



## Original article

# Molecular epidemiology, genetic diversity, and vaccine availability of viral acute gastroenteritis in the middle East and North Africa (MENA) region

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## ARTICLE INFO

## Article history:

Received 15 May 2022

Received in revised form 26 August 2022

Accepted 11 September 2022

## Keywords:

Acute gastroenteritis

Rotavirus

Norovirus

Adenovirus

Astrovirus

Sapovirus

Phylogenetic analysis

Rotavirus vaccine

Middle East

And North Africa

## ABSTRACT

Acute gastroenteritis is the cause of considerable mortality and morbidity worldwide, particularly among children under five years in underdeveloped countries. Most acute gastroenteritis (AGE) cases are attributed to viral etiologies, including rotavirus, norovirus, adenovirus, astrovirus, and sapovirus. This paper aimed to determine the prevalence rate of different viral etiologies of AGE in the Middle East and North Africa (MENA) region. Moreover, this paper explored rotavirus phylogenetic relatedness, compared VP7 and VP4 antigenic regions of rotavirus with vaccine strains, and explored the availability of vaccines in the MENA region. The literature search identified 160 studies from 18 countries from 1980 to 2019. The overall prevalence of rotavirus, norovirus, adenovirus, astrovirus, and sapovirus were 29.8 %, 13.9 %, 6.3 %, 3.5 %, and 3.2 % of tested samples, respectively. The most common rotavirus genotype combinations in the MENA region were G1P[8], G9P[9], and G2P[4], whereas GII.4 was the predominant norovirus genotype all of which were reported in almost all the studies with genotyping data. The comparison of VP7 and VP4 between circulating rotavirus in the MENA region and vaccine strains has revealed discrete divergent regions, including the neutralizing epitopes. Rotavirus vaccine was introduced to most of the countries of the MENA region; however, only a few studies have assessed the effectiveness of vaccine introduction. This paper provides a comprehensive update on the prevalence of the different viral agents of AGE in the MENA region.

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## 1. Introduction

Acute Gastroenteritis (AGE) is a common cause of gastrointestinal diseases in both developed and developing countries. It is characterized by inflammation of the stomach, small intestine, or large intestine accompanied by symptoms including diarrhea, fever, vomiting, abdominal cramps, lethargy, dehydration, and nausea [1]. Annually there are more than four million episodes and around 34,000 deaths due to diarrheal diseases in the MENA region [2]. Further, diarrhea is the second leading cause of preventable death in

children under five years of age [3], [4]. Different bacterial, viral, or parasitic agents are known to cause AGE; however, most AGE cases, particularly in children, result from viral infections [5]. The most common viruses associated with AGE are rotavirus, norovirus, astrovirus, adenovirus, and sapovirus. The transmission of infectious AGE occurs via various routes, but primarily the fecal-oral route is the main route of disease spread [6]. The features of the most common viral agents of AGE are shown in Fig. 1.

Rotavirus belongs to the *Reoviridae* family. It is a non-enveloped virus consisting of 11 segments of double-stranded RNA (dsRNA) genome enclosed by a triple-shelled capsid; these segments encode six nonstructural and six structural viral proteins [7]. The middle layer protein VP6 determines the group and subgroup specificity of rotavirus. To date, nine rotavirus serogroups have been described, A through I, four of which (groups A, B, C, and H) are capable of infecting humans [7,8]. Group A is the most important clinically as it is

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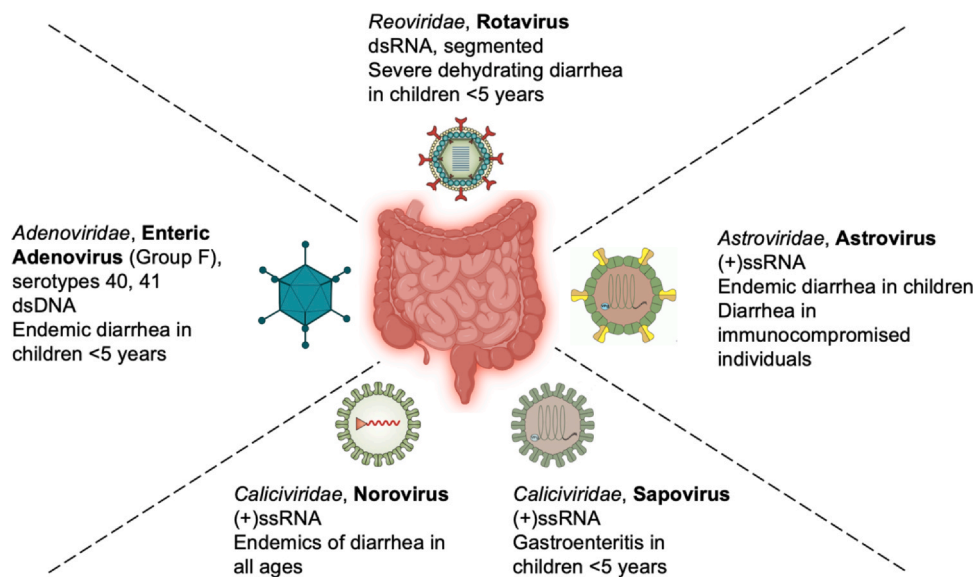


Fig. 1. The common viral agents of acute gastroenteritis and their features.

the primary cause of severe gastroenteritis in children below five years of age in both developed and developing countries [9]. Rotavirus group A is further classified based on outer capsid proteins VP7 (G protein) and VP4 (P protein) that elicit neutralizing antibodies. Currently, there are 37G (G1-G37) and 51P (P[1]-P[51]) rotavirus genotypes recognized in humans and animal species [10]. Globally, G1, 2, 3, 4, and 9 combined with P[4] or P[8] form the most common genotypes in humans [11].

Norovirus is the most common causative agent of AGE in all age groups worldwide and is associated with sporadic cases and AGE outbreaks in different settings. Moreover, in countries with high rotavirus vaccine coverage, norovirus replaced rotavirus as the leading cause of pediatric AGE [6–8]. Norovirus belongs to the *Caliciviridae* family and harbors a positive-sense single-stranded RNA genome. Norovirus is genetically classified into ten different genogroups (G1–GX), depending on the VP1 capsid sequences, of which GI, GII, and GIV are known to infect humans [12]. Multiple genotypes have been identified within these genogroups, where GII.4 is the most significant genotype and has caused many pandemics. Through its continuous antigenic drift, new variants of GII.4 arise every two to three years [13,14]. In addition, a new GII.17 genotype has emerged worldwide and has become the predominant genotype in several countries [15].

Human adenoviruses are members of the genus *Mastadenovirus* of the *Adenoviridae* family, which contains seven known species, A to G, which can cause a broad spectrum of diseases. Human adenovirus is the largest non-enveloped, double-stranded, linear DNA virus [16]. Adenovirus species F, types 40 and 41, are associated with gastroenteritis hence the name enteric adenoviruses. Enteric human adenovirus is the third leading cause of non-bacterial diarrhea among children and is associated with sporadic disease and outbreaks of acute diarrhea [17,18].

Astroviruses are small non-enveloped viruses harboring a single-stranded, positive-sense RNA genome belonging to the *Astroviridae* family [19]. After rotavirus, astrovirus is considered the second most common cause of AGE in children that present with mild infections [20]. It is also known to cause diarrhea in the elderly and immunocompromised patients [21].

Sapovirus belongs to the genetic cluster (genus) in the *Caliciviridae* family, which harbors a positive-sense, single-stranded RNA genome. Like norovirus, sapovirus can cause AGE sporadically

or in outbreaks among people of all ages but does not usually require hospitalization since the symptoms are generally mild [22].

This article aims to further the knowledge of the common viral agents associated with AGE in the MENA region among children and adults through a comprehensive update on the prevalence and molecular epidemiology of AGE viruses. Also, this paper examined the phylogenetic diversity of rotavirus, compared the VP7 and VP4 antigenic regions of rotavirus from MENA countries with vaccine strain, and discussed the availability of rotavirus vaccine in the MENA region.

## 2. Method

### 2.1. Search strategy

For this paper, an extensive literature search was conducted using PubMed, ScienceDirect, and Google scholar for all the studies published online reporting the causative agents of viral gastroenteritis in countries of the MENA region between January 1980 and December 2019. Search keywords included: viral gastroenteritis, rotavirus, norovirus, adenovirus/enteric adenovirus/adenovirus 40/41, astrovirus, and sapovirus. The list of references from relevant studies was hand-searched to expand the search further to include additional articles.

### 2.2. Inclusion and exclusion criteria and data extraction

All studies that reported the etiology of viral gastroenteritis in children and/ or adults in the MENA region using different detection methods were considered for this paper. Studies were excluded if they were in languages other than English, not between 1980 and 2019, conference or review papers, community-based, and reported nosocomial infections or an outbreak. For each study, the following information was extracted: first author, publication year, country, study period, age of patients, sample size, detection method, number of positive samples, rotavirus G and P types combination, and NoV genotypes (if reported). The pooled prevalence data were stratified by age (children/ adults), detection method, and reporting countries. The mean prevalence data were presented by taking the mean of the percentage prevalence of all studies reporting the prevalence of the different etiological agents. Similarly, age, detection method,

countries, rotavirus genotypes, and NoVgenotypes were represented as mean percentages. Studies reporting rotavirus G-P combinations and NoV genotypes were categorized by country.

### 2.3. Phylogenetic and sequence analysis

Nucleotide and amino acid sequences for the two rotavirus segments VP4 and VP7 from the MENA region were retrieved from the rotavirus database available at the NCBI Virus variation resource [23]. The most recent sequences with partial length available for each country were selected. Briefly, multiple sequence alignments were performed using CLUSTAL W in MEGA X software [24]. The phylogenetic analysis was also conducted in MEGA X using the Kimura2 parameter model and neighbor-joining method for tree construction [25,26]. The statistical significance was assessed by bootstrapping analysis with 1000 pseudoreplicates. The sequences of Rotateq and Rotarix vaccine strains and the representative strains were accessed from GenBank.

## 3. Results

### 3.1. Characteristics of included studies

The literature search identified a total of 160 articles that met the inclusion criteria. These studies were conducted between 1980 and 2019, with a duration varying between 1 month to 10 years, and included both children and adults. Data on the prevalence of viral gastroenteritis was available from the following countries: Bahrain [27,28], Egypt [29–45], Iran [46–67], Iraq [68–91], Israel [92–99], Jordan [100–107], Kuwait [108–113], Lebanon [114–121], Libya [122–129], Morocco [130–133], Oman [134–137], Palestine [138], Qatar [139–142], Saudi Arabia [143–161], Sudan [162–168], Tunisia [169–179], United Arab Emirates (UAE) [180–182], and Yemen [183–186]. The specimens were mostly tested by enzyme-linked immunosorbent assay (ELISA), enzyme immunoassay (EIA), and polymerase chain reaction (PCR), among other methods like immunochromatography (IC), latex agglutination (LA), polyacrylamide gel electrophoresis (PAGE), and electron microscopy (EM).

