Efficacy of rotavirus vaccine among vaccinated children in Baquba-Diyala province-Iraq

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Abstract:

Background: Rotavirus gastroenteritis (RGE) is the leading cause of diarrhea-associated hospitalization and death in children younger than 5 years of age. The WHO recommends rotavirus (RV) vaccine to be included in national routine vaccinations programs, the vaccines prevent 15–34% and 37–96% of severe RGE in developing and developed countries respectively. In Iraq the RV vaccine (Monovalent RotaRix and pentavalent RotaTeq) was licensed in the Iraqi Extended Program of Immunization since 2014.

Objectives: This study was designed to determine the protective efficacy of RV vaccine among children and to explore the effect of certain socio-demographic factors and vaccine characteristics.

Vaccinees and methods: This is a cross sectional control study conducted in Baquba, the center of Diyala province during August 2018 – June 2019. A total of 406 children were enrolled as follows; 286 children as vaccinated group (those received partial or complete RV vaccine schedule plus other vaccines), 80 children as other vaccines control group (those received all other vaccines except RV vaccine), and 40 children as no vaccine control group (those received no vaccine at all). 210 children were males and 196 were females. The age range was 8-84 months. Blood and stool samples were collected from each participant on the basis of a pre-established questionnaire form. The stool rotavirus antigen and serum anti-rotavirus IgG were determined by enzyme-linked immunosorbant assay (SinoGeneClon, Biotech). The human privacy was respected by obtaining a child's parents verbal consent. Statistical analysis of data was carried out using SPSS-25. Statistical significance was considered significant whenever the P value was equal or less than 0.05.

Results: All participants were negative for RV antigen in stool. Regarding the blood tests, the results revealed that the positivity rate of anti-rotavirus IgG in the vaccinated group was 25.9% which was significantly higher compared to the positivity rate in other vaccines group 20.0% and no vaccine group 5.0% (P=0.010) . Furthermore, within the three study groups, the mean ± SD of anti-rotavirus IgG concentration was significantly higher among positive children compared to their counterparts (P=0.0001). The RotaRix monovalent vaccine induced a significantly higher titer of anti-rotavirus IgG concentration compared to RotaTeq pentavalent vaccine (8.94±16.59 mIU/ml *vs* 3.33 ± 6.20 mIU/ml), (P= 0.036). The mean ± SD of anti-RV IgG concentration was insignificantly peaked after 2 years post vaccination 10.62±17.92 mIU/ml, (P= 0.573). The age and gender showed insignificant effect on the mean ± SD of anti-RV IgG concentration, (P=0.381) and (P=0.863) respectively.

Conclusion: About one quarter of children received RV vaccine following the universally recommended schedule had protective seropositive levels of anti-rotavirus IgG. Monovalent vaccine was more immunogenic than pentavalent irrespective of vaccine doses or duration.

Keywords: Rotavirus, RotaTeq, RotaRex, Rotavirus gastroenteritis

Introduction:

Rotavirus (RV) is a double-stranded RNA virus belongs to *Rotavirus* genus in the family *Reoviridae*. it is the most common cause of diarrheal disease among infants and young children, thus nearly every child in the world is infected with RV at least once by the age of 5 years [1]. Rotavirus gastroenteritis (RGE) is responsible for approximately 37% of deaths from diarrhea among children younger than 5 years worldwide mostly in sub-Saharan Africa and South Asia. Although episodes of RGE occur frequently in young children irrespective of living standards [2,3] . In Iraqi, 18.5 % of hospitalized children with gastroenteritis were infected with RV [4]. In Diyala province, the overall infection rate by RV in children with acute diarrhea was 20.3% and the highest infection rate was among those below 5 years old [5].

The WHO recommends that all children should be vaccinated with a monovalent RV vaccine (RV1; Rotarix, GlaxoSmithKline Biologicals) or a pentavalent RV vaccine (RV5; RotaTeq, Merck & Co., Inc.), with a stronger recommendation for countries where deaths due to diarrhea comprise more than 10% of all deaths. These two live, oral, attenuated RV vaccines have met the prequalification and stipulations requirements of the WHO [6]. Children fully vaccinated for RV were those who received 3 doses of the pentavalent RV vaccine, 2 doses of the monovalent RV vaccine, or ≥3 doses of either vaccine type [7]. More than half of world countries have introduced RV vaccines into their national immunization programmes since 2006 [8]. Rotavirus vaccines have shown high and durable efficacy against episodes of severe RGE in high-income settings but lower and less durable efficacy in low or middle income countries mostly sub-Saharan Africa and South Asia [9,10]. For instance, two RV vaccines are licensed for use in the USA since 2006, both of which have demonstrated good field effectiveness (78%–89%) against moderate to severe RGE [11]. However, other studies have reported that implementation of RV vaccines has substantially decreased hospitalizations from RGE in both high and middle-income countries [12,13].

