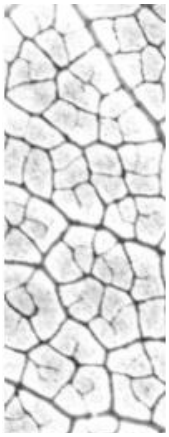

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Prevalence of rotavirus infection in pediatric patients after introduction of the Rotateq@ vaccine in Jordan

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Abstract
Rotavirus is the leading causative agent of acute gastroenteritis in children. Rotateq@ vaccine is one of the recommended rotavirus vaccines by WHO, which been approved in 2007. Jordan has introduced the Rotateq@ into the national vaccination program in 2015. This study aims to assess the impact of introducing the Rotateq@ on the prevalence of rotavirus infection in Jordan. A total of 191 stool samples were collected from patients under 5 years of age whom were admitted to the military Jordanian hospitals with symptoms of gastroenteritis associated with diarrhea. RT-PCR assays were carried out to detect the VP7 and VP4 genes of Rotavirus. An assay targeting the distinctive vaccine gene "NSP3" was also conducted to discriminate between wild and vaccine infection. Sequence analysis was applied to the VP7 and VP4 genes of positive rotavirus samples to confirm the results and identify the genotypes. The results showed that 11 samples out of 191 (<6%) were confirmed as rotavirus infection. No vaccine strains were detected in any of the samples. Sequence analysis for VP7 and VP4 genes identified the genotypes as G1P8 (36%), G2P4 (36%), G1NA (18%), and G2NA (9%). This study revealed the significant impact of the Rotateq@ vaccine in reducing the prevalence of rotavirus infection within the target population in Jordan.

Keywords: gastroenteritis, pediatrics, Rotateq@, rotavirus, vaccine

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INTRODUCTION

Rotavirus is one of the common causes of severe gastroenteritis associated with acute diarrhea in infants and children under 5 years of age worldwide. This condition is a life threatening and leads to death in some severe cases (Crawford et al. 2017). The rotavirus belongs to the Reoviridae family with dsRNA genome composed of 11 segments encoding structural and nonstructural proteins. The structural proteins (VP7 and VP4) are outer capsid proteins elicit neutralizing antibody responses. VP7 and VP4 proteins are considered the main elements for rotavirus classification for G and P genotypes, respectively. Local studies from 2003 to 2011 showed a high rate of rotavirus infection, especially in newborns up to five years of age (Kaplan et al. 2011, Khuri-Bulos and Al Khatib 2006, Nafi 2010, Salem et al. 2011). According to a local study conducted in 2011, 44% of gastroenteritis cases associated with acute diarrhea admitted to different hospitals were tested positive against rotavirus. The study involved more than one area over a specified period of time (Kaplan et al. 2011).

Based on the high rate of infection with the virus and the diversity of isolates that have emerged in different countries in the world, including Jordan, many researches focused on the development of a vaccine to reduce the continuous increase in infection rate. In 2007, WHO adopted two types of anti-rotavirus vaccines: Rotateq@ (RV5, (Merck & Co., Inc., West Point, PA, USA)) and Rotarix@ (RV1, GlaxoSmithKline Biologicals SA, Rixensart, Belgium) (Offit and Clark 2006), which have been shown by many scientific studies to be effective in reducing the incidence of rotavirus infection (Armah et al. 2010, Burnett et al. 2017). WHO recommended the countries with high prevalence of rotavirus infection to adopt one of these vaccines in their national immunization program. Currently, almost 100 countries introduced live oral vaccines in their national vaccination programs to protect against rotavirus infection (2013). WHO licensed other new rotavirus vaccines that are used in lesser extent until now;

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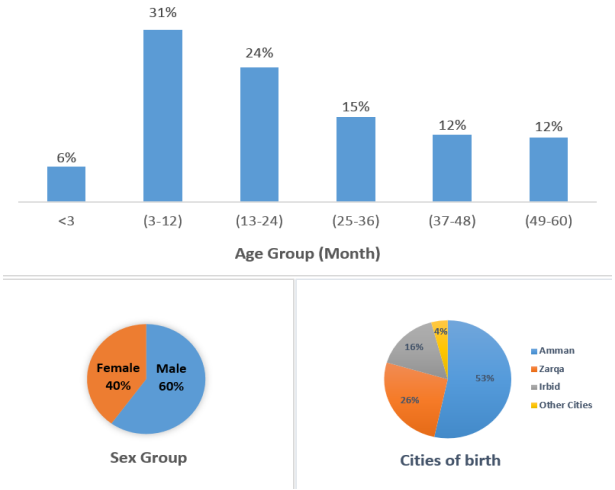

Fig. 1. Samples' Distribution & Characteristics

ROTAVAC (Bharat Biotech, Hyderabad, India) and ROTASIIL (Serum Institute of India PVT. LTD., Pune, India) (Kirkwood et al. 2019).

