Considerations for Introduction of a Rotavirus Vaccine in Oman: Rotavirus Disease and Economic Burden

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Rotavirus is the most common cause of fatal childhood diarrhea worldwide. We provide the first estimates of the health care and economic burden of severe rotavirus disease in Oman. We conducted active, hospital-based surveillance of rotavirus disease at 11 regional public hospitals in Oman, using the guidelines suggested by the generic World Health Organization protocol. From July 2006 through June 2008, all children aged <5 years who were hospitalized for acute gastroenteritis were enrolled in the surveillance program, and their stool samples were tested for rotavirus using a commercially available enzyme immunoassay (ID EIA Rotavirus Test; Dako Diagnostics). Rotavirus was detected in samples from 1712 (49%) of 3470 children. These children were hospitalized for a median of 3 days for severe diarrhea. A marked seasonal peak was evident with a majority of the cases occurring from December through May. Of the rotavirus cases, 69% occurred in children aged 6–17 months. We identified a diverse strain pattern in Oman, with G2 (37%), G1 (38%), and G9 (11%) accounting for most of typeable strains. By our burden estimates, the Omani government spends an estimated US$791,817 and US$1.8 million annually to treat rotavirus-associated diarrhea in the outpatient and hospital settings, respectively. A rotavirus vaccination program might substantially reduce the burden of severe diarrhea among children in Oman.

Rotavirus is the most common cause of severe dehydrating gastroenteritis and dehydration in children aged <5 years, accounting for 527,000 global deaths and >2 million hospitalizations annually [1, 2]. Two new vaccines with good safety profiles and vaccine efficacy of 85%–95% against severe disease have recently been licensed for use in >100 countries and are currently included in routine childhood immunization schedules in many countries in North America, South America, Europe, and Australia [3–5]. In many countries, however, limited data exist on the disease burden and epidemiology of rotavirus, which could be a potential barrier to vaccine introduction in these countries [5, 6].

The only published study from Oman identified rotavirus among 31% of young children admitted to the hospital with severe diarrhea from November 1990 through October 1992 [7]. To better assess the need for a vaccine and to present to decision makers data that are crucial for vaccine introduction in Oman, the Ministry of Health established nationwide surveillance of severe childhood diarrhea at sentinel hospitals in 2006. The goal of the surveillance was to describe the epi-

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demiology of rotavirus disease, to define the national disease burden and economic burden, and to characterize the strains of rotavirus circulating in Oman.

METHODS

Setting. The Sultanate of Oman is on the southeast coast of the Arabian Peninsula, with a population of 2.6 million and an annual birth cohort of 51,000. The health care infrastructure of Oman is well developed, with 57 hospitals providing primary and secondary elements of health care and with a network of 173 health centers, extended health centers, and outpatient clinics that provide government-subsidized health care to the citizens and residents of Oman. The communication and road networks are well developed, ensuring rapid access to health care for >95% of the population.

Surveillance. The Oman Ministry of Health established surveillance of diarrhea among children aged <5 years by using the procedures outlined in the World Health Organization (WHO) generic protocol for rotavirus surveillance [8]. On the basis of their high annual census numbers and regional representation, 11 regional referral hospitals in the country were selected as sentinel sites: Sultan Qaboos University Hospital (5.0% of all samples) and Royal Hospital (6.8%), Muscat; Sultan Qaboos Hospital (8.5%), Dhofar; Sohar Hospital (33.4%), North Batinah; Rustaq Hospital (16.8%), South Batinah; Nizwa Hospital (9.3%), Dakhliyah; Ibra Hospital (9.8%), North Sharqiyah; Sur Hospital (3.9%), South Sharquiyah; Khasab Hospital (1.8%), Musandam; and Buraimi Hospital (1.8%) and Ibri Hospital (3.1%), Dhahira, Oman.

From July 2006 through June 2008, all children aged <5 years who were hospitalized for acute gastroenteritis (defined by >3 liquid or semiliquid stools in 24 h) were enrolled in the surveillance program. A standard data entry form was completed at enrollment. Only children who provided a stool sample were included in the surveillance. Regional epidemiologists were assigned as focal points for the surveillance program and were responsible for training hospital staff, collating surveillance data, providing feedback to hospital staff, and monitoring surveillance indicators. Pediatricians at each hospital were routinely encouraged to enroll all children who met the surveillance case definition. Staff in the pediatrics department ensured enrollment of all potential participants by review of daily admission logs and by frequent discussions with pediatricians.