It has been reported that so many different factors may influence the humoral and cellular vaccine responses; including intrinsic host factors (age, sex, genetics, and comorbidities) [14], perinatal factors (gestational age, birth weight, feeding method, and

maternal factors) [15], and extrinsic factors (preexisting immunity, microbiota, infections, and antibiotics) [16]. Further, environmental factors (geographic location, season, family size, and toxins), behavioral factors and nutritional factors (body mass index, micronutrients, and enteropathy) also influence individual's response [17]. Moreover, vaccine factors (vaccine type, product, adjuvant, and dose) and administration factors (schedule, site, route, time of vaccination, and coadministered vaccines and other drugs) are also important [18]. In this regard, it has been found that immune responses induced by trivalent oral poliovirus vaccine and diphtheria, tetanus, and a cellular pertussis vaccine were not affected by the concomitant use of RV vaccine [19]. Even, a modest delay in RV vaccination start and increase in interval between doses were associated with lower severe RGE risk in low- and middle-income countries [20].

Vaccinees and methods:

This is a cross sectional control study conducted in Diyala province during August 2018 – June 2019. A total of 406 children were enrolled as follows; 286 children as vaccinated group, 80 children as other vaccines control group, and 40 children as no vaccine control group. 210 children were males and 196 were females. The age range was 8-84 months. 86% of vaccinated children received RotaRix (monovalent) vaccine and 14% received RotaTeq (Pentavalent) vaccine (The Iraqi Health Authorities was changed the RotaRix by RotaTeq vaccine). Blood and stool samples were collected by the healthcare personnels from each participant on the basis of a pre-established questionnaire (Participants data were collected from the official vaccination sheet). Serum anti-rotavirus IgG was determined by enzyme-linked immunosorbant assay (Sino Gene Clon, Biotech). RV vaccine positive response was defined as presence of serum anti-rota IgG concentration of $\geq$ 20 IU/mL following Rotarixor or RotaTeq vaccination. Human privacy was respected by obtaining a child's parents' verbal consent. Statistical analysis was carried out using the statistical package of SPSS-25 (Statistical Packages for Social Sciences- version 25). Data were presented in simple measures of frequency, percentage; mean, standard deviation, and range. The significance of difference of means were tested using Students-t-test for difference between two independent means or Paired-t-test for difference of paired observations, or ANOVA test for difference among more than two independent means. The significance of percentages was tested using Pearson Chi-square test (χ^2-test). Statistical significance was considered whenever the P value was equal or less than 0.05.

Results:

It is worthy to remember that a total of 286 children were included as vaccinated group, 80 children as other vaccines control group, and 40 children as no vaccine control group.

The results revealed that all children were negative for stool rotavirus antigen. Table (1) showed that the positive rate of anti-rotavirus IgG in the rota vaccinated group was 25.9% which was significantly higher compared to the positivity rate in other vaccines group 20.0% and no vaccine group 5.0% , P=0.010 .

Table (1): Distribution of study groups by anti-RV IgG positivity rate.

Anti-RV IgG	Rota vaccine		Other vaccines		No vaccine	
	No	%	No	%	No	%
Positive	74	25.9	16	20.0	2	5.0
Negative	212	74.1	64	80.0	38	95.0
P value	0.010*					

The results in table (2) found that the mean ± SD of anti-rotavirus IgG concentration of positive children in the vaccinated group was significantly higher than its counterpart in the negative children (25.15 ± 23.55 mIU/ml *vs* 2.22 ±1.81 mIU/ml. P=0.0001) Similarly, in the other vaccines group, the mean ± SD of the anti-rotavirus IgG concentration in the positive children was 24.34±14.34 mIU/ml which was significantly higher (P= 0.0001) compared to its counterpart of the negative children 4.77±15.15 mIU/ml. Again, in the no vaccinated group, the mean ± SD of the anti-rotavirus IgG concentration in the positive children was 7.36 ±2.68 mIU/ml which was also significantly higher (P= 0.0001) than its counterpart among negative children 1.33 ± 0.48 mIU/ml.