### 3.2. Etiology of viral gastroenteritis

Out of the 160 selected studies, 134 (83.8 %) reported the prevalence of rotavirus, while about two-thirds of the studies reported norovirus (28.1 %) and adenovirus (26.9 %) prevalence. Astrovirus and sapovirus were reported in 30 (18.8 %) and 7(4.4 %) studies, respectively. Overall, the most common virus associated with gastroenteritis was rotavirus, with a pooled prevalence of 28.9 % (95 % CI 26.5, 31.4), followed by norovirus 13.9 % (95 % CI 11.0, 16.9), adenovirus 6.3 % (95 % CI 4.3, 8.3), astrovirus 3.5 % (95 % CI 0.9, 8.0), and sapovirus 3.2 % (95 % CI 0.0, 8.0) as depicted in Table 1 and Fig. 2A.

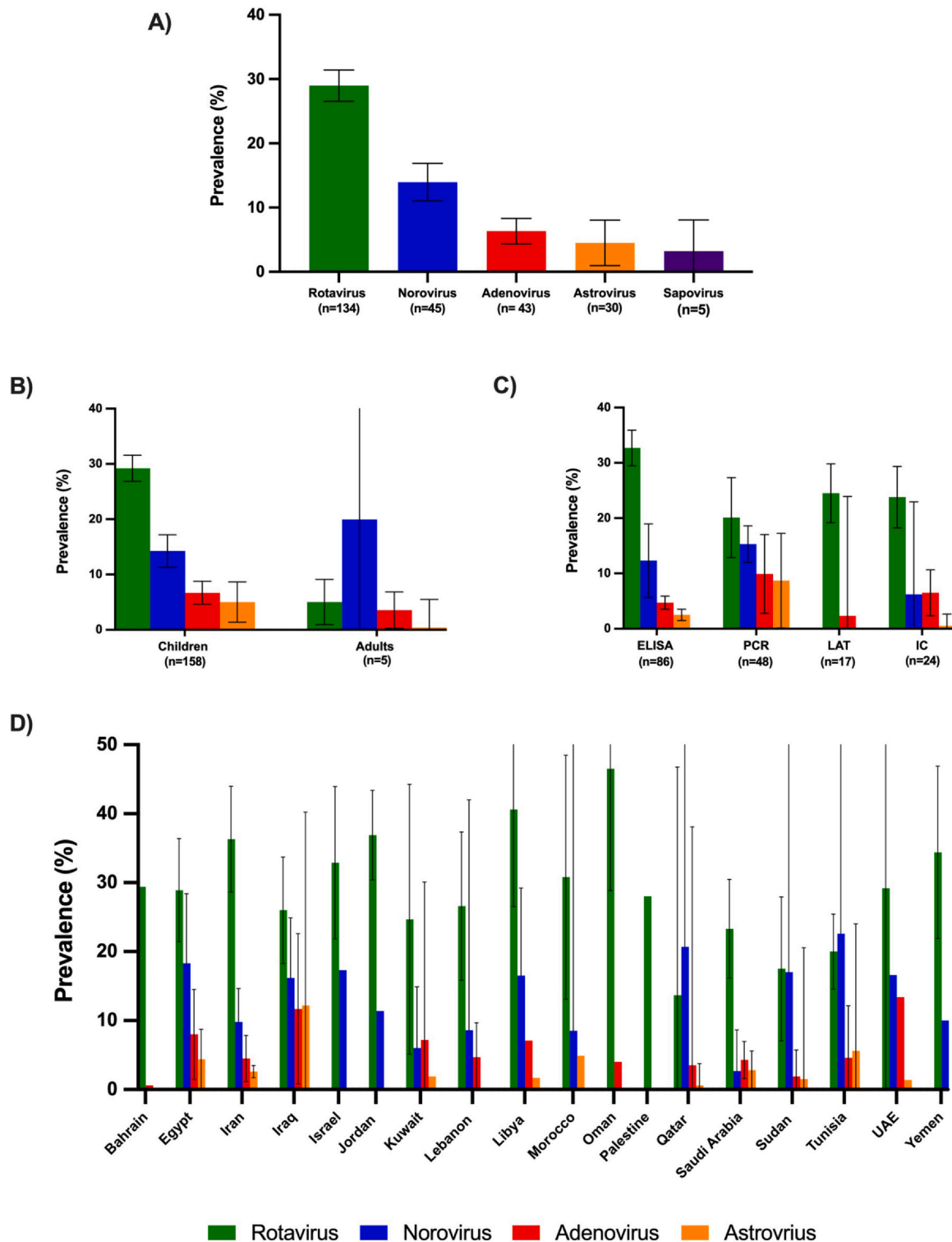
### 3.3. Etiological agents stratified by age, detection method, and country

A large majority of the studies (98.8 %) focused on children under five years, while only 11 studies involved adults. However, in the final analysis, the prevalence by age for adults was obtained from 5 studies because precise age data was not reported in 6 studies. As shown in Table 2 and Fig. 2B, the prevalence of rotavirus (29.2 %), adenovirus (6.7 %), and astrovirus (5.0 %) were significantly higher in children compared to adults. In comparison, norovirus was more prevalent in adult patients (20 %) compared to children (14.2 %). Among adult patients, the detection rates of rotavirus, adenovirus, and astrovirus were 5 %, 4 %, and 0.4 %, respectively.

Regarding diagnostics, most studies relied on ELISA or EIA to detect rotavirus infection yielding the highest detection rate (32.7%),

**Table 1**  
Overall prevalence (%) of the common etiological agents of viral gastroenteritis in the MENA region.

Virus	Number of studies	Prevalence (95% CI)	Reference
Rotavirus	134	28.9 (26.5, 31.4)	[27,28,30–33,35–38,40–44,47–49,51,53,54,58–61,64,65,67–70,72–75,77,79–82,84,87,89,90,92–95,97,99–110,112–116,118–128,130,132–140,142,144–173,175–177,179–181,183–186]
Norovirus	45	13.9 (11.0, 16.9)	[27,32,33,36,40,41,43,45,46,56–58,65,66,71,76,78,83,84,86,87,90,91,96,98,105,111–113,116,117,124,125,131,132,139–141,146,150,161,167,168,173,174,178,184]
Adenovirus	43	6.3 (4.3, 8.3)	[27,132,133,140–43,148,152,158,159,161,73,179,180,182,184,186,187,100,109,112,113,116,119–121,125,134,139,143,145,41,150,153,155,161,162,167,171–173,182]
Astrovirus	30	3.5 (0.9, 8.0)	[29,132–34,36,41,42,48,52,58,82,84,86,87,90,113,116,1116,1125,132,139,140,145,146,150,153,167,172,173,182]
Sapovirus	7	3.2 (0.0, 8.0)	[85,185,116,1132,140,173,182]



**Fig. 2.** Mean prevalence (%) of viral gastroenteritis in the MENA region stratified by **A)** The different viral agents, **B)** Age, **C)** Detection method, and **D)** Reporting countries. EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; PCR, polymerase chain reaction; RT-PCR, reverse transcription- polymerase chain reaction; IC, immunochromatography; LAT, latex agglutination; n, represent number of studies.

while RT-PCR, LA, and IC showed comparable detection rates (about 25 %). Whereas for norovirus, the most utilized detection method was RT-PCR, with the highest detection rate (15.3 %) compared to other detection methods. RT-PCR detected more adenovirus and astrovirus infections than the other methods (Table 2 and Fig. 2C).

Country wise, most of the studies were from Iraq (n = 24), Iran (n = 20), Saudi Arabia (n = 19), and Egypt (n = 17). All the 18 countries

included in this paper have reported the prevalence of rotavirus in at least one study. Moreover, apart from Bahrain, Oman, and Palestine, all the included countries within the MENA region reported norovirus prevalence. Thirteen countries have reported the prevalence of adenovirus, while 12 countries reported the prevalence of astrovirus. Regarding the prevalence of rotavirus, Qatar has reported the lowest mean prevalence (14 %), followed by Sudan (18%) and Tunisia

**Table 2**  
Summary of the studies (n = 160) reporting the prevalence of viral gastroenteritis in the MENA region.

	No. Of Studies	Rotavirus	Norovirus	Adenovirus 40/41	Astrovirus
<b>Age</b>					
Children	158	29.2 (26.9, 31.6) <sup>a</sup>	14.2 (11.3, 17.2)	6.7 (4.6, 8.8)	5.0 (1.4, 8.7)
Adults	5	5.0 (0.9, 9.1)	20.0 (0.0222.6)	3.6 (0.3, 6.8)	0.4 (0.0, 5.5)
<b>Detection Method</b>					
EIA/ELISA	86	32.7 (29.5, 35.9)	12.3 (5.7, 19.0)	4.7 (3.5, 5.9)	2.5 (1.4, 3.5)
PCR/RT-PCR	48	20.1 (12.9, 27.3)	15.3 (11.9, 18.6)	9.9 (2.8, 17.0)	8.7 (0.1, 17.2)
LAT	24	24.5 (19.1, 29.8)	–	2.3 (0.0, 23.9)	–
IC	17	23.8 (18.3, 29.4)	6.2 (0.0, 22.9)	6.5 (2.4, 10.7)	0.5 (0.0, 2.7)
<b>Country (period)<sup>b</sup></b>					
Bahrain (1998–2007)	2	22.2 (19.5, 25.1)	–	0.6 (0.2, 1.6)	–
Egypt (1995–2019)	17	28.9 (21.4, 36.4)	18.3 (8.7, 28.4)	8.0 (1.4, 14.5)	4.4 (0.0, 8.7)
Iran (2001–16)	20	36.3 (28.6, 43.9)	9.8 (4.9, 14.6)	4.5 (1.2, 7.9)	2.6 (1.7, 3.5)
Iraq (1998–2019)	24	26.0 (18.3, 33.7)	16.2 (7.5, 25.0)	11.7 (0.8, 22.6)	12.2 (0.0, 40.2)
Israel (2003–13)	9	32.9 (21.8, 43.9)	17.3	–	–
Jordan (1992–2008)	7	36.9 (30.4, 43.5)	11.4	–	–
Kuwait (1980–2017)	6	24.7 (5.1, 44.3)	6.0 (0.0, 14.8)	7.2 (0.0, 30.1)	1.9
Lebanon (2007–18)	8	26.6 (15.8, 37.4)	8.6 (0.0, 42.1)	4.7 (0.0, 9.6)	0.0
Libya (2000–13)	8	40.6 (26.5, 54.7)	16.5 (3.8, 29.2)	7.1	1.7
Morocco (2006–13)	4	30.8 (13.1, 48.5)	8.5 (0.0, 105.7)	–	4.9
Oman (1990–2013)	4	48.5 (47.5, 49.5)	–	4.0 (1.9, 7.7)	–
Palestine (2005)	1	28.0 (21.0, 35.9)	–	–	–
Qatar (2009–19)	4	13.7 (0.0, 46.8)	20.7 (0.0, 56.5)	3.5 (0.0, 38.2)	0.6 (0.0, 3.7)
Saudi Arabia (1992–2017)	19	23.3 (16.2, 30.5)	2.7 (0.0, 8.6)	4.3 (1.6, 7.0)	2.8 (0.0, 5.6)
Sudan (2006–17)	8	17.5 (7.1, 28.0)	17.0 (0.0, 167.5)	1.9 (0.0, 5.7)	1.5 (0.0, 20.6)
Tunisia (1995–2017)	12	20.0 (14.6, 25.4)	22.6 (0.0, 53.5)	4.6 (0.0, 12.2)	5.6 (0.0, 24.0)
UAE (1990–2019)	3	19.8 (17.2, 22.5)	16.7 (12.5, 21.6)	13.4 (9.6, 18.0)	1.4 (0.4, 3.7)
Yemen (2006–14)	4	34.4 (21.9, 46.9)	10.0	–	–

EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; PCR, polymerase chain reaction; RT-PCR, reverse transcription- polymerase chain reaction; IC, immunochromatography; LAT, latex agglutination

<sup>a</sup> Values represent mean prevalence (95 % CI)

(20 %). On the other hand, the highest prevalence was observed in Oman (47 %), followed by Libya (41 %) and Jordan (37 %). The reported prevalence of norovirus ranged from 3% as reported in Saudi Arabia and 18 % in Egypt. Across all the countries, adenovirus and astrovirus were less frequently detected; with the most prevalence rate of adenovirus found in UAE (13 %), followed by Iraq (12 %); while astrovirus was most prevalent in Iraq (12 %) and the UAE (6 %). The results are shown in [Table 2](#) and [Fig. 2](#)D.

### 3.4. Distribution of rotavirus G and P genotype combinations

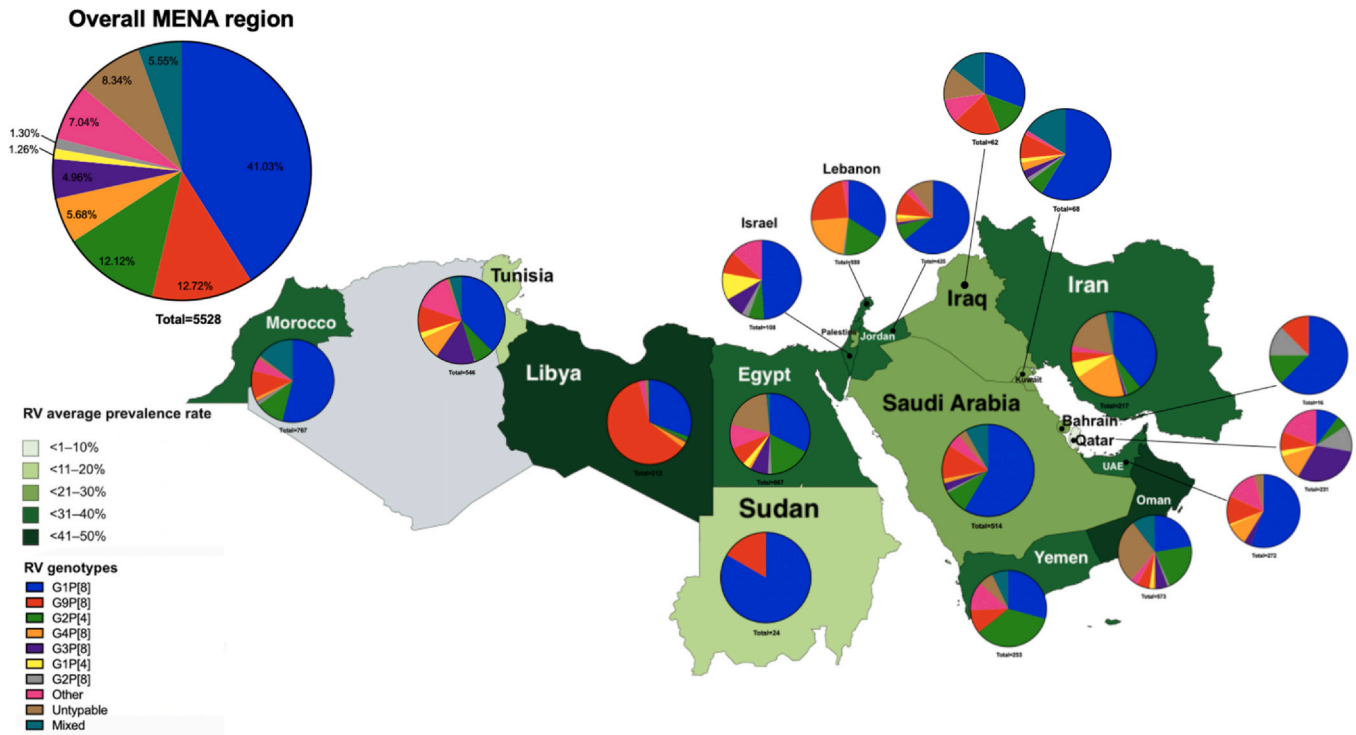
Of the 160 studies, 42 studies reported the distribution of G and P types of rotavirus. These studies were reported from 17 countries between 1995 and 2019, most of which used RT-PCR for genotyping. Overall, a total of 5528 rotavirus strains were detected in the MENA region, with eight different G types (G1–G5, G8, G9, and G12) and six P types (P [4], P [6], P [8]–P [10], and P [14]) forming at least 28 different G–P genotype combinations ([Table S.1](#) and [Fig. 3](#)). As shown in [Fig. 3](#), the overall distribution of rotavirus genotype combinations, where G1P[8] (2268, 41 %) was the most common genotype, followed by G9P[8] (703, 12.7 %), G2P[4] (670, 12.1 %), G4P[8] (314, 5.7 %), and G3P[8] (274, 5 %). G1P[4] (82, 1.2 %) and G2P[8] (71, 1.3 %) were also identified but at a lower frequency. Furthermore, rare genotype combinations (each with frequency < 1%), untypable and partially typable genotypes, and mixed genotypes accounted for 7 % (n = 372), 8 % (n = 448), and 5 % (n = 285), respectively. It is worth noting that the four globally common G–P combinations (namely, G1P[8], G2P[4], G3P[8], and G9P[8]) accounted for 71 % of all the circulating genotypes in the MENA region, however, when these global G–P combinations were broken down by country certain variations in the distribution were observed. For instance, these four common combinations in Egypt, Iran, Iraq, Oman, and Qatar showed lower frequency ranging from 49 % to 65 %. On the other hand, higher frequencies (< 80 %) of these common genotypes were observed in Sudan (100 %), Libya (93 %) and Bahrain (88 %). Notably, G1P[8] and G9P[8] were detected across all the countries within the

MENA region, although the proportion varied depending on the countries. In addition to the common genotypes, unusual G and P combinations were also observed in at least six countries, including G1P[6], G12P[8], G3P[4], G9P[6], and G9P[4], collectively accounting for 3 % of the identified genotypes. The proportion of these unusual genotypes was higher in Israel and Iraq than in Yemen and Morocco. The percentage of mixed genotypes was reported in 9 countries, ranging from 16% in Kuwait to 0.5 % in Libya. Meanwhile, the percentage of untypable (or partially typable) G and P genotypes was reported in 10 countries, with the highest percentage in Oman (28%) and the lowest in the UAE (1%).

The temporal distribution of the circulating rotavirus genotypes was analyzed in seven countries, reporting 20 studies conducted over different periods, as depicted in [Fig. 4](#). G1P [8] was the dominant genotype across each period in Egypt, Lebanon, Saudi Arabia, and Tunisia over at least ten years; but, the proportion of G1P[8] varied over time and between the countries. For instance, in Iran and Yemen, the proportion of G1P[8] substantially declined from 58 % to 9 % and from 51 % to 19 %, respectively. G9P[8] was detected in periods in the seven countries (except Iran 2004–2008, Oman 2005 and 2006–2008), which relatively increased or remained constant, except in Yemen. Similarly, G2P[4] was detected across all the periods in the seven countries (except Egypt 2010–2012, 2015–2016, and Iran 2004–2008); however, it relatively decreased or remained constant, except in Tunisia and Yemen. G4P[8] slightly increased in Iran, Saudi Arabia, and Tunisia over time but decreased in Lebanon. The emergent G12 with P[6] or P[8] was initially reported in Egypt in 2006 and 2007; moreover, it was also detected in Iran, Israel, Lebanon, Oman, Saudi Arabia, Tunisia, and Yemen (data not shown).