Stool specimens (>5 mL) were collected in screw-top containers as soon as feasible (within 48 h after admission), to avoid enrollment of children with nosocomial infection. All stool specimens were stored initially at 2°C–8°C and then at −20°C. Samples were subsequently transported to the Central Public Health Laboratory, where testing for rotaviruses was conducted in batches with use of a commercially available enzyme immunoassay (ID EIA Rotavirus Test; Dako Diagnostics). Results were reported to the hospital staff within 5 working days after sample shipment to the central laboratory. To examine the distribution of circulating rotavirus strains in Oman, 234 (20%) of the 1181 rotavirus-positive specimens were randomly selected, and their G and P genotypes were assessed by reverse-transcriptase polymerase chain reaction (RT-PCR) using methods described elsewhere [9]. For quality control purposes, a random selection of stool samples was sent to a WHO reference laboratory in Cairo, Egypt, and concordance was observed between the reference laboratory and the central laboratory in Oman.

Estimates of national rotavirus disease burden. In Oman, 95% of the population uses health care facilities operated by the government. To estimate the national burden of diarrheal disease leading to outpatient visits and hospitalizations in children aged <5 years, we reviewed the computerized records tallied by the Ministry of Health on total countrywide reports of each of these outcomes of diarrhea during the 2-year surveillance period (2006–2007). To estimate the annual rotavirus disease burden among children hospitalized with diarrhea, we multiplied the annual number of visits for acute gastroenteritis among children aged <5 years with the fraction of rotavirus among children hospitalized with diarrhea at the 11 surveillance sites. No data exist on the proportion of diarrhea-related outpatient visits that are attributable to rotavirus. Therefore, we estimated the outpatient rotavirus burden in Oman by applying rotavirus detection rates among outpatients (19%) from other published studies in countries with similar income status [2, 10]. Subsequently, we calculated the cumulative risk that a child would experience these events (outpatient visit or hospitalization) by age 5 years. Cumulative risks were expressed as the inverse of the annual birth cohort (~51,000) divided by the respective mean number of events among children aged <5 years from 2006 through 2007.

Estimates of economic burden of rotavirus disease. We examined the economic burden from the health care perspective of rotavirus-associated outpatient visits and hospitalizations in Oman, excluding any indirect costs and other societal costs. For hospitalized patients, the direct medical cost was estimated on the basis of the per diem cost of hospitalization for diarrhea; the costs of diagnostic tests, medications, and special services; and the mean length of stay (direct medical cost = length of stay × per diem cost + cost of services). Outpatient medical costs were derived using a similar equation (per-visit cost + cost of services).

The per diem and per-visit costs were estimated from country-specific figures developed by the WHO Choosing Interventions that are Cost Effective (WHO-CHOICE) project [11], after conversion to 2008 US dollars with use of the consumer price index. WHO-CHOICE estimates provide country-specific data on the basis of a "compromise between the derivation of

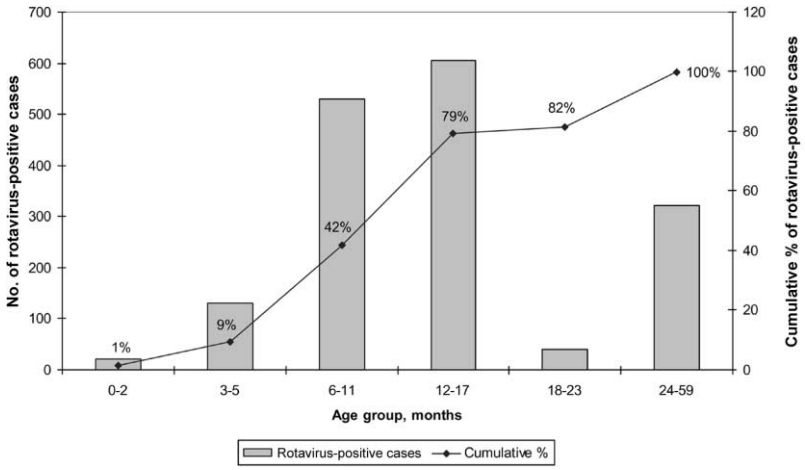

Figure 1. Age distribution and cumulative percentage of children with rotavirus-positive gastroenteritis in Oman. Age data were available for only 1627 of 1712 patients with rotavirus-positive gastroenteritis.

a single global estimate of the cost-effectiveness of an intervention (which, by definition, is unlikely to appropriately reflect costs and effects in a large number of countries), versus the generation of estimates for each and every member state" [12]. Because these estimates do not include the cost of medications or diagnostic tests, we estimated that medications and diagnostic tests add 33% to the per diem cost of hospitalization and add 65% to the cost of outpatient visits for diarrhea, on the basis of previously published studies on the cost of diarrhea treatment [13, 14]. The length of hospitalization for rotavirus gastroenteritis was calculated on the basis of data from the current study.