Table (2): Distribution of anti-RVIgG concentration in study groups.

Study groups	Status	Antibody titer (concentration)			P value
		No.	Mean ± SD	(Range)	
Rota vaccine	Positive	74	25.157±23.557	(1.14-95.784)	0.0001*
	Negative	212	2.224±1.815	(0.288-25.96)	
Other vaccines	Positive	16	24.348±14.343	(5.80-48.134)	0.0001*
	Negative	64	4.779±15.158	(0.86-86.471)	
No vaccines	Positive	2	7.362±2.682	(5.466-9.258)	0.0001*
	Negative	38	1.330±0.480	(0.14-3.047)	

According to the rota vaccine type, the results in table (3) revealed that the mean ± SD of the anti-rotavirus IgG concentration induced by vaccination with RotaRix vaccine was 8.94±16.59 mIU/ml which was significantly higher than that induced by vaccination with RotaTeq 3.33 ± 6.20 mIU/ml, (P= 0.036).

Table (3): Distribution of Anti-RV IgG concentration by vaccine type.

Vaccine type	Antibody titer (concentration)			P value
	No.	Mean ± SD	(Range)	
RotaRix	246	8.941±16.595	(0.29-95.78)	**0.036 ***
RotaTeq	40	3.339±6.206	(1.14-41.08)	

The duration is simple referred to the elapsed time (years) since last rotavaccine dose. Table (3) showed that the peak of mean ± SD of anti-RV IgG concentration was found after 2 years post vaccination 10.62±17.92 mIU/ml; However, this increment was statistically insignificant (P= 0.573) as compared to other durations.

Table (4): Distribution of anti-RV IgG concentration by duration.

Duration (Ys)	Antibody titer (concentration)			P value
	No.	Mean ± SD	(Range)	
<1y	42	8.345±10.586	(0.93-37.53)	**0.573**
1	72	9.973±18.959	(0.29-90.56)	
1.5	23	9.359±15.228	(1.16-54.32)	
2	22	10.622±17.926	(1.12-63.62)	
2.5	19	9.967±14.657	(1.05-44.97)	
3	32	9.105±19.569	(1.23-90.56)	
3.5	24	3.183±5.853	(0.98-30.44)	
4	16	2.175±1.053	(1.07-5.36)	
4.5	19	7.653±21.384	(1.07-95.78)	
=>5y	17	4.604±9.466	(1.26-41.08)	

From the first sight, results in table (5) showed that the anti-rotavirus IgG concentration was conversely proportionate with the number of vaccine doses, as those children received 3 vaccine doses had the lowest IgG concentration 4.33±8.28 mIU/ml. However, the difference was failed to reach the levels of statistical significance (P=0.441).

Table (5): Distribution of anti-RV IgG concentration by vaccine doses.

No. doses	Antibody titer (concentration)			P value
	No.	Mean ± SD	(Range)	
One	65	9.278±15.492	(0.29-90.56)	**0.441**
Two	199	8.215±16.338	(0.93-95.78)	
Three	22	4.335±8.281	(1.28-41.08)	

Discussion:

Rotavirus immunization strategies have become part of a comprehensive global public health program to control rotavirus-associated gastroenteritis, particularly in infants and children in developing countries. Certainly the importance of the current study comes through its being the leading one in this regard since the implementation of rotavaccine in Iraq was started in 2014. As the prevalence of RV infection in Iraq, like other developing countries is high [4, 21]. Probably the only limitations of this study are

the relatively small sample size and the inclusion of only one vaccine efficacy marker due to the expensiveness of laboratory materials as this study is personally funded. In an attempting to exclude children with naturally acquired RV infection and to be assured that the serum anti-rotavirus IgG was merely due to vaccine response, thus the negativity of RV antigen in the stool was employed as an inclusion criterion in this study since the positive RV antigenemia is usually associated with rotavirus infection [22].

The serum anti-rota IgG positivity rate and its concentration were the fundamental markers for evaluation of RV vaccine response in vaccinated children. Accordingly, a protective anti-rotavirus IgG was detected in 25.9% of vaccinated children. As if it was significantly higher than that of other vaccine group 20% and no vaccine group 5% ; However, it was considered as a low efficacy rate. This low efficacy rate was almost similar to those reported from other developing countries [9,23]. For instance, a review of articles from 27 countries, among RV vaccinated children <5 years of age, the median percentage reduction in acute gastroenteritis hospitalizations was 38% overall and 41%, 30%, and 46% in countries with low, medium, and high child mortality, respectively [10]. In Asia, the RV vaccine efficacy was 48.3% against severe RGE, suggesting that pentavalent RV vaccine is safe and efficacious and support expanded WHO recommendations to promote its global use [24]. Moreover, in most of the Africa countries despite the decreased efficacy of the vaccines, data from Sub-Saharan Africa have demonstrated a decrease in rotavirus-related morbidity supporting the beneficial effect and safety of WHO prequalified available vaccines and recommended a monitored surveillance system to follow up effectiveness and impact [13, 23, 25]. Reports from India, a country bear 22% of the 39% global death rate caused by RGE among children < 5 years. The RV vaccine is considered to be the most effective intervention in preventing severe RV disease, as India introduced an indigenous RV vaccine (Rotavac) since 2016 [26]. On the contrary, High income countries had reported a good efficacy rates [10, 12, 27].

The result also found that in the three study groups, the anti-rotavirus IgG concentration was significantly higher among children who were positive for IgG compared to their counterpart. Logically, the high concentration of anti-rota IgG in vaccinated children was vaccine induced response [21, 28]. While the most plausible explanation of the source of anti-rota IgG antibodies in other study groups is the previous community acquired RV infection or infection by RV strain other than that in the vaccine [25].For instance, three RV outbreaks were occurred in California among highly vaccinated populations and the genotype G12P was detected from all three outbreaks [29]. However, what is draw attention is that the anti-rota IgG concentration in other vaccine group is slightly lower than that in the vaccinated children (Mean ± SD 24.348±14.343 *vs* 25.157±23.557). These results indicate that naturally acquired RV infection is almost efficient as RV vaccination for induction of serum IgG concentration. Additionally, even the IgG positivity rate in vaccinated versus non-vaccinated was nearby (20% *vs* 25.9%). Again these results point out to the high RV infection rate in non-vaccinated children, and this is a previously documented fact as the prevalence of RV infection in Iraq as other Mediterranean countries is high[4,10,21, 30].

It has been intensively documented that the differences in the efficacy rates of RV vaccine in different countries can be attributed to a wide range of variables [19,24,31]. Most of these documents affirm the contribution of these factors in reduced RV vaccine efficacy in low and middle income countries [13,23,26]. Probably among the primary factors that may share responsibility of low efficacy of RV vaccine in Iraqi children are the malnutrition, low standard of water supply and health neglection. Malnutrition is associated with dysfunctions of innate and adaptive immunity and therefore is a major factor negatively affecting vaccine efficacy [23,33]. The gut microbiota of children in low-income countries are different from those of children in high- and middle-income countries: they are more diverse and more variable over time. These gut microbiota affects the immune system in different ways and a significant correlation between the composition of the infant gut microbiome and response to RV vaccination [16,17,34]. Furthermore concurrent enterovirus infections were correlated with poor seroresponse to Rv vaccine. Co-infections with RV and other enteric pathogens; *Giardia lambellia*, *E. coli*, *Shigella dysenteriae* acted synergistically. Similarly, children infected with *Clostridium difficile* had more severe clinical symptoms when co-infected with RV [14,18,28,31].

Beside the Environmental enteric dysfunction (EED) which refers to a subclinical disorder of intestinal function common in tropical countries and in settings of poverty and economic disadvantage. The enteropathy that syndrome is characterized by mucosal inflammation and villus blunting mediated by T cell activation. Epithelial cell disruption and microbial translocation drive systemic inflammation. EED in young children is associated geographically with growth failure, malnutrition, and greatly impaired responses to oral vaccines, notably RV and poliovirus vaccines [35]. Immaturity or functional reduction of the infant's immune system, since newborn child's immune system (both innate and acquired) is immature and develops during infancy and childhood. Intrinsic reduced immunogenicity to RV vaccination and

natural RV infection is a recognized condition in low-income countries [24, 28,36].

Data from Africa, Europe and the USA showed that rotavirus-specific antibodies passively transferred by mother's breast milk did not significant affects RV vaccine efficacy, as well as transient abstention from breastfeeding around the time of RV vaccination did not increase the efficacy of RV vaccination. On the other hand, several studies had demonstrated that transplacently acquired maternal RV-specific IgG before RV vaccination of their infants was negatively associated with infants' seroconversion after RV vaccination [14,15,34,37]. Other variables may include, genetic factors, as histo-blood group antigen phenotype determines susceptibility to genotype-specific RV infections and impacts RV vaccine efficacy [38], Immunogenicity of different dosing schedules [20], Effect of concomitant antibiotic and vaccine administration e.g. concurrently administered oral poliovaccine [14,23]. Rv strain diversity [19,31]. Timing and doses of Rv vaccine [20]. RV type and duration [24,28]. Regarding the post vaccination adverse effect, most data support that there was no increased risk of intestinal intussusception post vaccination [12, 23,39]. Rapid changes in circulating RV strains among children were also reported. Lastly, the role of healthcare workers has the primary influence on participants' decision on vaccination [40].

It seems that researches are failed to fully explain the reason for this difference of efficacy for RV vaccines, an observation made with other live oral vaccines for polio, cholera and typhoid fever. The uses of parenteral vaccines have been successful in overcoming this problem for both polio and typhoid and parenteral RV vaccines are now in development [31] or introduction of an indigenous RV vaccine (Rotavac) as in India into the universal immunization programme [26].

References:

1.Pikul, K.V.; Bobyreva, .LE.; Kushnereva, T.V.; Il'chenko, V.I, and Priluckiy, K.Y. Rotavirus infection in children as of today (literature review). Wiad Lek. 2017; 70(3 pt 2):622-7.

2. Global Burden of Disease; Diarrheal Diseases Collaborators. Estimates of global, regional, and national morbidity, mortality, and etiologies of diarrheal diseases: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Infect. Dis.2017; 17:909-48.

3. Tate, J.E.; Burton, A.H.; Boschi-Pinto, .; Parashar, U.D. and World Health Organization-Coordinated Global Rotavirus Surveillance Network. Global, regional, and national estimates of rotavirus mortality in children <5 years of age, 2000–2013. Clin. Infect. Dis. 2016; 62 (suppl 2): S96–105.

4. Alrifai, S.B.; Alsaadi, A.; Mahmood, Y.A.; Ali, A.A. and Al-Kaisi, L.A. Prevalence and etiology of nosocomial diarrhoea in children < 5 years in Tikrit teaching hospital. East. Meditterr. Health J. 2009;15(5):1111-8.

5. Hasan, A.SH.; Al-Duliami, A.A.; Mehdi, SH. And Al-Azawi, A.Y. The prevalence of rotavirus infection in Baquba- Diyala province. Iraqi J. Commun. Med. 2011;24(3):200-5.

6. Poelaert, D.; Pereira, P.; Gardner, R.; Standaert, B. and Benninghoff, B. A review of recommendations for rotavirus vaccination in Europe: Arguments for change. Vaccine 2018; 36(17):2243-53.

7.Lee, P.I.; Chen, P.Y.; Huang, Y.C.; Lee, C.Y.; Lu, C.Y.; Chang, M.H.; Lin, Y.Z.; Chiu, N.C.; Ni, Y.H.; Chen, C.M.; *et al*. Recommendations for rotavirus vaccine. Pediatr. Neonatal 2013; 54(6):355-9.

8. Burnett, E.; Parashar, U. and Tate, J. Rotavirus vaccines: effectiveness, safety, and future directions. Pediatr. Drugs 2018; 20(3):223-33.

9. Andrew, C.; Kevin, V.Z.; Stefan, F.; Colin, S.; Jule, B.; Jacquoline, T.; *et al*. Efficacy of live oral rotavirus vaccines by duration of follow-up: Meta-regression of randomized controlled trails. Lancet Infect. Dis. 2019;19: 717-27.

10. Burnett, E.; Jonesteller, C.L.; Tate, J.E.; Yen, C. and Parashar, U.D. Global impact of rotavirus vaccination on childhood hospitalizations and mortality from diarrhea. J. Infect. Dis. 2017; 215(11):1666-72.

11. Payne, D.C.; Selvarangan, R.; Azimi, P.H.; et al. Long-term consistency in rotavirus vaccine protection: RV5 and RV1 vaccine effectiveness in US Children, 2012–2013. Clin. Infect. Dis. 2015; 61:1792–9.

12. Hungerford ,D.; Smith, K.; Tucker, A.; Iturriza-Gomara, M.; Vivancos, R.; McLeonard, C. A.; *et al*. Population effectiveness of the pentavalent and monovalent rotavirus vaccines: a systematic review and meta-analysis of observational studies. BMC Infect. Dis. 2017;17(1):569.

13.Mwenda, J.M.; Mandomando, I.; Jere, K.C.; Cunliffe, N.A. and Duncan Steele, A. Evidence of reduction of rotavirus diarrheal disease after rotavirus vaccine introduction in national immunization programs in the African countries: Report of the 11th African rotavirus symposium held in Lilongwe, Malawi. Vaccine 2019; 37(23):2975-81.

14. Zimmermann, P. and Curtis, N. Factors that influence the immune response to vaccination. Clin. Microbiol. Rev. 2019 ;32(2). pii: e 00084-18.

15.Chen, M.Y.; Kirkwood, C.D.; Bines, .; Cowley, D.; Pavlic, D.; Lee, K.J.; *et.al*. Rotavirus specific maternal antibodies and immune response to RV3-BB neonatal rotavirus vaccine in New Zealand. Hum. Vaccine Immunother. 2017;13(5):1126-32.

16.Harris, V.; Ali, A.; Fuentes, S.; Korpela, K.; Kazi, M.; Tate, J.; *et al*. Rotavirus vaccine response correlates with the infant gut microbiota composition in Pakistan. Gut Microbes 2018; 9(2):93-101.

17. Magwira, C.A. & Taylor, M.B. Composition of gut microbiota and its influence on the immunogenicity of

oral rotavirus vaccines. Vaccine, 2018; 36(24):3427-33.

18. Araki, K.; Hara, M.; Tsugawa, T.; Shimanoe, C.; Nishida, Y.; Matsuo, M. and Tanaka, K. Effectiveness of monovalent and pentavalent rotavirus vaccines in Japanese children. Vaccine 2018 ;36(34):5187-93.
19. Mo, Z.; Ma, X.; Luo, P.; Mo, Y.; Kaplan, S.S.; Shou, Q.; *et.al*. Immunogenicity of pentavalent rotavirus vaccine in Chinese infants. Vaccine 2019;37(13):1836-43.
20. Gruber, J.F.; Becker-Dreps, S.; Hudgens, M.G.; Brookhart, M.A.; Thomas, J.C. and Jonsson Funk, M. Timing of rotavirus vaccine doses and severe rotavirus gastroenteritis among vaccinated infants in low- and middle-income countries. Epidemiology, 2018;29(6):867-75.
21. Hasan, A.SH.; Al-Azzawi, D.S.H.; Al-Duliami, A.A. and Al-Azawi, A.Y. Antirotavirus IgG seropositivity among healthy population and patients with acute diarrhea in Baquba-Diyala province Iraq. Iraqi J. Commun. Med. 2011; 24(2): 100-4.
22. Justino, M.C.A.; Campos, E.A.; Mascarenhas, J.D.P.; Soares, L.S.; Guerra, S.F.S.; Furlaneto, I.P.; *et al*. Rotavirus antigenemia as a common event among children hospitalized for severe, acute gastroenteritis in Belem, northern Brazil. BMC Pediatr. 2019; 19(1):193.
23. Zaman, K.; Dang, D.A.; Victor, J.C.; Shin, S.; Yunus, M.; Dallas, M.J.; *et.al*. Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in Asia: a randomized, double-blind, placebo-controlled trial. Lancet, 2010; 376(9741):615-23.
24. Gruber, J.F.; Hille, D.A.; Liu, G.F.; Kaplan, S.S.; Nelson, M. and Goveia, M.G.; Mast, T.C. Heterogeneity of rotavirus vaccine efficacy among infants in developing countries. Pediatr. Infect. Dis. J. 2017; 36:72–8.
25. Sindhu, K.N.C.; Babji, S. and Ganesan, S.K. Impact of rotavirus vaccines in low and middle-income countries. Curr. Opin. Infect. Dis. 2017; 30(5):473-81.
26. Nair, N.P.; Reddy, N.S.; Giri, S.; Mohan, V.R.; Parashar, U.; Tate, J.; Investigators of the Rotavirus Vaccine Impact Surveillance Network; *et al*. Rotavirus vaccine impact assessment surveillance in India: protocol and methods. BMJ Open.2019;9(4):e024840.
27. Aliabadi, N.; Tate, J.E.; Haynes, A.K. and Parashar, U.D. Sustained decrease in laboratory detection of rotavirus after implementation of routine vaccination—United States, 2000–2014. Morb. Mortal .Wkly. Rep. 2015; 64:337–42.
28. Dai, X.; Bai, R.; Jian, M.; Ji, Z.; Ding, Z.; Wang, F. ; Bi, Y.; *et al*. Immunogenicity of different dosing schedules of the human live attenuate rotavirus vaccine (RV1) in infants and children: a meta-analysis. Hum. Vaccine Immunother. 2019;15(6):1228-36.
29. Burke, R.M.; Tate, J.E.; Barin, N.; Bock, C.; Bowen,M.D.; Chang, D.; Gautam, R.; Han,G.; *et al*. Three rotavirus outbreaks in the postvaccine era - California, 2017. Morb. Mort. Wkly Rep. 2018; 67(16):470-2.
30. Zaraket, H.; Charide, R.; Kreidieh, K.; Dbaibo, G. and Melhem, N.M. (2017). Update on the epidemiology of rotavirus in the Middle East and North frica. Vaccine, 35(45):6047-58.
31. Desselberger, U. Differences of rotavirus vaccine effectiveness by country: likely causes and contributing factors. Pathogens, 2017; 6(4):65-78.
32. Church, J.A.; Rukobo, S.; Govha, M.; Lee, B.; Carmolli, M.P.; Chasekwa, B.; *et al*. The impact of improved water, sanitation and hygiene on oral rotavirus vaccine immunogenicity in Zimbabwean infants: sub-study of a cluster-randomized trial. Clin. Infect. Dis. 2019 ;16. pii: ciz140.
35. World Health Organization. Iraqi's neglected health and humanitarian crisis. Lancet, 2015; 13:2324.
36. Parker, E.P.; Ramani, S.; Lopman, B.A.; Church, J.A.; Iturriza-Gomara, M.; Prendergast, A.J. and Grassly, N.C. Causes of impaired oral vaccine efficacy in developing countries. Future Microbiol. 2018;13:97-118.
35. Marie, C.; Ali, A.; Chandwe, K.; Petri, W.A. Jr. and Kelly, P. Pathophysiology of environmental enteric dysfunction and its impact on oral vaccine efficacy. Mucosal Immunol. 2018; 11(5):1290-98.
36. Chiu, M.; Bao, C. and Sadarangani, M. Dilemmas with rotavirus vaccine: The neonate and immunocompromised. Pediatr. Infec. Dis. J. 2019;38(6S Suppl 1):S43-S46.
37. Yang, H.; Luo, G.; Zeng, Y.; Li, Y.; Yu, S.; Zhao, B.; An, R.; *et al*. The distinct impact of maternal antibodies on the immunogenicity of live and recombinant rotavirus vaccines. Vaccine, 2019 ;37(30):4061-7.
38. Lee, B.; Dickson, D.M.; deCamp, A.C.; Ross, C.E.; Diehl, S.A.; Uddin, M.I.; *et al*. Histo-Blood Group Antigen Phenotype Determines Susceptibility to Genotype-Specific Rotavirus Infections and Impacts Measures of Rotavirus Vaccine Efficacy. J. Infect. Dis. 2018;217(9):1399-1407.
39. Ratu, F.T.; Reyburn, R.; Tuivaga, E.; Tuiketei, A.; Jenkins, K.; Mulholland, K. ; *et al*. Epidemiology of intussusception before and after rotavirus vaccine introduction in Fiji. Sci. Rep. 2018;8(1):11194.
40. Benninghoff, B.; Pereira, P. and Vetter, V. Role of healthcare practitioners in rotavirus disease awareness and vaccination - insights from a survey among caregivers. Hum. Vaccin. Immunother. 2019; 16:1-9.