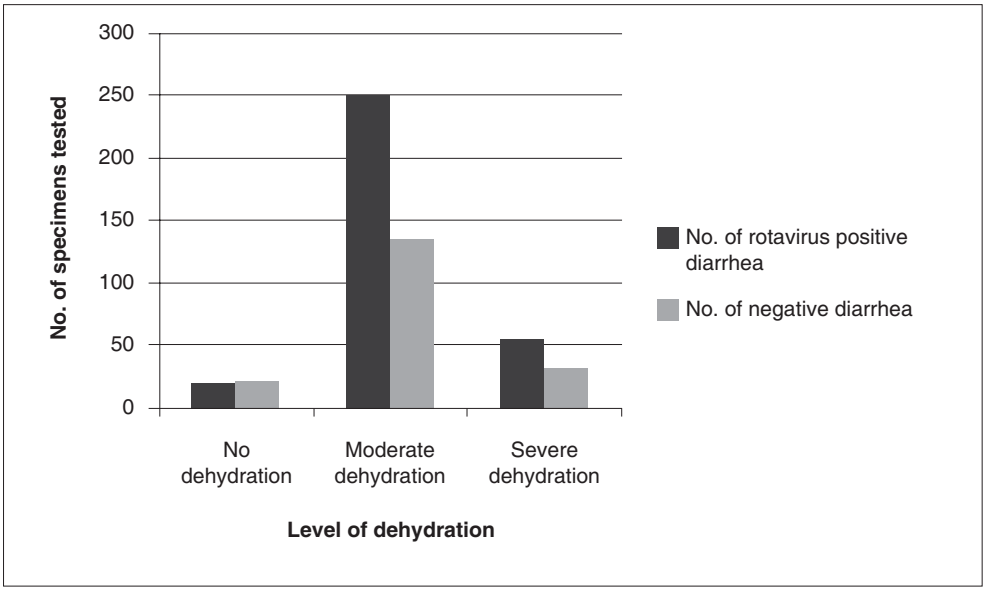

Figure 4. Dehydration levels in children with rotavirus diarrhea compared to those with non-rotavirus diarrhea

G- and P-typing was performed on 40 specimens. The most common G-serotype rotaviruses present were G9 (62.5%), followed by G1 (10%) and G2 (5%). Mixed infections were observed in 15% of cases. The majority of P-serotypes detected were P[6] (72.5%) and P[4] (5%). Mixed infections were observed in the remaining specimens (12.5%). Untypeable strains were detected in 7.5% of the G strains and 10% of the P strains.

Table 1. Clinical manifestations in children with rotavirus diarrhea hospitalized at Mohammad Hoesin Hospital, Palembang

Clinical symptoms	Rotavirus (+) cases n = 326	Rotavirus (-) cases n = 187	RR (95% CI)	P value
Dehydration, n (%)	307 (94.2)	166 (88.8)	1.06 (1.0 to 1.12)	0.03*
- Severe, n (%)	55 (16.9)	31 (16.6)	1.25 (0.96 to 1.62)	0.08
- Moderate, n (%)	252 (77.3)	135 (72.2)	1.07 (1.00 to 1.15)	0.03
- None, n (%)	19 (5.8)	21 (11.2)	Reference	
Vomiting, n (%)	287 (88.0)	130 (69.5)	1.27 (1.14 to 1.40)	<0.001
Mucous stool, n (%)	146 (44.8)	97 (51.9)	0.86 (0.72 to 1.04)	0.12
Bloody stool, n (%)	10 (3.1)	16 (8.6)	0.36 (0.17 to 0.77)	0.006
Fever (%)	147 (45.1)	73 (39.0)	1.16 (0.93 to 1.43)	0.18

* compared to no dehydration as the reference

Discussion

We observed a large percentage (64%) of diarrheal cases in children aged under 5 years to be infected with rotavirus. The peak incidence of rotavirus diarrhea occurred in subjects under 2 years of age (85%), with the highest incidence in children aged between 6 months to 2 years. This finding is consistent with a number of epidemiological studies from other countries.[6,8,9,11]

This study revealed that in the Mohammad Hoesin Hospital, Palembang, rotavirus diarrhea occurred year-round, similar to that found in other developing tropical countries.[12,13] The peak incidence of rotavirus diarrhea occurred from July to August, when the rainfall was low. However, it is difficult to demonstrate a seasonal pattern of rotavirus diarrhea in Palembang because the study period was less than 2 years in duration.