Analysis. All data were collected and stored in an Access (Microsoft) database and were analyzed using Excel (Microsoft) and SAS, version 9.1 (SAS). To assess seasonal trends, we plotted the number of monthly visits for all-cause and rotavirus-associated diarrhea among children aged <5 years during the 2-year surveillance period.

RESULTS

From July 2006 through June 2008, we enrolled a total of 3470 children in the rotavirus surveillance system at the 11 hospitals in Oman. Of these 3470 children, 1712 (49%) tested positive for rotavirus. Of the hospitalized children with rotavirus infection, most were aged 6–17 months, followed by those aged 18–59 months (21%) and 0–6 months (11%) (Figure 1). A marked seasonal peak was evident, with a majority of the cases occurring from November through May in year 1 and from January through May in year 2 (Figure 2). Of all hospitalized children with rotavirus infection, 79% were aged <18 months, and 54% were male. All children had diarrhea, 68% had rectal

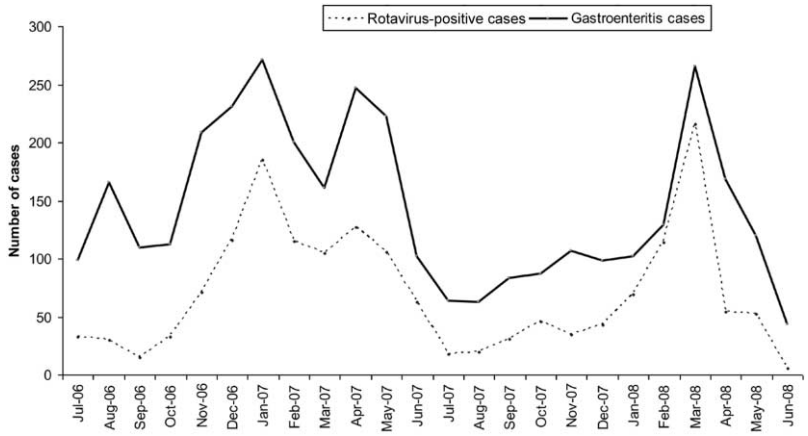

Figure 2. Seasonality of rotavirus disease among children. Shown are the numbers of monthly diarrhea admissions and rotavirus-positive case patients among children aged <5 years in Oman, by month, 2006–2007.

Table 1. Demographic and Clinical Characteristics of Children Aged <5 Years with Rotavirus and Nonrotavirus Diarrhea in Oman, July 2006–December 2007

Characteristic	Children with rotavirus diarrhea (n = 744)	Children with nonrotavirus diarrhea (n = 893)
Age, months		
Median	12.0	12.0
Mean	14.5	16.8
Male sex	405 (54)	511 (57)
Temperature >38.4°C at hospital admission	506 (68)	607 (68)
Receipt of intravenous fluids	737 (99)	884 (99)

NOTE. Data are no. (%) of children, unless otherwise specified. These data were collected during the first 18 months of the study (July 2006–December 2007) but not during the last 6 months of the study (January 2008–June 2008).

temperature >38.4°C at arrival to the hospital, and 99% received hydration therapy with intravenous fluids (Table 1). Children with rotavirus-positive stool samples were similar in age (median, 12 months), compared with those who had samples test negative for rotavirus. All children fully recovered (mean length of hospital stay, 3 days) and were discharged to home after treatment in the hospital.