### 3.5. Distribution of NoV genotypes

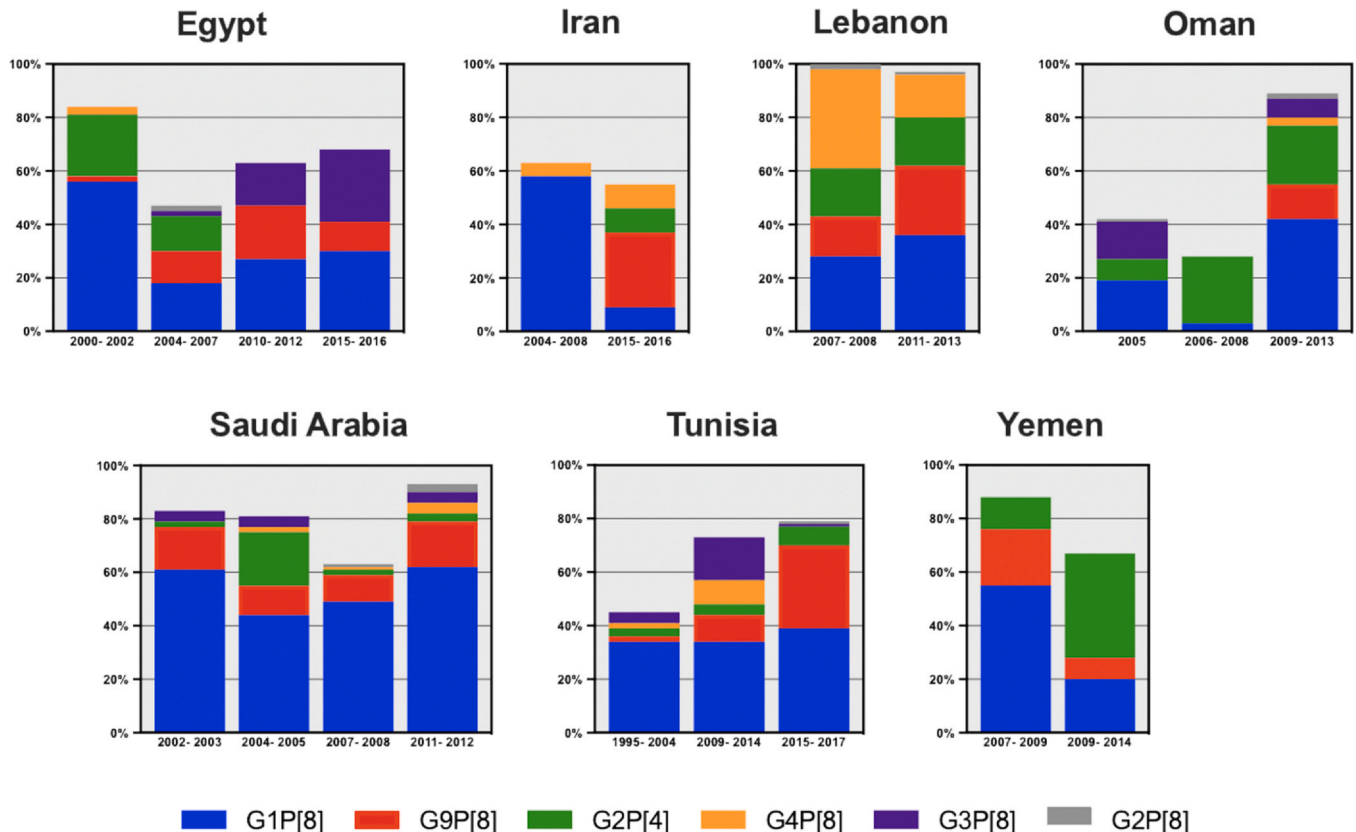
Data on the circulating norovirus genotypes was available for 12 countries reporting a total of 14 studies [33], [56], [78], [91], [96], [105], [111], [117], [124], [131], [141], [174], [178], [184]. The summary proportions for each genotype are shown in [Fig. 5](#) and [Table](#)



**Fig. 3.** Geographical distribution of rotavirus G and P genotype combinations in the MENA region. Other include rare genotypes (overall proportion <1%). Mixed represent infections with multiple G and/or P genotypes. Untypable include untypable samples for G and/or P genotypes.

S.2. These studies were conducted between 2003 and 2018 and described 28 genotypes, where 11 genotypes belonged to GI genogroup and 17 to GII genogroup. Overall, GII.4 was the most common and

widely distributed genotype reported in all the countries (n = 12) and represented 54% of all norovirus genotypes. GII.4 was the predominant genotype in all the reporting countries apart from Jordan



**Fig. 4.** Temporal distribution of rotavirus G and P genotypes observed in selected countries across the MENA region.

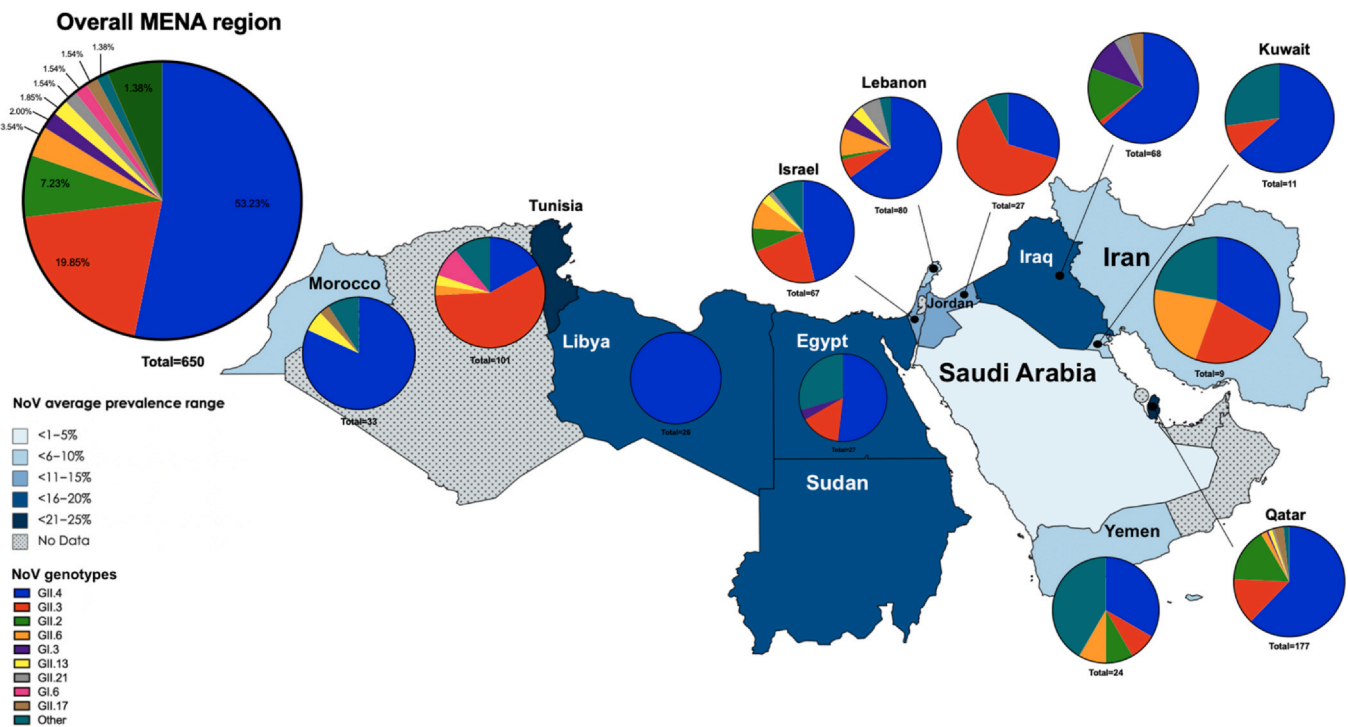


Fig. 5. Geographical distribution of norovirus genotypes in the MENA region. Other include less-common genotypes.

and Tunisia. The second most common genotype was GII.3, which was detected in 10 countries accounting for 20 % of detected norovirus genotypes, and was the predominant genotype in Jordan and Tunisia. GII.2 and GII.6 accounted for 10 % of all the genotypes and were reported in 5 and 6 countries, respectively. Other norovirus genotypes were detected in a few countries (at least four countries) with lower prevalence (< 2 % each), including GI.3, GII.13, GII.1, GII.21, and GI.6.

### 3.6. Phylogenetic analysis of circulating rotavirus strains in the MENA region

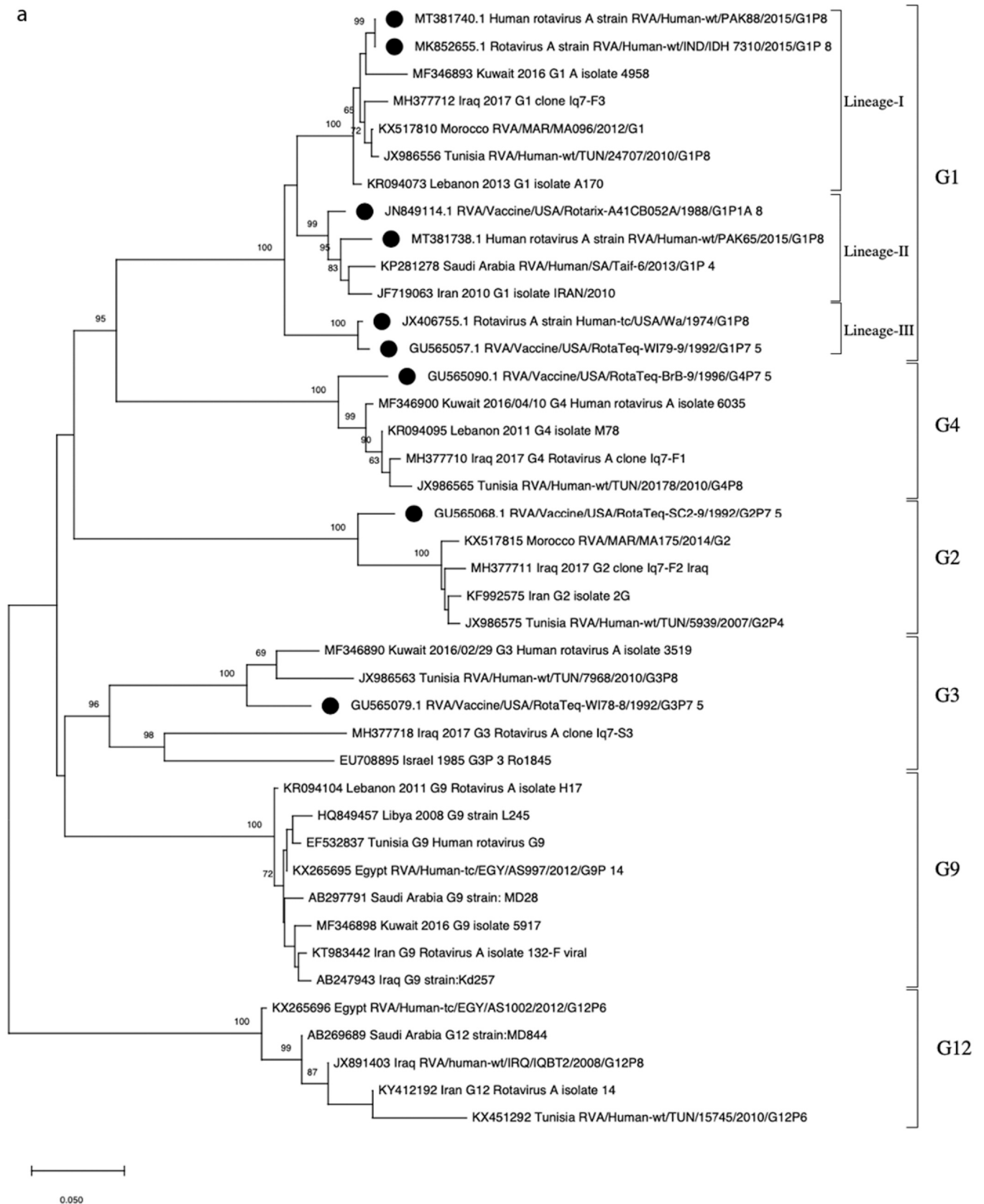
Phylogenetic analysis was performed on partial-length nucleotide sequences of VP7 and VP4 genes available from 10 countries of the MENA region (namely, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Saudi Arabia, and Tunisia). The G1, G2, G3, G4, G8, G9, and G12 VP7 tree was constructed based on 32 strains from the MENA region in addition to 4 representative strains and five vaccine strains (Fig. 6A). The lineages of the specific genotypes were assigned based on previous literature [187]. The G1 strains from the MENA region clustered in two lineages (lineage I and III), while the Rotarix and Rotateq vaccine strains clustered in lineage II and III, respectively. Lineage I encompassed most of the G1 strains of the MENA region, including strains from Kuwait (2016), Iraq (2017), Morocco (2012), Tunisia (2010), and Lebanon. G1-lineage III consisted of two strains (Saudi Arabia 2013 and Iran 2010) co-clustered with a strain from Pakistan reported in 2015. Within the G2 strains, limited genetic diversity was observed; however, these sequences were collected from different countries (Morocco, Iraq, Iran, and Tunisia) in different years (2007, 2014, and 2017); also, these sequences showed close similarity with the Rotateq vaccine strain (SC2–9). Of the four G3 strains, two strains (Kuwait 2016 and Tunisia 2010) clustered closely with Rotateq vaccine strain (WI78–8), while the strains from Iraq (2017) and Israel (1985) clustered together. G4 strains of the MENA region clustered closely with Rotateq vaccine strain (BrB–9). The G9 strains from Tunisia, Libya (2008), and Egypt (2012) were phylogenetically distinct from those isolated from Saudi

Arabia, Kuwait (2016), Iran, and Iraq. There was significant genetic diversity among the G12 strains from the MENA region.

The P[4] and P[8] VP4 phylogenetic tree was constructed based on 16 strains from the MENA region with eight representative and two vaccine strains (Fig. 6B). The P[4] component of the selected sequences of the MENA region clustered into three distinct lineages II, IV, and V. The strains clustering in P[4]-lineage II (Lebanon 2012 and Iraq 2017) showed close similarity with a Japanese strain reported in 2016. Four P[4] strains from the MENA region clustered into lineage IV, in which the strain from Saudi Arabia (2013) grouped closely with the strain isolated from India in 2013, while the strains from Iran, Morocco (2012), and Tunisia (2006) clustered together. Lineage V of P[4] consists of a strain from Kuwait (2016) clustered with a strain from Pakistan isolated in 2016. The P[8] strains from the MENA region clustered into lineage III and IV. The Rotarix and Rotateq belong to lineages I and II, respectively. The majority of the P[8] strains clustered into lineage III, where the strains from Saudi Arabia, Iran (2013), and Iraq (2017) clustered closely with the USA (2011) strain. The strains from Lebanon (2013), Morocco (2009), and Tunisia (2012) grouped closely with a strain isolated from Pakistan in 2015 (PAK37), while the strain from Kuwait (2016) clustered with another strain isolated from Pakistan in 2015 (PAK88). Two strains (Jordan 2007 and Israel 2010) were placed into P[8]-lineage IV, which also comprises a strain reported from Pakistan (PAK65/2015).

### 3.7. Comparison of the VP7 and VP4 antigenic epitopes of rotavirus strains from the MENA region and vaccine strains

Variations between the circulating rotavirus strain within the MENA region and the antigenic epitopes of the VP7 and VP4 proteins could potentially influence the effectiveness of rotavirus vaccines. Therefore, such variations were investigated by comparing the neutralizing epitopes on the VP7 and VP4 of amino acid sequences of rotavirus strains in the MENA region and vaccine strains. The VP7 protein contains two antigenic epitopes, 7–1 (7–1a and 7–1b) and 7–2, which encompass 29 amino acids as depicted in Fig. 7A [188]. The analysis showed that out of 29 amino acids within the VP7



**Fig. 6.** Neighbor-joining phylogenetic tree of partial length VP7 (A) VP4 (VP8\*) (B) nucleotide sequences reported in the MENA region. Representative and vaccine strains are marked with black filled circle. The trees were generated using the Kimura-2-parameter model in MEGA X software. Bootstrap (1000 replicates) values above or equal to 60 are shown above the branches. Scale bar:0.05 base substitution per site.



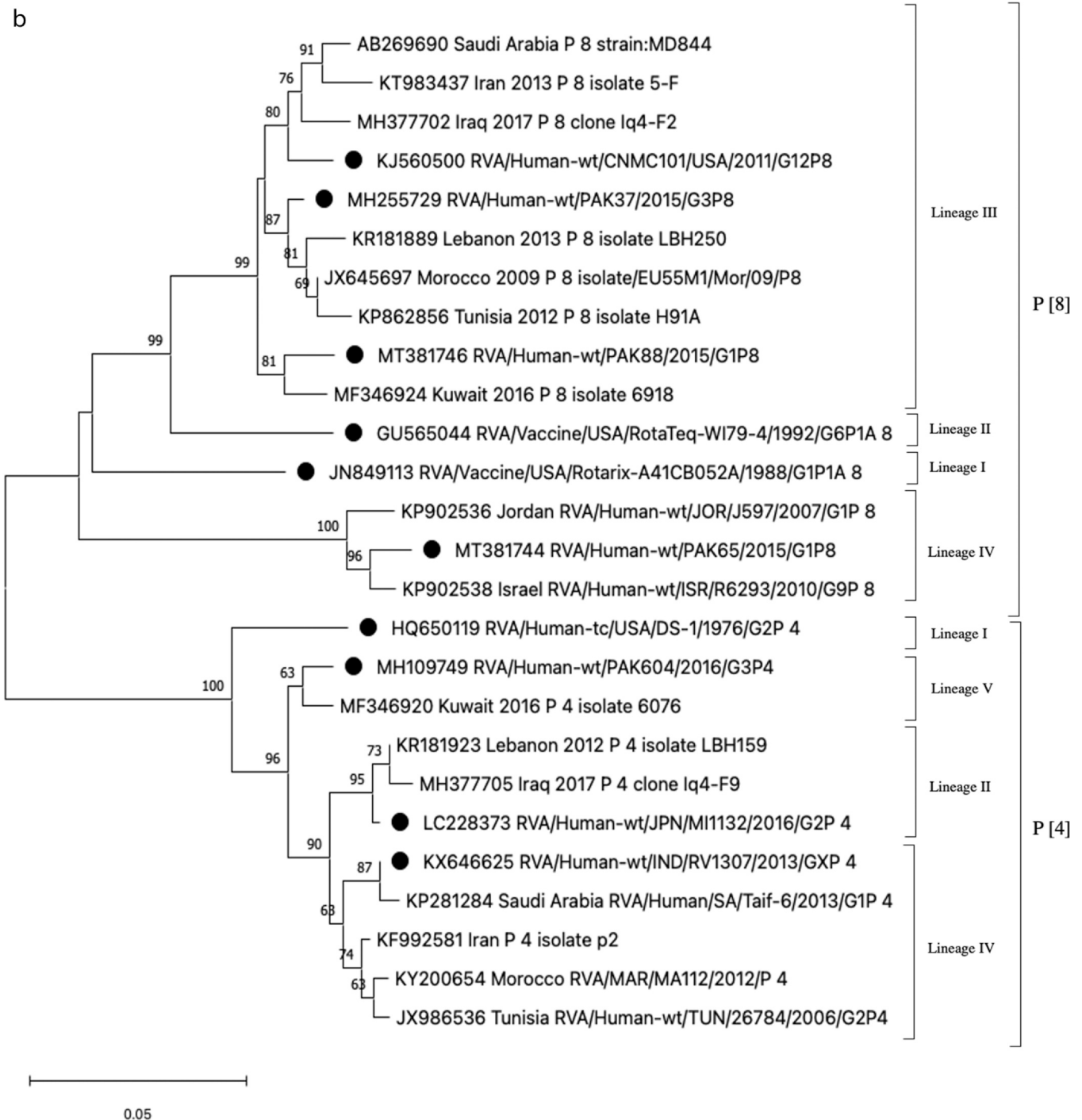


Fig. 6. (continued)

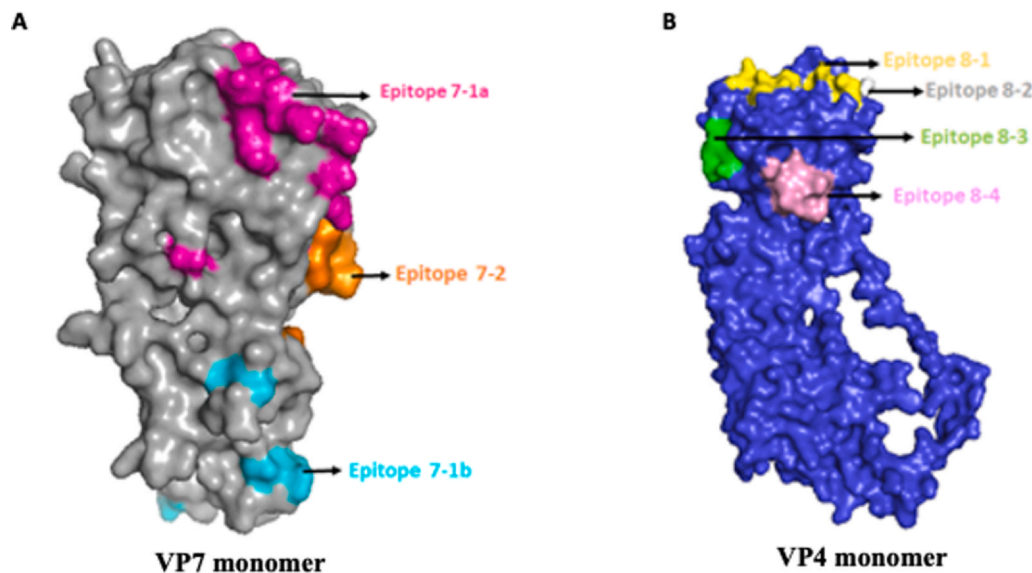
antigenic epitopes, only four (positions: 98, 104, 201, and 246) were conserved among all the strains from the MENA region compared to the vaccine strains (Fig. 8A).

The G1 strains of the MENA region showed up to seven differences in comparison with both vaccine strains and two differences with the G1 strain of Rotateq (WI79-9). The epitope 7-1b was more conserved than 7-1a and 7-2, containing only one amino acid substitution (V212T). All the analyzed G1 strains had the substitutions D97E and S147N in epitope 7-1a and 7-2, respectively, compared with the Rotateq G1 vaccine strain (WI79-9).

The antigenic epitopes of the G2 strains from the MENA region showed up to three amino acid differences with both vaccine strains

(G/D96N, K291R, and T/S242N). In comparison with the G2 strain of Rotateq (SC2-9) all the G2 strains of the MENA region contained two amino acid differences within the 7-1a (A87T) and 7-1b (S213D) epitopes. In contrast, all the G2 strains from the MENA region differed in 16 amino acid residues from the Rotateq G2 vaccine strain (SC2-9); these differences were in the three epitope regions, mostly 7-1a and 7-2.

The G3 strains from the MENA region showed 2-5 (per strain) amino acid differences with both strains of Rotarix and Rotateq (WI78-9). There were 7-10 amino acid differences between the G3 strains from the MENA region and the G1 strain of Rotarix vaccine. The differences were found in the three antigenic regions. Compared



**Fig. 7.** Protein structure analysis and modeling of VP7 and VP4 from RV G1P [8] strains. The model was built using the UCSF Chimera-Molecular Modeling System v1.11. (A) Antigenic sites of VP7 are distributed in three main epitopes (7–1a, 7–1b, and 7–2). (B) Antigenic sites of VP4 are distributed in four main epitopes (8–1, 8–2, 8–3 and 8–4).

with Rotateq, the G3 strains from the MENA region showed 1–2 amino acid differences in the 7–1b antigenic region.

The G4 strains from the MENA region showed the least divergence from both vaccine strains; only two differences were noted at amino acid positions D130E (epitope 7–1a) and A/D145T (epitope 7–2). The G4 strains showed up to 14 differences from the Rotarix vaccine strain in the three epitopes and only 1–2 differences for the Rotateq vaccine strain (BrB-9) in epitope 7–1b.

The G8, G9, and G12 were compared to G1 protein of Rotarix and G1 to G4 of Rotateq vaccine strains. Of note, G9 contained more conserved amino acid residues than G8 and G12. All the G8 strains from the MENA region showed four amino acid substitutions in epitope 7–1a (positions 94 and 96), 7–1b (position 213), and 7–2 (position 145) that were different from all Rotateq and the Rotarix vaccine strains. The G8 strains had up to 11 amino acid differences with the G1 of Rotarix strain (within the three epitopes) and two amino acid differences with all the Rotateq strains (epitopes 7–1a and 7–2). Interestingly, the G9 strains reported from the MENA region showed the least variations (up to 3 amino acid variations) to all vaccine strains. 11 variations in the G9 strains with the G1 strain of Rotarix spread across all the antigenic regions. In contrast, VP7 antigenic epitopes of the G12 strains from the MENA region showed the largest variations with both vaccine VP7 epitopes. Specifically, the G12 strains contained eight to nine residues that differed from both vaccine strains. The majority of these variations were located in 7–1a epitope. There were up to 9 differences found between the G12 strains of the MENA region and G1 strain of Rotarix. These differences were mapped to all three epitopes.

The VP4 protein of rotavirus is cleaved into the VP8 head and VP5 stalk that contain four (8–1–8–4) and five (5–1–5–5) antigenic regions, respectively, as depicted in Fig. 7B. Together the VP8 and VP5 contain 37 amino acid residues [189]. Most of the selected sequences from the MENA region only covered the VP8 epitope regions; therefore, the VP5 was not included in the analysis (Fig. 8B). Upon comparison with both vaccine strains, all the strains from the MENA region contained nine conserved amino acid residues in the VP8 antigenic epitopes. Moreover, epitope 8–2 of P[4] and epitope 8–4 of P[8] strains of the MENA region was completely conserved among all strains. Almost all the VP8 proteins of P[4] strains showed up to 10 amino acid differences (per strain) in comparison with both P[8] vaccine strains. These differences were located in 8–1, 8–3, and 8–4 epitopes. The P[4] strains from the MENA region showed more

differences with Rotarix (three amino acid changes: S190N, S125N, and N135D) than with Rotateq vaccine strain (one amino acid change: D196N). The comparison between the P[8] strains of the MENA region and vaccine strains showed several amino acid substitutions (four to five substitutions with respect to Rotarix, and two substitutions with respect to Rotateq) observed in epitopes 8–1 and 8–3. Most of these substitutions occurred in epitope 8–1 and to a lesser extent in epitopes 8–2 and 8–3. The P[8] strains analyzed in this study showed three to nine variations (within 8–1, 8–2, and 8–3 epitopes) from both P[8] of vaccine strains.

### 3.8. Availability of vaccine in MENA region

Rotavirus is the most common cause of vaccine-preventable diarrhea [190]. Currently, two live rotavirus vaccines are available in the market, Rotarix® (GlaxoSmithKline, Rixensart, Belgium) and Rotateq® (Merck and Co, Whitehouse Station, NJ, USA; Sanofi Pasteur MSD, Lyon, France). Rotarix (RV1) is a monovalent G1P[8], human live attenuated vaccine. On the other hand, Rotateq (RV5) is a pentavalent human-bovine vaccine containing four reassortant rotaviruses expressing VP7 protein (G1, G2, G3, or G4; human strain) and (P7[5]; bovine strain) [191]. Recently, two additional rotavirus vaccines were licensed and manufactured in India and prequalified by the WHO in 2018, Rotavac (Bharat Biotech) and RotaSiil (Serum Institute of India). Rotavac contains single rotavirus (G9P[11]) strain, while Rotasill contains five human-bovine rotavirus reassortant strains (G1–G4, and G9) [192], [193].

In the MENA region, 13 out of 19 countries (Bahrain, Iraq, Israel, Jordan, Kuwait, Libya, Morocco, Palestine, Qatar, Saudi Arabia, Sudan, UAE, and Yemen) have introduced rotavirus vaccination to national immunization programs (NIPs). Iran and Oman plan to introduce the vaccine to their NIPs, while Algeria, Egypt, Lebanon, Syria, and Tunisia have yet to decide to introduce the vaccine [194]. Among introducing countries (Table 3), Bahrain was the first to introduce the vaccine in 2008, followed by Qatar (2009), Morocco, and Israel (2010). Rotavirus vaccine was introduced most recently in Kuwait (2017) [194]. Although more than ten years have passed since the first introduction of rotavirus vaccine to the MENA region, only four studies from Israel, Morocco, and Yemen ( $n = 2$ ), respectively, have reported the impact of immunization on rotavirus hospitalization as well as rotavirus genotype distribution pre and post-vaccination [195], [133], [185], [186]. In Saudi Arabia, one study has reported the

Strain	Epitope 7-1a										Epitope 7-1b						Epitope 7-2												
	87	91	94	96	97	98	99	100	104	123	125	129	130	291	201	211	212	213	238	242	143	145	146	147	148	190	217	221	264
Rotarix-A41CB052A-G1P1A[8]	T	T	N	G	E	W	K	D	Q	S	V	V	D	K	Q	N	V	D	N	T	K	D	Q	N	L	S	M	N	G
RotaTeq-W179-9-G1P7[5]	T	T	N	G	E	W	K	D	Q	S	V	V	D	K	Q	N	V	D	N	T	K	D	Q	S	L	S	M	N	G
AEF01215/Iraq/2010/G1	T	T	N	G	E	W	K	D	Q	S	V	V	D	K	Q	N	V	D	N	T	K	D	Q	N	L	S	M	N	G
AYU56533/Iraq/2017/G1	T	T	S	G	E	W	K	D	Q	N	V	V	D	-	Q	N	V	D	N	T	K	D	Q	N	L	S	T	N	G
ASY08025/Kuwait/2016/G1	T	T	S	G	E	W	K	D	Q	N	V	V	D	K	Q	N	V	D	N	T	K	D	Q	N	L	S	T	N	G
ALK28219/Lebanon/2013/G1	T	T	S	G	E	W	K	D	Q	N	V	V	E	R	Q	N	V	D	N	T	K	D	Q	N	L	S	T	N	G
APO16141/Morocco/2012/G1	T	T	S	G	E	W	K	D	Q	N	V	V	D	-	Q	N	T	D	N	T	K	D	Q	N	L	S	T	N	G
ALD51916/Saudi_Arabia/2013/G1	T	T	N	G	E	W	K	D	Q	S	V	V	D	-	Q	N	V	D	N	T	K	D	Q	N	L	S	M	N	G
AFW04523/Tunisia/xxxx/G1	T	T	S	G	E	W	K	D	Q	N	V	V	D	-	Q	N	T	D	N	T	K	D	Q	N	L	L	T	N	-
RotaTeq-SC2-9-G2P7[5]	A	N	S	D	E	W	E	N	Q	D	T	M	N	K	Q	D	V	S	N	S	R	D	N	T	S	D	I	S	G
AHL27868/Iraq/xxxx/G2	T	N	S	N	E	W	E	N	Q	D	T	M	N	R	Q	D	V	D	N	N	R	D	N	T	S	D	I	S	G
AYU56532/Iraq/2017/G2	T	N	S	N	E	W	E	N	Q	D	T	M	N	-	Q	D	V	D	N	N	R	D	N	T	S	D	I	S	-
ALK28228/Lebanon/2012/G2	T	N	S	N	E	W	E	N	Q	D	T	M	N	K	Q	D	V	D	N	N	R	D	N	T	S	D	I	S	G
APO16146/Morocco/2014/G2	T	N	S	N	E	W	E	N	Q	D	T	M	N	-	Q	D	V	D	N	N	R	D	N	T	S	D	I	S	G
AFW04542/Tunisia/xxxx/G2	T	N	S	N	E	W	E	N	Q	D	T	M	N	-	Q	D	V	D	N	N	R	D	N	T	S	D	I	S	-
RotaTeq-W178-9-G3P[5]	T	T	N	N	S	W	K	D	Q	D	A	V	D	K	Q	D	A	N	K	D	K	D	A	T	L	S	E	A	G
AYU56539/Iraq/2017/G3	N	T	N	N	S	W	K	D	Q	D	A	V	D	-	Q	D	A	T	D	A	K	D	A	T	M	S	E	A	-
ACH97400/Israel/1985/G3	T	T	N	N	S	W	K	D	Q	D	A	V	D	K	Q	D	V	S	D	T	K	D	A	A	L	S	E	T	G
ASY08022/Kuwait/2016/G3	T	T	N	N	S	W	K	D	Q	D	A	V	D	K	Q	D	T	N	N	N	K	D	A	T	L	S	E	A	G
AFW04530/Tunisia/xxxx/G3	T	T	N	N	S	W	K	D	Q	D	A	V	D	-	Q	D	T	A	N	N	K	D	A	T	L	S	E	A	-
RotaTeq-BrB-9-G4P7[5]	S	T	S	T	E	W	K	D	Q	N	L	I	E	K	Q	D	T	A	D	T	R	A	S	G	E	S	T	S	G
AYU56531/Iraq/2017/G4	S	T	S	T	E	W	K	D	Q	N	L	I	E	-	Q	N	T	A	D	T	K	T	S	G	E	S	T	S	G
ALK28241/Lebanon/2011/G4	S	T	S	T	E	W	K	D	Q	N	L	I	E	K	Q	N	T	A	D	T	K	T	S	G	E	S	T	S	G
ASY08032/Kuwait/2016/G4	S	T	S	T	E	W	K	D	Q	N	L	I	E	K	Q	N	T	A	N	T	K	V	S	G	E	S	T	S	G
AFW04532/Tunisia/xxxx/G4	S	T	S	T	E	W	K	D	Q	N	L	I	E	-	Q	N	T	A	D	T	K	T	S	G	E	S	T	S	-
AAD04930/Egypt/G8	T	T	A	S	S	W	K	D	Q	D	A	I	N	K	Q	D	T	T	N	T	K	N	A	N	S	S	E	A	G
AGI03826/Iraq/2008/G8	A	T	A	S	S	W	K	D	Q	D	A	I	N	-	Q	D	T	T	N	T	K	N	A	N	S	S	E	A	G
AXS77078/Morocco/2011/G8	T	T	A	S	S	W	K	D	Q	D	A	I	N	K	Q	D	T	T	N	T	K	N	A	N	S	S	E	A	G
ABQ43352/Tunisia/xxxx/G8	T	T	A	S	S	W	K	E	Q	D	A	I	N	K	Q	D	T	T	N	T	K	S	A	N	S	S	E	A	G
APA34107/Egypt/2012/G9	T	T	G	T	E	W	K	D	Q	D	A	I	D	K	Q	N	T	A	D	N	K	D	S	T	L	S	E	S	G
ALP83520/Iraq/xxxx/G9	T	T	G	T	E	W	K	D	Q	D	A	I	D	N	Q	N	T	A	D	N	K	D	S	T	L	S	E	S	G
BAE78589/Iraq/xxxx/G9	T	T	G	T	E	W	K	D	Q	D	A	I	D	K	Q	N	T	A	D	N	K	D	S	T	L	S	E	S	G
ASY08030/Kuwait/2016/G9	T	T	G	T	E	W	K	D	Q	D	A	I	D	K	Q	N	T	A	D	N	K	D	S	T	L	S	E	S	G
ALK28250/Lebanon/2011/G9	T	T	G	T	E	W	K	D	Q	D	A	I	D	K	Q	N	T	A	D	N	K	D	S	T	L	S	E	S	G
AEK48101/Libya/2008/G9	T	T	G	T	E	W	K	D	Q	D	A	I	D	-	Q	N	T	A	D	N	K	D	S	T	L	S	E	S	G
BAF49015/Saudi Arabia/xxxx/G9	T	T	G	T	E	W	K	D	Q	D	A	I	D	K	Q	N	T	A	D	N	K	D	S	T	L	S	E	S	G
ABQ18269/Tunisia/xxxx/G9	T	T	G	T	E	W	K	D	Q	D	A	I	D	K	Q	N	T	A	D	N	K	D	S	T	L	S	E	S	G
APA34108/Egypt/2012/G12	S	T	T	P	D	W	T	N	Q	D	S	V	D	K	Q	D	V	T	N	N	Q	Q	N	S	L	S	E	A	G
ASN64557/Iraq/xxxx/G12	S	T	T	P	D	W	T	S	Q	D	S	V	D	K	Q	D	V	T	N	N	Q	Q	N	S	L	S	E	A	G
AGI03818/Iraq/2008/G12	S	T	T	P	D	W	T	N	Q	D	S	V	D	K	Q	D	V	T	N	N	Q	Q	N	S	L	S	E	A	G
BAF02906/Saudi Arabia/xxxx/G12	S	T	T	P	D	W	T	S	Q	D	S	V	D	-	Q	D	V	T	N	N	Q	Q	N	S	L	S	E	A	G
AQM57599/Tunisia/2010/G12	S	T	T	P	D	W	T	S	Q	D	S	V	D	-	Q	D	-	-	-	-	Q	Q	N	S	L	S	-	-	-

a

Strain	Epitope 8-1						Epitope 8-2		Epitope 8-3				Epitope 8-4													
	100	146	148	150	188	190	192	193	194	195	196	180	183	113	114	115	116	125	131	132	133	135	86	87	88	89
Rotarix-A41CB052A-G1P1A[8]	D	S	S	N	S	S	A	N	L	N	N	E	R	N	P	V	D	S	S	N	D	N	S	N	T	N
RotaTeq-W179-4-G6P1A[8]	D	S	S	N	S	N	A	N	L	N	D	E	R	N	P	V	D	N	R	N	D	D	S	N	T	N
AHL27874/Iraq/P[4]	D	G	S	S	S	N	A	D	L	N	N	E	R	S	Q	T	N	N	E	N	S	D	S	N	T	D
AYU56526/Iraq/2017/P[4]	D	G	S	S	S	N	A	D	L	N	N	E	R	S	Q	T	N	N	E	N	S	D	S	N	T	D
ASY08052/Kuwait/2016/P[4]	D	G	S	S	S	N	A	D	L	N	N	E	R	S	P	T	N	N	E	N	S	D	S	N	T	D
ALK28298/Lebanon/2012/P[4]	D	G	S	S	S	N	A	D	L	N	N	E	R	S	Q	T	N	N	E	N	S	D	S	N	T	D
APO16135/Morocco/2014/P[4]	D	G	S	S	S	N	A	D	L	N	N	E	R	S	Q	T	N	N	E	N	S	D	S	N	T	D
ALD51922/Saudi_Arabia/2013/P[4]	D	G	S	S	S	N	A	D	L	N	N	E	R	S	Q	T	N	N	E	N	S	D	S	N	T	D
AFW04503/Tunisia/P[4]	D	G	S	S	S	N	A	D	L	N	N	E	R	S	Q	T	N	N	E	N	S	D	S	N	T	D
ALP83515/Iraq/2013/P[8]	D	G	S	N	S	N	V	N	L	N	G	E	R	D	P	V	D	N	R	N	D	D	S	N	T	N
AYU56522/Iraq/2017/P[8]	D	G	S	N	S	N	A	N	L	D	G	E	R	N	P	V	D	N	R	N	D	D	S	N	T	N
AKD33384/Israel/2010/P[8]	D	G	S	S	G	N	S	D	L	T	S	E	G	D	P	V	D	S	R	N	D	N	S	N	T	N
AKD33382/Jordan/2007/P[8]	D	G	S	S	G	N	S	D	L	I	S	E	G	D	P	V	D	S	R	N	D	N	S	N	T	N
ASY08056/Kuwait/2016/P[8]	D	G	S	N	S	N	A	N	L	N	D	E	R	N	P	V	D	N	R	N	D	D	S	N	T	N
ALK28264/Lebanon/2013/P[8]	D	G	S	N	S	N	A	N	L	D	G	E	R	N	P	V	D	N	R	N	D	D	S	N	T	N
AFV71275/Morocco/2009/P[8]	D	G	S	N	S	N	A	N	L	D	G	E	R	N	P	V	D	N	R	N	D	D	S	N	T	N
BAF02907/Saudi Arabia/xxxx/P[8]	D	G	S	N	S	N	A	N	L	N	G	E	R	D	P	V	D	N	R	N	D	D	S	N	T	N
AJX18185/Tunisia/2012/P[8]	D	G	S	N	S	N	A	N	L	D	G	E	R	N	P	V	D	N	R	N	D	D	S	N	T	N

b

**Fig. 8.** Alignment of amino acid residues in VP7 (A) VP4 (B) antigenic epitopes of rotavirus strains circulating in the MENA region with rotavirus vaccine strains. The amino acid residues that differ from Rotarix are shown in blue color while those that differ from RotaTeq are in green color. The amino acid residues different from both Rotarix and RotaTeq are in orange color. The amino acid positions of neutralization escape mutation sites are shown in red color.

prevalence and genotype distribution of rotavirus post-vaccination [196]. Furthermore, one study from Lebanon has compared the efficacy of rotavirus vaccine among vaccinated and unvaccinated children [118].

The impact of the rotavirus vaccine in these studies differs according to the number of years after vaccine introduction and the different geographical locations with epidemiological heterogeneity. In general, the introduction of rotavirus vaccination led to 40–65%

**Table 3**  
Rotavirus vaccine introduction in the MENA region and a summary of available studies on rotavirus genotypes before and after vaccine introduction.

Country	Reference	Year of vaccine introduction	Current vaccine	Decline (%) of rotavirus infections post-vaccination	Predominant genotypes post-vaccination
Bahrain	[194]	2008	Rotarix	–	–
Israel	[195]	2010	Rotateq	61 <sup>a</sup>	G1P[8], G3P[8], G9P[8], G12P[8], and G2P[4]
Jordan	[215]	2015	Rotateq	–	–
Kuwait	[194]	2017	Rotateq	–	–
Lebanon <sup>b</sup>	[118]	Not introduced	Rotateq Rotarix	–	–
Libya	[194]	2013	Rotateq	–	–
Morocco	[133]	2010	Rotateq	41.5	G1P[8], G2P[4], G9P[8], G4P[8], G2P[8], and G1P[6]
Palestine	[197], [194]	2016 2018	Rotarix Rotavac	64.6	–
Qatar	[194]	2009	Rotarix	–	–
Saudi Arabia	[196]	2013	Rotarix	39.8	G1P[8], G2P[4], G9P[8] and G12P[8]
Sudan	[194]	2011	Rotarix	–	–
UAE	[194]	2013	Rotarix	–	–
Yemen	[186]	2012	Rotarix	48	G1P[8], G9P[8], G2P[4], and G9P[4]

<sup>a</sup> Decline in rotavirus (%) vaccinated vs unvaccinated children

<sup>b</sup> The vaccine is available in the market but has not been introduced to the national immunization program.

decline in rotavirus infections [95], [133], [185], [186]. In Palestine, Qatar, and the UAE, incidence rate of rotavirus infection after the introduction of the vaccine ranged from 6 % to 28 % [142], [182], [197].

Studies reporting the impact of vaccination on rotavirus genotype distribution showed that the dominance of G1P[8] remained persistently in the post-vaccination period. Other trends were observed, including the emergence or reemergence of G2P[4], G9P[8], and G12P[8]. Additional genotype combinations were observed in the post-vaccination period, including G4P[8], G1P[6], and G9P[4].

#### 4. Discussion

Acute gastroenteritis remains one of the most common infectious diseases in humans, causing a significant burden to public health worldwide. Viral agents have been recognized as the most common causes of AGE, of which rotavirus is the predominant virus. Most of the available papers from the MENA region focused on the prevalence of rotavirus exclusively in children, leaving a gap in understanding the role of the other etiological viral agents in other age groups. In this context, this paper highlights the prevalence of the different viral agents associated with AGE among adults and children over three decades in 18 countries of the MENA region. This paper also demonstrates the genotype distribution of rotavirus and norovirus and sheds light on the genetic diversity and vaccine availability of rotavirus in the region.

Overall, rotavirus was the most widely studied and most prevalent virus detected in the MENA region (29 %), followed by norovirus (14 %), adenovirus (6 %), astrovirus (4 %), and sapovirus (3 %). The dominance of rotavirus and norovirus and comparatively the lower prevalence rates of adenovirus in patients with AGE have been reported in several countries worldwide. Although data on the prevalence of astrovirus and sapovirus were limited in the MENA region, in line with previous reports, this paper showed that they are less common but significant causes of viral AGE [198–203]. Notably, there were variations in the observed prevalence of the different viruses within and between the countries. These variations might represent actual differences in the prevalence, or they could be attributed to variations in study design, age distribution, detection methods, and reporting countries, which will pose a challenge to establishing the epidemiological literature for AGE in the MENA region. Therefore, the prevalence data were stratified by these factors to assess the bases of these variations.

As expected, rotavirus infections were significantly higher in children < 2 years old presenting with AGE; in contrast, norovirus was more prevalent in older patients > 18 years. Rotavirus is the most common cause of childhood diarrhea, whereas norovirus is associated with epidemics and sporadic gastroenteritis affecting people of all age groups [204], [205]. Similarly, young children were more commonly infected with astrovirus than adults, which is in agreement with previous reports [206]. This may be partly because maternal antibodies protect against these viruses in children in the first three months of life, making these infections less common or milder at such an age. In the case of older children, repeated infections contribute to their protection as they approach adulthood. However, this immunity will wane with advanced age. Moreover, the continuous mutations and recombination of norovirus that contribute to the emergence of new strains that may potentially cause sporadic gastroenteritis or outbreak events could explain its persistence in all age groups, particularly adults [207]. Knowing these aspects entails that preemptive and control measures should be implemented optimally for the susceptible populations.

This paper shows that antigen detection methods were most commonly used to detect rotavirus, adenovirus, and astrovirus. Whereas molecular methods, including PCR and RT-PCR, were more commonly utilized for the detection of norovirus and were the only method for sapovirus detection. According to previous reports, antigen detection assays demonstrated good specificity and sensitivity for the detection of viral AGE, particularly rotavirus infections in children, as they can shed the virus for a more extended period in higher quantities than adults [208]. Furthermore, commercial kits are readily available with the added advantages of low cost and fast turnaround time. Nonetheless, molecular techniques are reliable tools for virus detection, and in the MENA region, they outperformed other techniques in the detection of norovirus, adenovirus, and astrovirus. They are easy to automate and standardize for reproducible results in genotyping, monitoring, and surveillance studies [209].

Worldwide prevalence and distribution of the viral agents of AGE are not homogenous, and according to different reports, the prevalence and severity of enteric viruses may be related to the influence of socioeconomic status, which includes maternal health literacy, overcrowding, malnutrition, access to health care, and clean water [210]. For instance, in many studies, high-income countries like Saudi Arabia and Kuwait have reported a lower prevalence of the different AGE viruses. Conversely, in lower-middle income countries like Iran, Egypt, and Tunisia, the prevalence of these viruses was higher, as reported by several studies. Nonetheless, the variations in

prevalence of these viral agents between the countries might be linked to additional factors. One factor could be the scarcity of studies reporting these viruses due to the absence of adequate resources or political instability in several countries within the MENA region, which could cause over- or underestimation of the role of these viral agents in AGE. Moreover, treatment-seeking behavior for self-limiting or moderate infections is lower in these countries due to the economic burden.

Over the last three decades, most countries in the MENA region have reported the distribution of rotavirus genotypes. Despite the large number of genotype combinations reported in this paper, only five genotypes, G1P[8], G9P[8], G2P[4], G3P[8], and G2P[8], accounted for over 75 % of isolates. Previously it has been shown that globally there are six major genotypes, including G1P[8], G2P[4], G3P[8], G4P[8], G9P[8], and G12P[8], that account for 90 % of all rotavirus infections [211], [212]. Comparatively, this paper showed that G9P[8] became the second most common genotype (12.7 %); this is in line with previous studies that reflected its global emergence [213]. In contrast, the frequency of the emergent G12P[8] is negligible (0.7 %) in the MENA region compared to a higher proportion in South and North America (5.2 %) and Africa (10 %) [212]. These findings indicate that G9 strains in the MENA region are becoming more adapted to replicate in humans than G12 strains. Interestingly, some countries like Egypt, Iraq, Israel, Qatar, Tunisia, UAE, and Yemen showed considerable genotype diversity where the uncommon genotypes (including G1P[6], G3P[4], G9P[4], G9P[6]) accounted for 9–19 % of typed samples. This finding concord with previous studies in Africa and Asia, where high diversity was reported compared to Europe and the U.S. [214–217]. The proportion of partially typed and untypable genotypes ranged from 1 % to 28 %. One reason for this variation is the presence of single nucleotide polymorphism at the binding sites of the primes that cause mistyping or failure in typing [218–221].

Temporal variations of specific genotypes were observed for some countries in the MENA region. For instance, G1P[8] persisted and remained the dominant genotype in almost all the countries over many years. Whereas G9P[8] and G2P[4] were constantly detected across the years and transiently became the dominant genotypes, these trends have been observed elsewhere [212]. Other rotavirus genotypes co-circulate with these dominant genotypes across several years, including G3P[8] and G4P[8] but at a lower prevalence. Although this study showed some trends in genotype distribution within the region, there is still a need for continuous long-term surveillance to monitor the trends of the circulating genotypes, which is essential to ensure and assess vaccine effectiveness.

This paper identified 28 norovirus genotypes reported in the MENA region, with GII.4 identified as the most common genotype, which is expected as GII.4 has been reported as the most prevalent and virulent genotype worldwide [222], [223]. Other commonly detected genotypes included GII.3, GII.2, and GII.6, reported in children with sporadic gastroenteritis [224]. Compared to other genotypes, GII.4 undergoes antigenic drift allowing it to escape from neutralizing antibodies explaining its predominance [225]. The GII.17 genotype emerged in many countries worldwide and replaced the dominant GII.4; however, it is rare in the MENA and detected in only three countries [15]. More studies on norovirus antigenic and genetic diversity are needed, which is essential for developing vaccine candidates with broader protection.

Phylogenetic analysis and genetic characterization were conducted in the most recent VP7 and VP4 nucleotide and amino acid sequences circulating in the MENA region. Phylogenetic analysis of the VP7 genes showed that the majority of the G1 strains belonged to lineage I and co-clustered with strains identified in India and Pakistan in 2015. In contrast, two other strains from Iran and Saudi Arabia clustered in lineage II, with a Pakistani strain circulating in 2015. In comparison with vaccine strains, lineage II was more

conserved with fewer amino acid differences from vaccine strains (Rotarix and Rotateq) compared to lineage I. All strains within both lineages have shown two amino acid variations from Rotateq vaccine strain at positions 97 and 147, previously shown as important sites of neutralization escape mutants [226]. Studies from different countries reported these variations [227–237] in addition to Europe and America, where the vaccine efficacy is high, indicating that the effect of these variations might not be detrimental [238–240]. For G2 strains, all the strains clustered distantly from the G2 of the Rotateq vaccine. Moreover, the VP7 of G2 strain showed the highest amino acid differences from the VP7 of Rotarix. This finding could explain the relatively low efficacy of Rotarix against the G2 strains compared to other genotypes reported elsewhere [241], [242]. Furthermore, the amino acid substitution D96N has been linked to the abrupt spread or reemergence of G2P[4] in many countries, which might indicate its role in conferring fitness advantage to the G2 strains [243–247]. In this paper, G2P[4] represented the third most common strain circulating in the MENA region. Since the G2 strains are mostly associated with P[4], the protection against G2 strains provided by the vaccine strains depends on the G2 component of the vaccine. Consequently, the variations in the antigenic sites of the G2 strains circulating in the MENA region are of concern as they might impact the vaccine efficacy. The G3 strains from Tunisia and Kuwait possessed a potential N-glycosylation site formed by substitution K238N, which has been previously shown to block neutralization by hyperimmune sera and monoclonal antibodies [248], [249]. Expectedly, the VP7 epitopes of G12 strains had a high number of differences in amino acid residues compared to Rotateq vaccine strains. Various studies attributed the emergence of G12 strains to the introduction of the rotavirus vaccine; however, increased prevalence of G12 has been reported in countries that have yet to introduce the vaccine [250–254]. Fortunately, in the MENA region, the G12 strains are mostly associated with P[8], which will provide the protection afforded by the vaccination against severe AGE. Still, continuous monitoring of the variation in antigenic epitopes is essential to determine the impact of vaccination and if the changes in the circulating strains over time are actually due to vaccine-induced selective pressure.

Based on the phylogenetic analysis, the VP4-P[4] sequences from the MENA region belonged to lineage II, IV, and V. Moreover, the antigenic epitopes of the P[4] strains have exhibited a high number of variations with both vaccine strains, as expected. Despite these differences, the monovalent Rotarix and pentavalent Rotateq showed comparable efficacy against non-vaccine strains in several countries around the globe [255]. Meanwhile, the majority of VP4-P[8] sequences clustered in lineage III, and only two sequences clustered in lineage IV, both of which are divergent from vaccine strains. This observation is consistent with the literature as P[8] lineage III is widely distributed worldwide [256]. The VP4 epitopes of the P[8] strains of the MENA region contained multiple residues that differed from P[8] strains of Rotateq and Rotarix at known neutralization escape mutant sites [257]. