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Is rotavirus still a major cause for diarrheal illness in hospitalized pediatric patients after rotavirus vaccine introduction in the Saudi national immunization program?

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Abstract

Previous studies in Jeddah, western Saudi Arabia, showed rotavirus (RV) prevalence around 40% in pediatric inpatients with gastroenteritis (GE) with a maximum level during cooler months. Currently, there are no data on impact of rotavirus vaccine (RVV) on RV-GE in Saudi Arabia. Therefore, this study was conducted to assess impact of RVV on incidence and severity of RV-GE in hospitalized pediatric patients; 3 years after introduction of RVV in Saudi immunization program (SIP) in January, 2013.

This cross-sectional observational study included GE cases under 5 years of age admitted to 2 tertiary hospitals, in Jeddah, from October to December, 2015. All included GE-cases had RV antigen detection in stool by immunochromatographic assay, complete data collection including RVV status and severity assessment (Vesikari score) in initial admission.

During study period, a total of 359 GE cases in children under 5 years of age were hospitalized with 14 (3.9%) RV-GE confirmed cases. Mean age of RV-GE patients was 13.10 ± 5.70 months. All RV cases had severe GE and 1 case received RVV. Among other 345 GE cases, 35.7% did not receive RVV and 46.1% had severe GE. Severe GE (Vesikari score > 11) was more significantly identified among RV-GE cases than in other all-cause GE ($P < .001$). During same period of this study in 2012, 369 RV-GE out of 1193 total GE cases (31%) were hospitalized at 2 hospitals, so, number of hospitalized pediatric patients for all-cause and RV-GE in children under 5 years of age decreased significantly in 2015 RV season (compared to 2015 RV season, odds ratio for RV-GE in 2012: 11.04, 95% CI: 6.38–19.09).

Logistic regression analysis of variables of this cross-sectional, hospital-based study in Jeddah, Saudi Arabia, 3 years after introduction of RVV in SIP, showed that among the studied variables, RVV was associated with remarkable reduction of hazard of all-cause and RV-GE in vaccinated and even in unvaccinated children under 5 years of age possibly by RVV herd effect. However, RV was still associated with severe GE-related hospitalizations in unvaccinated children against RV who were younger than 2 years and particularly in the 1st year of life, indicating need for more optimum rate of RVV coverage. Hopefully, further improvement in RVV coverage rate may make RV-GE a disease of the past in Saudi children.

Abbreviations: AHR = adjusted hazard ratio, CI = confidence interval, GE = gastroenteritis, HJH = Hai Al-Jameah Hospital, IGA = immunochromatographic assay, MCH = Maternity and Children Hospital, OR = odds ratio, RV = rotavirus, RVV = rotavirus vaccine, SD = standard deviation, SIP = Saudi immunization program.

Keywords: hospitalized pediatric patients, rotavirus diarrheal illness, rotavirus vaccine, Saudi immunization program

1. Introduction

Globally, rotavirus (RV) is still the leading cause of vaccine-preventable diarrhea among children under 5 years of age.[1] Acute diarrheal disease caused by RV is still a major cause of morbidity and mortality in children under 5 years of age in developing countries.[2] Worldwide, RV is estimated to cause more than 111 million cases of diarrhea annually in children younger than 5 years of age. Of these, 18 million cases are considered at least moderately severe, with approximately 500,000 deaths per year. Even in developed countries as United States, RV causes 3 million cases of diarrhea, 80,000 hospitalizations, and 20 to 40 deaths annually.[3] In China, RV is the most common diarrhea-causing pathogen detected in 29.7% of cases of diarrhea among children under 5 years of age.[4]

The main symptoms of RV-gastroenteritis (GE) are mild to moderate fever, vomiting and frequent watery stools that may lead to dehydration, and hypovolemic shock. Severe cases may lead to death.[5] RV infection tends to be most severe in patients 3 to 24 months of age, with serologic evidence of infection developing in virtually all children by 4 to 5 years of age.[4]