Diarrhea and rotavirus disease burden. In the Oman Ministry of Health's national computerized records of health care facilities for 2006 and 2007, there were an annual mean of 60,806 outpatient visits and 6800 hospitalizations for diarrhea among children aged <5 years (Table 2). Applying detection rates of 49% from our hospital-based surveillance to the national data and typical outpatient rotavirus detection rates from other middle- and high-income countries (19%), we estimate that rotavirus-associated diarrheal disease in children aged <5 years results annually in 11,553 outpatient visits and 3332 hospitalizations (Table 2). Thus, by age 5 years, nearly all children in Oman will seek outpatient care for diarrhea, and 1 in 7 will develop severe diarrhea requiring hospitalization and intravenous hydration. For rotavirus diarrhea, cumulative risks were ~1 in 4 for outpatient care and 1 in 16 for hospitalization by age 5 years (Table 2).

Economic burden of rotavirus disease in Oman. To assess the health care costs associated with our estimates of rotavirus disease burden, we multiplied the WHO-CHOICE estimates of the costs of hospitalizations and outpatient visits for diarrhea in Oman by our estimated number of outpatient visits and hospitalizations, respectively, taking into account the mean length of stay (3 days) for a rotavirus-related hospitalization from our surveillance data. Using these estimates, we determined that the Oman Ministry of Health spends an estimated $2.6 million annually for treatment of rotavirus-associated diarrhea: ~$791,817 for outpatient treatment and $1.8 million for treatment in the hospital setting.

Rotavirus strain characterization. To assess the prevalence of circulating rotavirus strains in Oman, we randomly selected 234 (20%) of the 1181 rotavirus-positive stool samples collected from June 2006 through December 2007. During this period, the distribution of circulating strains was diverse, with genotypes G2 (87 strains [37%]), G1 (38 [16%]), and G9 (25 [11%]) accounting for most of the typeable strains (Figure 3). Of the strains with P type identified, 96 (41%) were characterized as P[4], 13 (6%) as P[10], and 9 (4%) as P[8]; 103 (44%) of the strains were nontypeable for P type with the current VP4 genotyping primers. Preliminary DNA sequencing results of the con3/con2 PCR amplicon, however, suggest that the majority of the P-nontypeable strains are common types, particularly P[8], in which the sequence in the binding site of primer 1T-1 has significantly drifted (authors' unpublished results). The

Table 2. Estimated Burden of Rotavirus-Associated and All-Cause Diarrhea and Medical Costs of the Management of Diarrhea

	All-cause diarrhea		Rotavirus diarrhea			Estimated health care system costs, US dollars	
Event	Total annual no. of visits	Cumulative risk per child by age 5 years	Percentage of all diarrhea episodes	Total annual no. of visits	Cumulative risk per child by age 5 years	Per event	Annual total
Outpatient visit	60,806	1.2 in 1	19	11,553	1 in 4	68.5	791,817
Hospitalization	6800	1 in 7	49	3332	1 in 16	538.8	1,795,397
Total	…	…	…	…	…	…	2,587,214

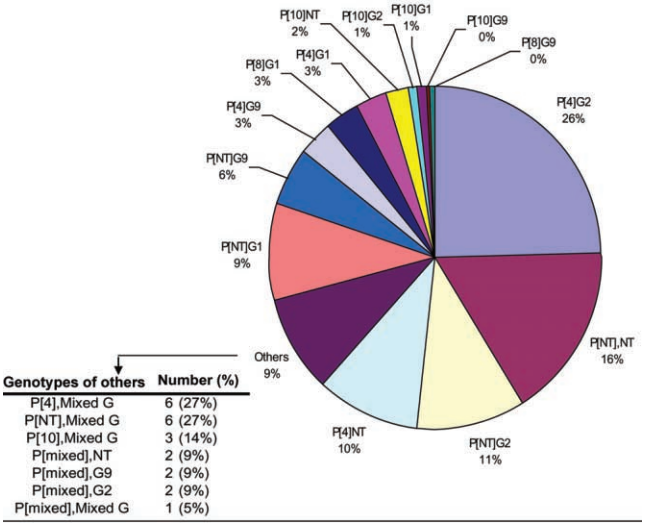

Figure 3. G and P genotypic distribution of rotavirus strains obtained from sentinel hospital surveillance of children aged <5 years with gastroenteritis, Oman, 2006–2007. NT, nontypeable.

most common combinations of G and P genotypes were G2P[4] (25% of strains), G9P[3] (4%), G1P[8] (3%), and G1P[4] (3%). Overall, only 38 (16%) of 234 strains were nontypeable for both G and P genotypes by RT-PCR.