In Jordan, the Ministry of Health decided to introduce the RotaTeq@ vaccine into the Jordanian National Vaccination Program in February 2015. Rotateq@ (RV5) is an oral pentavalent live vaccine composed of five reassortant rotavirus strains (Chandran and Santosham 2008, Keating 2006, Plosker 2010, Vesikari et al. 2006). The genetic materials of five different human and bovine rotavirus isolates were rearranged in this vaccine. This vaccine is given to children orally on three doses according to a specific schedule (Chandran and Santosham 2008, Keating 2006, Offit and Clark 2006, Plosker 2010, Vesikari et al. 2006).

This study aims to assess the impact of introducing the Rotateq@ vaccine into the National Vaccination Program in Jordan, and show its role in reducing the prevalence of rotavirus infection after almost five years from starting vaccination against rotavirus infection in Jordan. The study also aims to check the potential presence of the vaccine strains in the stool samples of pediatric patients presented with gastroenteritis infection.

MATERIALS & METHODS

Ethical approval

All procedures performed in this study were approved by the Committee of Ethics and the Pharmaceutical and Clinical Studies and Researches at the Jordanian Royal Medical Services (JRMS; Amman-Jordan); Approval Number (9/2018).

Target Population and Samples Collection

A total of 191 stool samples were collected during the period (December 2018 and August 2019). The samples were collected from pediatric patients with gastroenteritis associated with acute diarrhea and whom were admitted to JRMS hospitals in Amman, Zarqa, and Irbid. The targeted patients were infants and children between 3-60 months of age. All procedures performed in this study were approved by the Committee of Ethics. Samples were classified based on three categories: age group, sex, and city of birth (**Fig. 1**). As the vaccine was introduced in February 2015, it was assumed that all pediatrics with an age under 42 months took the vaccine. The samples were preserved in DNA/RNA shield™ fecal collection tubes (Zymo Research, CA, USA) and transported to the Biosafety and Biosecurity Center at the Royal Scientific Society (RSS) of Jordan. The samples were stored in -80°C freezer until conducting laboratory analyses.

Extraction of Viral dsRNA

Viral dsRNA was extracted from 300 µl of homogenized stool samples stored in DNA/RNA shield by conventional method using TRIzol reagent (Gibco BRL, Grand Island, NY, USA) as previously described (Jeong et al. 2016). The obtained pellet was re-suspended in 20-50 µl TE buffer, then stored at -80°C until conducting the RT-PCR analysis. The dsRNA was also extracted from the Rotateq@ vaccine to be used as a positive control for NSP3 RT-PCR assay. The vaccine was provided to RSS by the Ministry of Health/the Department of Vaccines and Immunization (Amman-Jordan).

Detection of Rotavirus VP7 and VP4 Glycoproteins Genes

Rotavirus strains were screened using One-Step RT-PCR (Qiagen, Germany) assay targeting a universal 1062 bp fragment within the VP-7 gene, as previously described (Gouvea et al. 1990). A total of 50 µl reaction mixture was prepared for each reaction tube, with 0.6 µM concentration of each primer, and 5 µl of RNA template. The mixture was incubated in a thermal cycler (Applied Biosystems, USA) at the following temperature program: 50°C for 30 minutes to launch the RT step, 95°C for 15 minutes to stop the RT enzyme activity, and 35 cycles of 94°C for 1 minute, 52°C for 1 minute, 72°C for 1 minutes, and final extension step with 72°C for 10 minutes. While a Two-Step RT-PCR assay was conducted to screen the presence of VP4 gene for all positively identified samples, targeting an 876 bp fragment as previously described (Gentsch et al. 1992). The cDNA template was built using Power cDNA Synthesis Kit (iNtRON Biotechnology, South Korea) according to the manufacturer's instructions. Two microliter from the generated cDNA were used as template for PCR assay in a total of 25 µl reaction mixture using Go Taq@ Green Master Mix (Promega Co. WI, United States). The PCR products were observed and documented in 1.2 % agarose gel for both assays.

Differentiation between the Wild Type and the Vaccine Type Rotavirus Infection

In combination with the One-Step RT-PCR for VP-7 gene or alone, RotaTeq® derived strains were screened using specific primers targeting the highly conserved region (555 bp) of the bovine NSP3 gene from the parent vaccine bovine strain (WC3 - G6, P7[5]e), using the same PCR mixture and assay as mentioned in the VP-7 RT-PCR step. If the two PCR bands (1062 bp and 555 bp) were detected in the sample, this means that the root cause of the infection is either from a vaccine strain alone or from both strains (a wild strain and a vaccine strain) (Jeong et al. 2016).

Sequence Analysis

Positive rotavirus VP7 and VP4 samples were subjected to sequence analysis to confirm the PCR results and identify the genotypes circulating in these samples. The PCR products were treated using ExoSAP-IT^{TM} PCR Product Cleanup kit (Applied Biosystems, USA) before submitting for sequencing using Sanger sequencer at Macrogen Company (Seoul, South Korea). The primer sets Beg9 and End9 for VP7 gene and Con3 and Con2 for VP4 gene were used for sequencing (Gentsch et al. 1992, Gouvea et al. 1990). VP7 and VP4 sequences were viewed and edited using the Editseq interface of the DNASTAR Lasergene Software. Sequences were aligned using Cluster W interface present in the Megalign interface. VP7 and VP4 sequences were subject to evolutionary analyses using MEGA7. The evolutionary history was inferred using the neighbor-joining method. Nucleotide substitution model testing was performed using MEGA 7. The percentage of replicate trees in which the associated taxa clustered together in the bootstrap test (1000 replicates) are shown next to the branches. The 'partial deletion' option was used for gaps/missing data sequences of VP7 and VP4 of the Jordanian isolates were submitted to GenBank.

RESULTS

Summary of Samples Classification and Characteristics

The number of samples collected from the three hospitals were 191 diarrheal stool samples obtained from pediatric under the age of 5 years. The patients admitted to hospital, suffered from digestive system problem. The majority of patients (31%) belong to the age group (3-12) months and 24% of them belong to the age group of (13-24) months. While the minimum number of samples (6%) were taken from patients under 3 months of age. The number of samples collected from male patients were more than those taken from females (60% *vs* 40%). More than 50% of the samples were collected from children admitted to King Hussein Medical City Hospital (Amman). While 26% of the children were admitted to Prince Hashem Hospital (Zarqa) and 16% of the cases were in Prince Rashid Hospital (Irbid). The summary of samples' characteristics and distribution are demonstrated in **Fig. 1**.

Prevalence of Rotavirus Infection

Rotavirus VP7 gene was detected in 14 samples (7.3 %). All positive samples were subjected to subsequent analysis against NSP3 gene to exclude infection associated with vaccine strains. None of the samples contained vaccine strains, which means that all samples are wild infection. The 14 positive samples were also subjected to RT-PCR to detect VP4 gene for subsequent genotyping. In 5 samples (2.6 %), out of the 14 samples, the target VP4 gene were detected.

Sequence Analysis and Circulating Genotypes

All positive samples (14 for VP7 and 5 for VP4) were sequenced to confirm the PCR results and to identify the G and P genotypes of detected rotavirus strains. All sequences resulted from this study are available on GenBank sequence data base (MN561339-MN561349) and (MN585733-MN585737). Out of 14 sequenced positive VP7 samples, the results of 11 samples (<6 %) were confirmed as wild rotavirus infection. Two G genotypes (G1 & G2) and two P genotypes (P4 & P8) were identified in the samples. G1 genotype was observed in 6 samples, while G2 genotype was identified in 5 samples. G1P8 and G2P4 are the dominant genotypes circulating in the samples (4 samples for each genotype). It was not able to identify P genotypes in three samples (2 of G1NA and 1 of G2NA). Phylogenetic trees were built for the detected rotavirus isolates of this study and clustered within the corresponding genotype cluster. Four G1 rotavirus isolates were clustered as within genotype IIc, while two isolates were clustered within genotype Ic (**Fig.2** in supplementary material). For G2 rotavirus isolates, all five isolates were located within genotype IIc (**Fig.3** in supplementary material). All four P4 Jordanian isolates were clustered within genotype Vc (**Fig. 4** in supplementary material). The P8 isolate was located within genotype III. Two P8 Jordanian isolates retrieved from Genbank (KP902536 and KP902537) were clustered within genotype IV (**Fig. 5** in supplementary material) (Zeller et al. 2015).

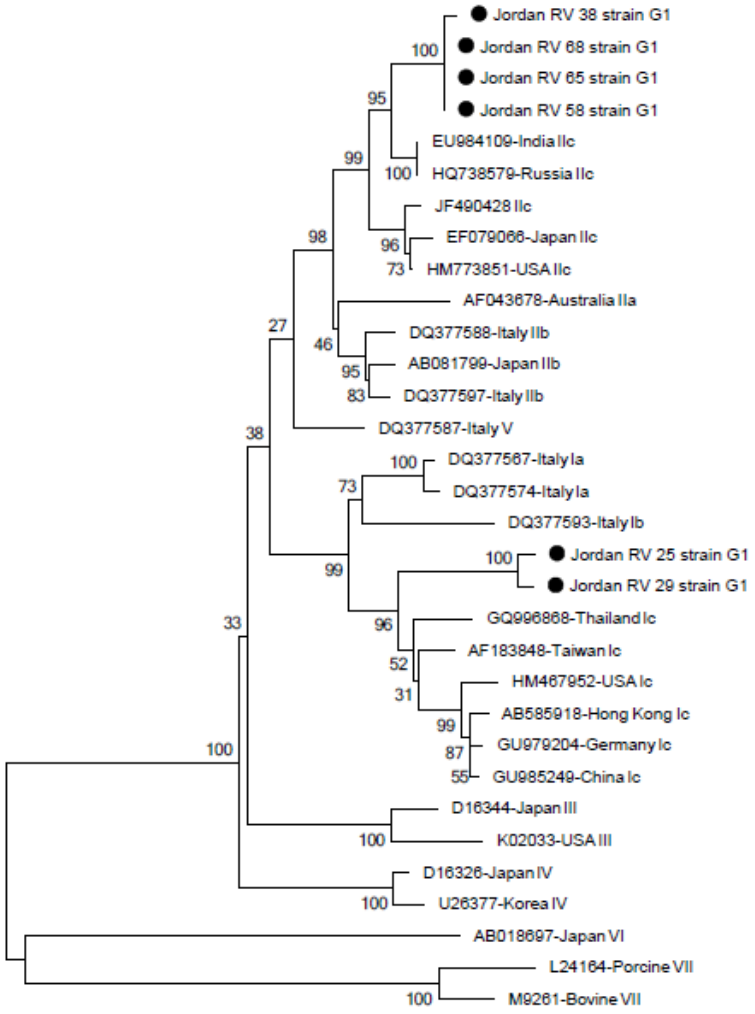

Fig. 2. Neighbor-joining tree showing the relationship of the VP7 fragment region of Jordanian G1 isolates (black circles) to other Human rotaviruses type A. The percentage of replicate trees in which the associated taxa clustered together in the bootstrap test (1000 replicates) are shown next to the branches. The sequences of the G isolates are available on GenBank (MN561339-MN561349)

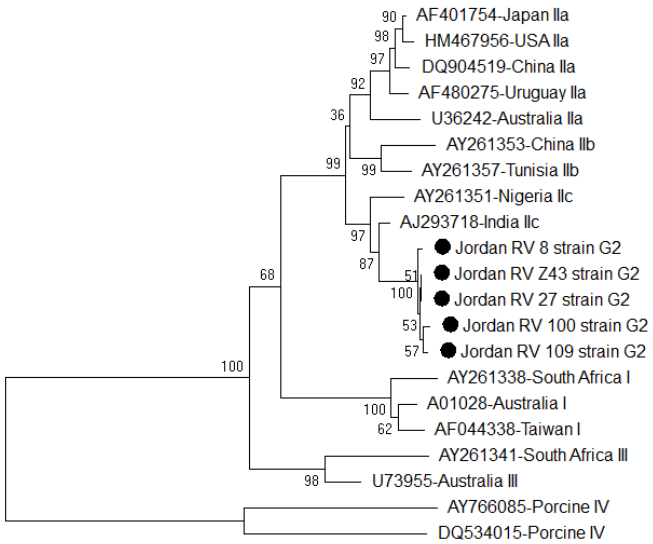

Fig. 3. Neighbor-joining tree showing the relationship of the VP7 fragment region of Jordanian G 2 isolates (black circles) to other Human rotaviruses type A. The percentage of replicate trees in which the associated taxa clustered together in the bootstrap test (1000 replicates) are shown next to the branches. The sequences of the G isolates are available on GenBank (MN561339-MN561349)

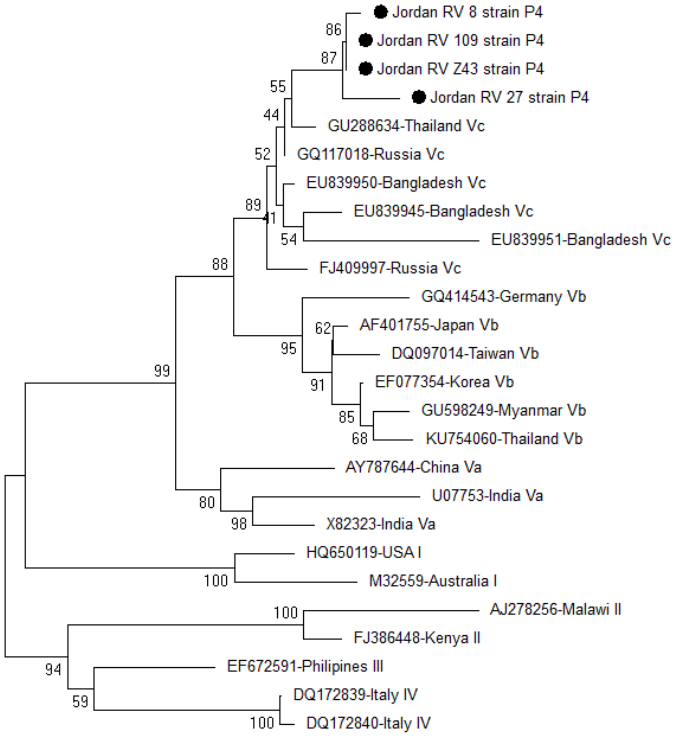

Fig. 4. Neighbor-joining tree showing the relationship of the VP4 fragment region of Jordanian P4 isolates (black circles) to other Human rotaviruses type A. The percentage of replicate trees in which the associated taxa clustered together in the bootstrap test (1000 replicates) are shown next to the branches. The sequences of the P isolates are available on GenBank (MN585733-MN585737)

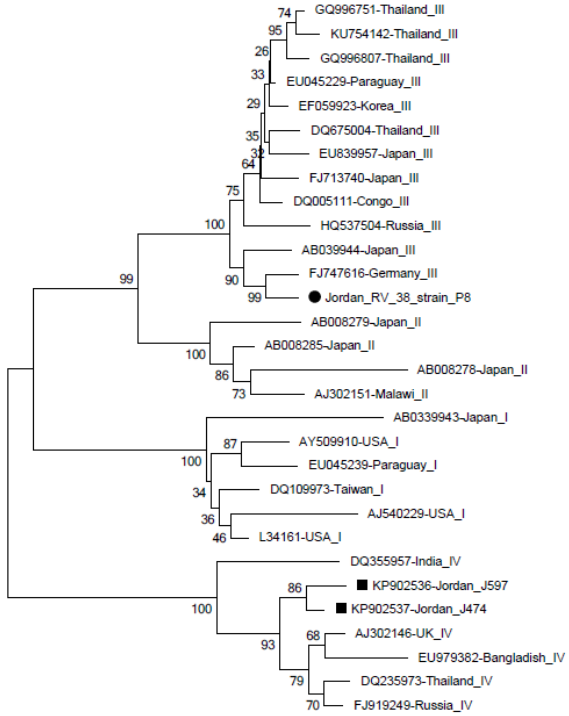

Fig. 5. Neighbor-joining tree showing the relationship of the VP7 fragment region of Jordanian P8 isolates (black circles) to other Human rotaviruses type A. Two Jordanian isolates were retrieved from the GenBank were shown with black square. The percentage of replicate trees in which the associated taxa clustered together in the bootstrap test (1000 replicates) are shown next to the branches. The sequences of the P isolates are available on GenBank (MN585733-MN585737)

Almost all positive rotavirus infections were detected in samples collected from King Hussein Medical Center (Amman); only one positive sample was identified in the samples collected from Prince Hashem Hospital (Zarqa). No rotavirus infections were identified in samples collected from Prince Rashid Hospital (Irbid). Six positive samples were from male patients, while five samples from females. The results show that none of the age group was dominating in hosting the infection; positive rotavirus infections were evenly observed (3 samples each) in age groups (3-12, 13-24, and 49-60 months of age), while 2 samples belong to age group (25-36 months of age). Samples from age groups <3 and 37-48 months did not show any positive rotavirus.