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Often, children suffering RV-GE require outpatient medical care, but in the presence of severe GE with dehydration, hospitalization, and intravenous rehydration are necessary. By the age of 5 years, nearly every child will have an episode of RV-GE, 1 in 5 will visit a clinic, and 1 in 65 will be hospitalized. Thus, RV-GE imposes a heavy burden, not only by incurring direct medical costs, but also indirect costs due to productivity loss and other expenses.[6,7]

RV is an important cause of severe diarrhea in Saudi children with a variable prevalence of RV infection that ranged between 10% and 65.5%.[8–12] In our locality, Jeddah, previous studies showed RV prevalence ranging from 42% to 46% in hospitalized children with GE with a maximum level during cooler months.[11,13] In another more recent study, RV infection was still the most important causative organism of GE that accounted for 42.9% of all pediatric cases admitted with GE to one of the biggest tertiary hospitals in Jeddah.[14]

Currently available rotavirus vaccines (RVVs) protected against severe RV-GE and were well tolerated; the implementation of immunization programs would be expected to reduce disease burden with considerable healthcare cost savings in developed countries.[15] Rotavirus vaccination has been shown to prevent severe RV infections with varying efficacy by region.[1]

Currently, there are no available data or up-to-date studies on impact of RVV on RV-GE in Saudi Arabia. Jeddah is the 2nd large city in Saudi Arabia with the 2nd highest previously recorded prevalence of RV infection. Therefore, this study was conducted to assess impact of RVV on incidence and severity of RV-GE among children under 5 years of age hospitalized with GE at 2 large medical centers in Jeddah city. This study was conducted 3 years after introduction of RVV in Saudi immunization program (SIP) in January, 2013.

2. Methods

2.1. Study design and patient selection

This prospective, cross-sectional, hospital based, observational study included GE cases under 5 years of age admitted from the beginning of October, 2015 to the end of December, 2015 to Maternity and Children Hospital (MCH-Al-Mosaadia) in North Jeddah and Hai Al-Jameah Hospital (HJH) in South Jeddah. This study was approved by the research and ethical committees of MCH and HJH. Written informed consents were obtained from caregivers of all children before enrollment.

MCH is a governmental hospital affiliated to Saudi Ministry of Health with a large work burden being a major referral center for the management of sick infants and children from Jeddah and Western region of the kingdom, with an average of 200 children visiting emergency room (ER)/day and an average of 18 admissions/day. HJH is a large private tertiary hospital in South Jeddah, with an average of 130 children visiting ER and pediatric clinics/day and an average of 12 admissions/day.

This study included Saudi infants and children under 5 years of age presenting with diarrhea and/or vomiting of less than 2 weeks' duration and diagnosed as acute GE that required hospitalization at MCH and HJH. Patients were excluded from the study if their ages were equal to or more than 5 years, were not Saudi citizens and if they have any chronic illness, congenital anomalies, or history of prematurity. Patients were also excluded if they had received RVV within 2 weeks before admission as live rotavirus shedding in stool occurs in approximately 25% of recipients, with peak excretion occurring around day 7 after dose 1.[16] The vaccine used in the national SIP is the monovalent vaccine, Rotarix (Manufactured by GlaxoSmithKline Biologicals),[17,18] which is administered as 2 doses at the 2nd and 4th month of age.

The period of this study was selected to be from the beginning of October, 2015 to the end of December, 2015 because in Jeddah city, which has high temperatures and high humidity, RV infection was present throughout the year with a maximum level during the cooler months of the year, November to January.[11,13] However, the period of this study from the beginning of October, 2015 to the end of December, 2015 was particularly selected to compare it with the same period in 2012 RV season with availability of the required clinical and laboratory data as well as detection of RV antigen in stools by the same immunochromatographic assay (IGA) test used in this prospective study. This was of utmost importance and necessary for optimum and accurate comparison between the period before and after RVV introduction in SIP.