DISCUSSION

In this comprehensive assessment of the burden of rotavirus disease in Oman, which to our knowledge is the first, we demonstrate that rotavirus is the single most common cause of diarrhea in young children, accounting for one-half of all hospitalizations for acute gastroenteritis. From our active surveillance data and national data on hospitalizations and outpatient visits for diarrhea, we estimate that ~3300 rotavirus-associated hospitalizations occur annually in Oman and that an additional 11,500 children present to the clinic for outpatient treatment of rotavirus diarrhea. The annual cost of medical care for rotavirus-associated hospitalizations and outpatient visits exceeds ~US$2.6 million, and this economic burden is particularly impressive given that it does not account for the indirect (ie, societal) costs of rotavirus illness. Further examination of total costs (including indirect and societal costs) would allow decision makers in Oman to formally assess the cost-effectiveness of a vaccination program. However, the large health care burden of rotavirus-associated hospitalizations and outpatient visits among children in Oman and their associated health care costs alone suggests that vaccination could offer substantial health and economic benefits.

In 1985, the Oman Ministry of Health launched a program (the Control of Diarrhoeal Disease program) to implement control measures for reducing the morbidity and mortality from diarrhea. The Control of Diarrhoeal Disease program consists of 3 strategies: (1) standardization of clinical management of cases, (2) universal availability and accessibility of oral rehydration solution, and (3) health education and promotion activities. A substantial reduction in diarrhea-associated mortality was noted subsequent to the implementation of the Control of Diarrhoeal Disease program, with virtual elimination of the 6–12 annual deaths among children aged <5 years by 1996 (Ministry of Health, unpublished data). The incidence of diarrheal episodes was also reduced by 60%, from 745 episodes per 1000 children aged <5 years in 1991 to 298 episodes per 1000 children aged <5 years in 2003. Although substantial strides against diarrheal disease overall were made in Oman, severe childhood gastroenteritis continues to be a public health concern for the Ministry of Health, responsible for ~10% of all hospitalizations in this age group. We have shown that rotavirus accounts for nearly one-half of all hospitalizations for gastroenteritis, so the introduction of an effective rotavirus vaccine could substantially extend the progress in the control of childhood gastroenteritis in Oman. Of note, we demonstrated that ~90% of severe rotavirus disease occurs in children aged >6 months, which indicates that an effective vaccine administered before age 6 months could prevent a majority of the severe rotavirus disease in Oman.

We were intrigued with the finding of diverse circulating rotavirus strains in Oman. Globally, particularly in most industrialized countries similar to Oman, 4 common rotavirus serotypes (G1–G4) represent >90% of the circulating rotavirus strains. However, in Oman, genotype G9 (in combination with P[10], P[8], P[4], and P nontypeable) was detected in 11% of the samples. Although uncommon in most countries, G9 is considered to be an emerging strain and could be of relevance to a future vaccine program, because this serotype antigen is not included in either of the currently licensed vaccines, although cross-protection has been noted in clinical trials [15, 16]. Our strain typing data, however, should be interpreted with caution, given that only 20% of the rotavirus-positive samples from 2006 through 2007 were typed. The percentage of rotavirus-positive samples sent for typing from each hospital varied from 8% to 32%, which further limits the representativeness of the strain diversity in Oman. Monitoring of strains will be important before and after vaccine introduction, to assess for emergence of new strains and to monitor for strains that may escape protection from the vaccine.

Our surveillance was limited, in that we did not collect detailed clinical information on all participants and, instead, resources were directed toward enrollment of all eligible participants in most national pediatric hospitals in Oman, thus providing decision makers who are considering vaccine introduction with the most specific and nationally representative data on rotavirus burden. It is possible that we overestimated the burden of severe disease by enrolling patients who were

admitted for milder disease or for reasons other than dehydration. However, ~99% of the children received intravenous fluids, indicating that most children were indeed admitted for dehydration. Lastly, our cost estimates should be considered to be preliminary, because they rely on extrapolation of health care system costs from other similar socioeconomic settings. However, these data do not consider societal or indirect costs of rotavirus diarrhea and likely underestimate the true economic burden that rotavirus diarrhea places on the affected families and the government of Oman.

In conclusion, our findings confirm the substantial health burden of severe rotavirus disease among children in Oman, and our data should help pediatricians and decision makers to assess the potential benefits of implementation of rotavirus vaccine in Oman. An optimally effective rotavirus vaccine will avert a substantial proportion of childhood diarrhea cases and the associated health care costs in Oman.

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