DISCUSSION

In this study, the prevalence of rotavirus infection was investigated after introducing the revealed significant decrease in the prevalence of rotavirus infection in the pediatric patients under five years of age in Jordan. Out of 191 tested stool samples, rotavirus was detected in 11 samples (<6%). A previous study conducted in 2011 prior to vaccine introduction shows that the prevalence of rotavirus was more than 45% of the tested sample(4). The detected rotavirus genotypes in this study are G1P8 (36%) and G2P4 (36%). It was not possible to identify the genotypes for the rest of positive strains because of the undetected VP4 gene. G1P8 genotype is recognized as the major circulating genotype within all rotavirus strains worldwide, followed by G2P4 genotype (Banyai et al. 2012). In Jordan, it has been previously identified that G1P8 and G2P4 are the predominant genotypes within rotavirus cases throughout the Kingdom (Kaplan et al. 2011, Salem et al. 2011). Several recent studies reported increasing in the incidence of G2P4 genotype after the Rotateq@ vaccine has been used in many countries (Donato et al. 2014, Gurgel et al. 2014, Kirkwood et al. 2011, Thanh et al. 2018, Vizzi et al. 2017). The results of this study did not identify the main affected age group. The majority of samples belong evenly to the age groups (3-24, and 49-60 months of age). Previously, children within the age group 6-24 months were the main affected population (Kaplan et al. 2011, Khuri-Bulos and Al Khatib 2006, Nafi 2010).

Sequence analysis and phylogenetic trees for the detected rotavirus isolates revealed that those isolates are located within IIc and Ic clusters for G1 isolates, IIc for G2 isolates, Vc for P4 isolates, and III for P8 isolates (**Fig. 2**-**5** in supplementary material). Except two P8 rotavirus isolates clustered within IV genotype from 2007 (Zeller et al. 2015), no other Jordanian rotavirus strains were previously identified in the literature to be clustered for each detected genotypes. This study provides comprehensive information about the Jordanian rotavirus isolates' sequences, genotypes, and clusters' classification. However, the P8 genotype (III cluster) detected in this study is located in different cluster from the previous P8 genotype detected in 2007 (IV cluster). This confirms that the genetic diversity and the genotypes dominancy have been definitely changed since 2007.

Globally, it has been demonstrated that Rotateq@ vaccine has a critical role in reducing the acute gastroenteritis cases associated with rotavirus infection in countries which introduced rotavirus vaccine in their national immunization programs (Chavers et al. 2018, Kirkwood et al. 2011, Muendo et al. 2018, Mwenda et al. 2019, Payne et al. 2019).

However, several concerning points have been raised regarding the future safety and efficacy of the rotavirus vaccine, which must be taken in consideration to be addressed. From one hand, few studies confirmed the ability of the vaccine isolates to shed from infected person's stools and potential transmission to non-immunized persons (Kaneko et al. 2017, Markkula et al. 2015, Payne et al. 2010). In this study, the Rotateq@ strains were not detected in the tested samples; however, this does not exclude the importance of monitoring the vaccine-associated infection periodically. From the other hand, evidence of mutations occurring in some regions of rotavirus genome that led to the emergence of variants for some rotavirus genotypes in post vaccination period has been reported, as well as changing in the dominancy and the diversity of some rotavirus genotypes (Doan et al. 2011, Esposito et al. 2019, Roczo-Farkas et al. 2018, Thanh et al. 2018, Vizzi et al. 2017, Zeller et al. 2015).

CONCLUSION

The study proves that the introduction of Rotateq@ vaccine into the Jordanian National Immunization Program has reduced the prevalence of acute gastroenteritis associated with rotavirus infection of pediatric patients under 5 years of age in Jordan. This revealed the great impact of this oral live vaccine after almost 5 years of its introduction. However, future studies should target larger population with known vaccination history of rotavirus vaccine. The efficacy and the safety of this vaccine should be continuously monitored for viral mutations and vaccine-associated infection.

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