Only hospitalized infants and children with GE were recruited for 3 main reasons. First, such cases are mostly presenting with considerable severity that requires hospitalization posing a substantial burden on any health care system. Second, studies showed significantly higher prevalence of RV infection in hospitalized patients than those where outpatients were included.[11,12,13] Moreover; admission of such cases gives the chance to confirm RV infection by examination of stools for RV antigen.

The main outcomes of this study were to identify the numbers of RV-GE and non-RV-GE during the selected period of the study (incidence) as well as the severity of RV-GE and non-RV-GE in relation to almost possible factors that could be associated with risk of RV-GE especially RVV status. Also, clinical data and laboratory findings were compared between RV positive and RV negative cases to determine characteristics of RV-GE cases.

Before 1st of January, 2013, RVV coverage in Saudi Arabia was probably still low as RVV was not free and only provided at private hospitals and clinics costing about 600 SR which could not be afforded by some low income families. Therefore, data from this prospective cross-sectional study in 2015 RV season were compared with retrospective data during the same period in 2012 RV season to assess for possible differences in incidence and severity of RV-GE before and after RVV introduction in SIP hypothesizing that an improvement in RVV coverage being freely provided at health centers of Saudi Ministry of Health could be mostly associated with favorable protective effect of RVV in decreasing the incidence and possibly the severity of RV-GE, 3 years after RVV introduction in SIP.

It would have been better to have a full calendar year of enrolment that would provide a better picture of RV hospitalizations after RVV introduction but as we stated earlier that we were obliged to select this period of the study due to availability of required data and implementation of the same methodology of RV antigen detection in stools, which are necessary for optimum and accurate comparison between the period before and after RVV introduction in SIP.

2.2. Data collection

A well-designed and organized form was used to collect data. This data collection form included almost all possible variables or potential confounders that could be associated with risk of RV-GE including especially RVV status (No RVV, partial vaccination with 1 dose, or full vaccination with the required 2 doses), the demographic and socioeconomic risk factors that could be

associated with RV infection. Also, the clinical, laboratory, and treatment data of hospitalized infants and children were collected. The severity of GE was assessed for all recruited cases on initial admission by Vesikari Clinical Severity Scoring System,[19] which is recognized as the most common system for use in vaccine trials.[20,21] The Vesikari scale is a numerical system used to assess RV-GE disease severity, based on the duration and intensity of diarrhea and vomiting, intensity of fever and dehydration, and the need for treatment and hospitalization. A Vesikari score ≥11 is indicative of severe disease.[19]

2.3. Stool collection and RV antigen detection

Stools were collected from all included GE cases within 7 days of the onset of the illness and within 48 hours of hospital admission and freshly examined at both medical centers (MCH & HJH) for RV antigen in stool by the same IGA with Standard Diagnostics BIOLINE One Step Rotavirus Antigen Test (Standard Diagnostics, Inc 65, Borahagal-ro, Giheung-gu, Yongin-si, Gyeonggi-do, Republic of Korea, www.standardia.com). The overall agreement, positive agreement, and negative agreement rates of the IGA for RV detection, as compared to mRT-PCR, are 95.6%, 100%, and 94.9%,[22] so retesting by other methods as PCR or ELISA was not done. Moreover, IGA allows not only for qualitative detection of the presence of RV with high sensitivity and specificity, but also it is rapid and easy to perform in the routine clinical laboratory and offers comparison of a positive result to a control to give accurate results. The test was performed according to the manufacturer's instructions.[22]

2.4. Statistical analysis

Statistical analysis was done using SPSS program (version 22). The qualitative data were presented in the form of numbers and percentages. The quantitative data were presented in the form of mean, standard deviation (SD), and range. Chi-square was used as a test of significance to compare between groups regarding qualitative data while Student *t* test was used to compare between means. Unadjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated to estimate risk factors of RV infection. Further statistical analysis with multiple logistic regressions was done to adjust for confounders and to determine the most significant risk factor(s) associated with RV infection, and the adjusted hazards ratios (AHRs) were calculated. Significance was considered at *P* value less than 0.05.