Children with rotavirus infection were more likely to have dehydration and vomiting compared to those with non-rotavirus diarrhea. We observed the major clinical sign of rotavirus diarrhea in Palembang to be dehydration (94% of rotavirus cases), thus, children with rotavirus diarhea often required hospitalization.

Due to the prominence of frequent vomiting, oral rehydration solution was not effective for replenishing lost body fluid, therefore, intravenous fluid therapy was usually given. The use of intravenous therapy implies that rotavirus diarrhea causes not only significant clinical impact, but also economic impact, since intravenous rehydration is more expensive than oral rehydration. A study in Yogyakarta and Central Java showed that rotavirus diarrhea was more likely to increase cost by 25%.[14]

There have been few studies investigating the strains of rotavirus in Indonesia. The first study conducted in Yogyakarta in the 1970s showed the prevailing strains to be G1, G2, G3, and G4, with G3 (53%) the most common. G1 was only found in 2% of rotavirus cases at the time.[15] A study conducted in Central Java and Yogyakarta in 2004 reported that G1 was the most common strain, accounting for 60% of identified cases. G3 was not identified.[16]

We found G9 to be the predominant strain in Palembang, constituting 62.5% of the rotavirus identified. Serotype G9 was documented as an emerging strain worldwide and was also recently identified in Indonesia by Putnam *et al*.[17] Findings in five other hospitals also showed diversity in rotavirus strains. G1 and G9 were also the predominant strains in other hospitals, but G3 and G4 were only observed in Yogyakarta. Interestingly, P[6] which was uncommon globally, was found to be predominant in our study. Similarly, a study in Bangladesh reported that P[6] was the major strain found in neonates.[18] Overall, our finding supports the idea that strains of rotavirus differ by location and time. Continuous monitoring of rotavirus strains is, therefore, highly important to determine the circulating strains and provide steps for vaccine implementation.

We found the burden of rotavirus in Palembang to be high. Rotavirus is, indeed, a common pathogen and an important cause of hospitalization in children with diarrhea[1, 9].[1,4] As such, a bold attempt must be made to reduce the disease burden.

Rotavirus vaccine is currently recommended by WHO as the best method to prevent rotavirus infection.[19] The decision to implement a rotavirus vaccine program in Indonesia has been hindered by the lack of awareness of the true disease burden of

rotavirus and the importance of rotavirus vaccines.[20] An assessment of rotavirus vaccine rationale and potential barriers should be undertaken prior to vaccine program implementation.[21] Our results provide support for one of the key steps for policy-makers in assessing the importance of rotavirus vaccine implementation.

Acknowledgments

We thank I.P. Sukanto (PT Bio Farma) for laboratory work, Abdul Wahab and Althaf Setyawan (Community Health and Nutrition Research Laboratory, Gadjah Mada University Medical School) for data analysis, as well as the doctors, nurses and administrative staff at the Pelembang sites, for help with this study. We are grateful to all research assistants in the Child Health Department, Gadjah Mada University Medical School: A.W. Erlin Mulyadi, Era Agustin, Muhammad Bayu Sasongko, Dara Rosmaillina Pabittei, Retno Palupi and Maya Indriati for their valuable contributions to this work.

References

1. Parashar UD, Gibson CJ, Bresee JS, Glass RI. Rotavirus and severe childhood diarrhea. Emerg Infect Dis. 2006; 12:304–6.
2. Parashar UD, Hummelman EG, Bresee JS, Miller MA, Glass RI. Global ilness and death caused by rotavirus disease in children. Emerg Infect Dis.2003;9:565-72.
3. Kim JS, Kang JO, Cho SC, Jang YT, Min SA, Park TH, et al. Epidemiological profile of rotavirus infection in the Republic of Korea: result from prospective surveillance in the Jeongeub district, 1 July 2002 through 30 June 2004. J Infect Dis. 2005;192:S49-56.
4. Tate JE, Boshi-Pinto C, Steela AD, Duque J, Parashar UD. The WHO-coordinated Global Rotavirus Surveillance Network 2008. Estimation of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programme: a systematic review and meta-analysis. Lancet Infect Dis. 2011;S1473-3099:70253-5.
5. Soriano-Gabarro M, Mrukowicz J, Vesikari T, Verstraeten T. Burden of rotavirus disease in European union countries. Pediatr Infect Dis J. 2006;25:7-11.
6. Glass RI, Kilgore PE, Holman RC, Jin S, Smith JC, Woods PA, et al. The epidemiology of rotavirus diarrhoea in the United States: surveillance and estimates of disease burden. J Infect Dis. 1996;174:S5-11.
7. Grimwood K, Huang QS, Cohet C, Gosling IA, Hook SM, Teele DW, et al. Rotavirus hospitalisation in New Zealand children under 3 years of age. J Paediatr Child Health. 2006;42:196-203.
8. Chen KT, Chen PY, Tang RB, Huang YB, Lee PI, Yang JY, et al. Sentinel hospital surveillance for rotavirus diarrhea in Taiwan, 2001-2003. J Infect Dis. 2005;192:S44-8.
9. Bresee JS, Fang ZY, Wang B, Nelson EA, Tam J, Soenarto Y, et al. First report from the Asian rotavirus surveillance network. Emerg Infect Dis. 2004;10:988-95.
10. Gentsch JR, Glass RI, Woods P, Gouvea, V, Gorziglia M, Flores J, et al. Identification of group A rotavirus gene 4 types by polymerase chain reaction. J Clin Microbiol. 1992;30:1365-73.
11. Fang ZY, Yang H, Zhang J, Li YF, Hou AC, Ma L, et al. Child rotavirus infection in association with acute gastroenteritis in two Chinese sentinel hospitals. Pediatr Int. 2000;42:401-5.
12. Moe K, Hummelman EG, Oo WM, Lwin T, Htwe TT. Hospital-based surveillance for rotavirus diarrhea in children in Yangon, Myanmar. J Infect Dis. 2005;192:S111-3.
13. Hsu VP, Abdul Rahman H, Wong SL, Ibrahim LHJ, Yusoff AFHJ, Chan LG, et al. Estimates of the burden of rotavirus disease in Malaysia. J Infect Dis. 2005;192:S80-6.
14. Wilopo SA, Kilgore P, Kosen S, Soenarto Y, Aminah S, Cahyono A, et al. Economic evaluation of a routine rotavirus vaccination programme in Indonesia. Vaccine. 2009;27: F67-74.
15. Bishop RF, Unicomb LF, Soenarto Y, Suwardji H, Ristanto, Barnes GL. Rotavirus serotypes causing acute diarrhea in hospitalized children in Yogyakarta, Indonesia during 1978 – 1979. Arch Virol. 1989;107:207–13.
16. Wilopo S A, Soenarto Y, Bresee JS, Tholib A, Aminah S, Cahyono A, et al. Rotavirus surveillance to determine disease burden and epidemiology in Java, Indonesia, August 2001 through April 2004. Vaccine. 2009;27:F61-6.
17. Putnam SD, Sedyaningsih ER, Listiyaningsih E, Pulungsih SP, Komalarini, Soenarto Y, et al. Group A rotavirus-associated diarrhea in children seeking treatment in Indonesia. J Clin Virology. 2007;40:289-94.
18. Kilgore PE, Unicomb LE, Gentsch JR, Albert MJ, McElroy CA, Glass RI. Neonatal rotavirus infection in Bangladesh: strain characterization and risk factors for nosocomial infection. Pediatr Infect Dis J. 1996;15:672-7.
19. WHO. Rotavirus vaccine. Wkly Epidemiol Rec. 2007; 82:285–95.
20. Simpson E, Wittet S, Bonilla J, Gamazina K, Cooley L, Winkler JL. Use of formative research in developing a knowledge translation approach to rotavirus vaccine introduction in developing countries. BMC Public Health. 2007;7:281.
21. Van Damme P, Van der Wielen M, Ansaldi F, Desgrandchamps D, Domingo JD, Sanchez FG, et al. Rotavirus vaccines: considerations for successful implementation in Europe. Lancet. 2006;6:805–12.