3. Results

During the study period, from the beginning of October, 2015 to the end of December, 2015, a total of 208 GE cases in children under 5 years of age were hospitalized at MCH with only 9 (4.3%) RV-GE confirmed cases and a total of 151 GE cases in children under 5 years of age were hospitalized at HJH with only 5 (3.3%) RV-GE confirmed cases. There was no significant difference in the numbers of positive RV cases between the 2 study centers (OR: 1.32, 95% CI: 0.43–4.02). Consequently, data from the 2 centers were added together resulting in a total of 359 all-cause GE cases which were divided into 2 main groups; RV group, comprising RV confirmed cases (14 cases representing 3.9% of total GE cases) and non-RV group, comprising non-RV GE cases (345 cases representing 96.1% of total GE cases).

3.1. Demographic and socioeconomic data

3.1.1. Age. The mean age and SD of RV and non-RV groups were 13.10±5.70 months and 21.36±16.26 months, respectively. The mean age of RV group was significantly lower than the mean age of non-RV group ($P<.001$) (Table 1). All RV cases were less than 2 years compared to 251 cases (72.8%) in non-RV group ($P=.02$). Eight RV cases (57.1%) were less than 1 year compared to 152 non-RV cases (44.1%) (OR: 1.69, 95% CI: 0.58–4.98) (Fig. 1).

3.1.2. Sex. In RV group, 9 cases (64.3%) were males compared to 162 cases (47%) in non-RV group while 5 cases (35.7%) were females in RV group compared to 183 cases (53%) in non-RV group without significant differences between the 2 studied

Table 1

Comparison of demographic and socioeconomic data between cases with and without RV infection at the 2 study centers (MCH & HJH).

Variable	RV group N=14 N, %	Non-RV group N=345 N, %	Odds ratio (95% CI)	*P*
Age, mo*				
(Mean±SD)	13.10±5.70	21.36±16.26	NA	<0.001
Range	(7–20)	(2–59)		
Gender†				
Male	9 (64.3)	162 (47)	2.03 (0.67–6.19)	0.20
Female (reference category)	5 (35.7)	183 (53)		
Residence†				
Urban (reference category)	13 (92.9)	329 (95.4)		0.67
Rural	1 (7.10)	16 (4.6)	1.58 (0.19–12.85)	
Crowding (≥3 persons/room)†	14 (100)	197 (57.1)	NA	0.001
Family monthly income†				
(<10,000 SR)	5 (35.7)	91 (26.4)	1.55 (0.51–4.75)	0.44
Maternal education†	10 (71.4)	217 (62.9)	1.47 (0.45–4.8)	0.52
Less than secondary school level				
Paternal education†	8 (57.1)	176 (51.0)	1.28 (0.44–3.77)	0.65
Less than secondary school level				

CI = confidence interval, HJH = Hai Al-Jameah Hospital, MCH = Maternity and Children Hospital, NA = not applicable, RV = rotavirus, SD = standard deviation.

* Independent samples *t* test.

† Chi square test.

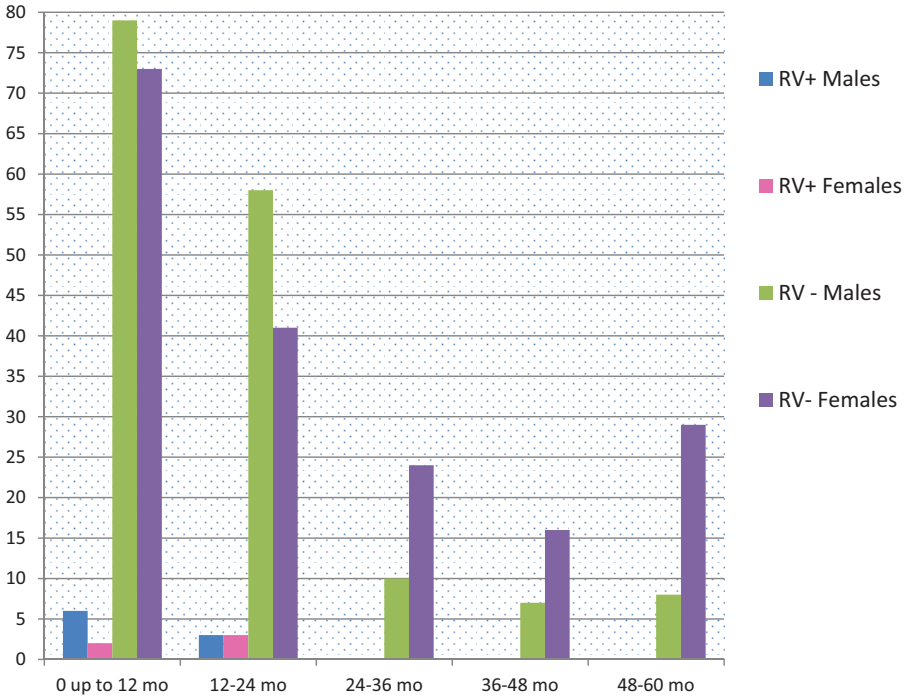

Figure 1. Distribution of cases with and without RV infection at the 2 study centers (MCH & HJH) according to age groups and gender. HJH = Hai Al-Jameah Hospital, MCH = Maternity and Children Hospital, RV = rotavirus.

groups ($P = .2$). Male gender represented a relatively small increased risk for RV infection (OR: 2.03, 95% CI: 0.67–6.19) (Table 1 and Fig. 1).

3.1.1. Residence. More patients from urban areas were found in both RV (13 cases, 92.9%) and non-RV groups (329 cases, 95.4%) without significant difference between the 2 groups ($P = .67$), (Table 1).

3.1.1. Socioeconomic risk factors. The only significant socioeconomic risk factor associated with RV infection was crowding with 3 or more persons/room ($P = .001$). There were no significant differences in family monthly income, maternal, and paternal level of education between RV and non-RV groups ($P = .44$, 0.52, and 0.65, respectively). However, family monthly income below 10,000 SR, maternal education less than secondary school level, and paternal education less than secondary school level were associated with slightly increased risk for RV infection (OR: 1.55, 95% CI: 0.51–4.75, OR: 1.47, 95% CI: 0.45–4.8, and OR: 1.28, 95% CI: 0.44–3.77, respectively) (Table 1).

3.2. Clinical and laboratory data

Before hospitalization, the number of loose motions and the duration of diarrhea as well as the number of vomiting episodes and the duration of vomiting were more in RV group compared to non-RV group. It was noticed that high grade fever was not reported in any of children of RV group (Table 2).

It has been found that 13 of RV-GE cases (92.9%) did not receive RVV compared to 123 (35.7%) of non-RV cases (OR: 23.46, 95% CI: 3.03–181.51) (Table 3). A total of 222 non-RV cases received full vaccination with the 2 required doses of Rotarix. All RV cases had significantly severe GE (Vesikari score ≥11) versus only 159 cases (46.1%) severe cases in non-RV group ($P < .0001$). Moreover, treatment with intravenous fluid was required in all RV cases versus 167 cases (48.4%) in non-RV group ($P < .0001$). Electrolytes and acid base disturbances were significantly more in RV group compared to non-RV group ($P < .0001$) (Table 3).

Table 2

Clinical characteristics of cases with and without RV infection at the time of admission to the 2 study centers (MCH & HJH).

Symptoms and signs	RV group N = 14 N, %	Non-RV group N = 345 N, %
Number of loose motions/day before admission		
1–3	0 (0%)	96 (28%)
4–5	7 (50%)	193 (56%)
≥6	7 (50%)	56 (16%)
Duration of diarrhea (days) before admission		
1–4	3 (21%)	156 (45%)
5	6 (43%)	145 (42%)
≥6	5 (36%)	44 (13%)
Number of vomiting episodes/day before admission		
1	1 (7%)	94 (27%)
2–4	6 (43%)	191 (56%)
5	7 (50%)	60 (17%)
Duration of vomiting before admission		
1	1 (7%)	114 (33%)
2	2 (14%)	142 (41%)
≥3	11 (79%)	89 (26%)
Temperature on admission		
37.1–38.4 °C	6 (43%)	202 (59%)
38.5–38.9 °C	8 (57%)	115 (33%)
≥39.0 °C	0 (0%)	28 (8%)
Degree of dehydration before admission		
No dehydration	0 (0%)	181 (53%)
1–5%	11 (79%)	160 (46%)
≥6%	3 (21%)	4 (1%)

HJH = Hai Al-Jameah Hospital, MCH = Maternity and Children Hospital, RV = rotavirus.

Table 3

Comparison of clinical and laboratory data between cases with and without RV infection at the 2 study centers (MCH & HJH).

Variable	RV group N = 14 N, %	Non-RV group N = 345 N, %	Odds ratio (95% CI)	P*
RVV is not given	13 (92.9)	123 (35.7)	23.46 (3.03–181.51)	<0.001
Severe GE (Vesikari score ≥11)	14 (100)	159 (46.1)	NA	<0.001
IV fluids given	14 (100)	167 (48.4)	NA	<0.001
Hyponatremia	8 (57.1)	44 (12.8)	NA	<0.001
Hypernatremia	4 (28.6)	21 (6.10)	NA	0.001
Hypokalemia	11 (78.6)	49 (14.2)	NA	<0.001
Metabolic acidosis	12 (85.7)	80 (23.2)	NA	<0.001

Hyponatremia is defined as serum sodium level below135 mEq/L. Hypernatremia is defined as serum sodium level above 145 mEq/L. Hypokalemia is defined as serum potassium level below 3.5 mEq/L. CI = confidence interval, HJH = Hai Al-Jameah Hospital, MCH = Maternity and Children Hospital, NA = not applicable, RV = rotavirus, RVV = rotavirus vaccine.
* Chi square test.

3.3. Multiple logistic regressions

Logistic regression analysis of the studied variables during RV 2015 season confirmed that the hazard of RV infection was still associated with lack of RVV (AHR: 57.53 and 95% CI: 6.39–517.74). Younger age was also significant but its AHR was only 0.90 and 95% CI: 0.83 to 0.97, while the significant effect of crowding disappeared (significance at 0.99) (Table 4).

3.4. Comparisons with 2012 RV season

During the same period of this study in the year 2012, 369 RV-GE out of 1193 total GE cases (31%) were hospitalized at MCH and HJH. So, number of hospitalized pediatric patients for all-cause and RV-GE in children below 5 years of age decreased significantly in 2015 RV season (compared to 2015 RV season, OR for RV-GE in 2012: 11.04, 95% CI: 6.38–19.09). Also in 2012, RVV coverage rates with receiving at least 1 RVV dose were identified as 15 out of 369 (4%) in RV-GE hospitalized cases and 264 out of 824 (32%) in non-RV GE hospitalized cases at the 2 study centers; so, RVV coverage in 2015 significantly increased in all-cause GE cases and non-RV GE cases ($P < .001$) but did not increase significantly in RV-GE cases ($P = .57$).

4. Discussion

In January 2013, Saudi Arabia introduced RVV into the national immunization program and it was freely provided at all health centers of Saudi Ministry of Health which should have markedly improved RVV coverage.

In this study, RV infection was confirmed in only 14 out of 359 (3.9%) of total GE cases in children under 5 years of age, admitted to the 2 study centers during the period from the beginning of October, 2015 to the end of December, 2015. There was a marked decrease in number of hospitalized pediatric patients for all-cause GE and RV-GE in children under 5 years in 2015 RV season compared to 2012 RV season when 369 RV-GE cases out of 1193 total GE cases (31%) were hospitalized at the 2 study centers. This represents a sharp significant decline ($P < .001$) in RV-GE among children under 5 year of age, 3 years after introduction of RVV in SIP. Similar remarkable decline in hospital admissions and even deaths from RV-GE was recorded within 3 years of introduction of RVV in childhood routine immunization programs in many countries.[1,15]

Table 4

Multiple logistic regressions for determination of the most significant factor(s) associated with RV infection in 2015 RV season.

Variable	B*	Significance	AHR (95% CI)
RVV is not given	4.05	<0.001	57.53 (6.39–517.74)
Younger age	−0.11	0.005	0.90 (0.83–0.97)
Male gender	0.26	0.73	1.29 (0.31–5.45)
Crowding (≥3 persons/room)	19.15	0.99	NA
Rural residence	0.24	0.85	1.27 (0.11–14.50)
Family monthly income (<10,000 SR)	−0.09	0.90	0.92 (0.23–3.68)

AHR = adjusted hazard ratio, CI = confidence interval, NA = not applicable, RV = rotavirus, RVV = rotavirus vaccine.
* B: coefficient.

In the present study, the hazard of RV-GE was mainly associated with lack of RVV as significantly more RV cases were not vaccinated compared to non-RV GE cases who received RVV (OR: 23.46, 95% CI: 3.03–181.51) and also RVV coverage in 2015, compared to 2012, significantly increased in all-cause GE cases and non-RV GE cases ($P < .001$) but did not increase significantly in RV-GE cases ($P = .57$). The vaccine used in Saudi Arabia, the monovalent one, is derived from a single common strain of RV, and tested for safety and efficacy in more than 60,000 infants in Europe and Latin America.[15] Field effectiveness of the vaccine in Europe and the USA against severe RV-GE has been above 90% and in Latin America around 80%.[17] Moreover, the results of a 2016 systematic review confirm the protective efficacy and effectiveness of RV vaccination against RV diarrheal outcomes among children under 5 years of age globally.[1] Although in our study, RVV was given to only 222 children (64.3%) in non-RV group, RVV was mostly effective in preventing RV infection in vaccinated as well as unvaccinated children possibly by good RVV herd effect. A herd effect is present whereby infants who were not immunized have a lower risk of hospitalization for diarrhea and an older age of infection.[15] These findings are in line with other studies which demonstrated that the burden of as well as hospitalization-rates from RV-GE, since the introduction of RVV, has been reduced significantly in children of all age groups, even in those not eligible for vaccination according to their age, suggesting herd immunity induced by universal mass vaccination against RV-GE.[15,23]

Regarding disease severity, all RV cases in the current study had significantly severe GE (Vesikari score ≥11) with significantly more electrolytes and acid base disturbances in RV group than in non-RV group ($P < .0001$) that required hospitalization and treatment with intravenous fluid in all RV cases. In fact, an association was found between GE severity on the Vesikari scale

and RV-positive status.[24] Other studies confirmed that RV infection has a higher prevalence among children with more severe diarrhea.[5,13] This can point to the desirable protective effect of RVV against severe GE found in non-RV group.

In the present study, the mean age of RV group was significantly lower than the mean age of non-RV group, and all RV cases were less than 2 years, denoting that RV infection was mainly associated with age under 2 years. Although statistically insignificant, age under 1 year was associated with more increased risk for RV-GE compared to non-RV GE (OR: 1.69, 95% CI: 0.58–4.98). These findings were similarly reported in previous Saudi studies,[12] where RV infection was more common in children younger than 2 years of age and infants in the 1st year of life were at highest risk of infection.

Moreover, this can show that infants under 2 years are the most vulnerable to RV infection which tends to be most severe at this age.[4] One systematic literature review that included 14 studies conducted among hospitalized children in the Eastern Mediterranean Region had found that nearly all RV-GE hospitalizations occurred among children under 2 years of age, and most detections affected infants less than 12 months of age.[13] One more recent study from Sudan showed that of the infected children with RV, 88.4% were less than 2 years with high prevalence found in the age group between 3 and 12 months.[25] Similar results were reported from United Arab Emirates[24] and other non-Arab countries.[26,27] Regarding gender of our RV GE cases, male gender represented a relatively small increased risk for RV infection. This is an agreement with the finding that boys are more susceptible to RV infection than girls and are more likely to be hospitalized.[25,28] Yet, it is not known whether this is due to a greater susceptibility to RV exposure in boys or a greater likelihood of parents of affected boys seeking medical care.[28]

In the current study, the only significant socioeconomic risk factor associated with RV infection was crowding with 3 or more persons/room ($P=.001$). A similar finding is reported where more percentage of RV positive cases was found if there were 4 or more people in house compared to RV negative cases but the difference did not reach statistical significance.[26] However, 1 study from England looked at a wide range of social deprivation indices found that accommodation with fewer rooms was significant risk factors for sporadic RV infection.[29]

In addition, family monthly income below 10,000 SR and maternal/paternal education less than secondary school level were associated with slightly increased risk for RV infection (Table 1). This is an agreement to what was found by Dennehy et al[27] in the USA where children of mothers with a lower education level were more likely to have RV diarrhea. This may be explained by the fact that the more educated parents will have the skills, practice, and knowledge to protect their children from likely exposure to RV.[23] Our finding about family income is in contrast to previous studies that indicated increased hospitalizations attributable to RV with increasing income, presumably because of improvements in hygiene and sanitation that decrease exposure to bacterial and parasitic pathogens that also cause diarrhea.[30]

A major strength of this study is being the first cross-sectional, hospital-based study in Jeddah and in the whole kingdom of Saudi Arabia to assess the impact of RVV on incidence and severity of RV-GE in hospitalized pediatric patients. Furthermore, since the study was conducted in 2 large pediatric referral hospitals across the city, the findings are likely to be representative of the whole population of Jeddah.

Some of the limitations of our study included inability to have a full calendar year of enrolment that would have provided a better picture of RV hospitalizations after RVV introduction but as we stated earlier that we were obliged to select this period of the study due to availability of the required clinical and laboratory data and implementation of the same methodology of RV antigen detection in stools particularly at the selected retrospective and prospective study periods, which are necessary for optimum and accurate comparison between the period before and after RVV introduction in SIP. Moreover, we were unable to obtain complete data about breastfeeding status, being exclusive or partial and its exact duration as well as birth weight for all recruited patients especially in 2012 RV season; so, we preferred not to include breastfeeding and birth weight variables in our study. However, prematurity as a cause for considerable proportion of low birth weight infants was included as a main exclusion criterion in the design of this study as a partial solution to overcome the problem of unavailability of birth weight. Yet, it is noteworthy that a protective effect of breastfeeding has not been consistently found for RV infections, with some population-based studies finding absent or marginal protection.[29] Others have shown evidence that breastfeeding confers protection against severe RV infections only[26] and that it may postpone rather than prevent severe infection suggesting that breastfeeding simply postpones RV disease to an older age.[31] We think that the role of breastfeeding in protection against RV diarrhea deserves to be explored further in a detailed prospective study especially designed for this purpose to gather complete data about breastfeeding being exclusive or partial and its exact volume and duration.

Also, we did not identify the specific RV serotypes. However, according to Vesikari,[32] for practical purposes surveillance of RV serotypes are becoming obsolete as it has been convincingly shown that the efficacy and effectiveness of RV vaccines against severe RV-GE are not serotype-specific. Moreover, the number of stools tested for RV may have underestimated the real impact of vaccination as we concentrated on hospitalized cases because they represent more severe cases and directly affect the medical and economic resources; so, future national studies may include all RV-GE cases whether inpatients or outpatients of any severity. Thus, a community-based surveillance is needed in order to monitor the impact of RVV program throughout the kingdom.

5. Conclusions

Logistic regression analysis of variables of this cross-sectional, hospital-based study in Jeddah, Saudi Arabia, 3 years after introduction of RVV in SIP, showed that among the studied variables, RVV was associated with remarkable reduction of hazard of all-cause and RV-GE in vaccinated and even in unvaccinated children under 5 years of age possibly by RVV herd effect. However, RV was still associated with severe GE-related hospitalizations in unvaccinated children against RV who were younger than 2 years and particularly in the 1st year of life, indicating need for more optimum rate of RVV coverage. Hopefully, further improvement in RVV coverage rate may make RV-GE a disease of the past in Saudi children.

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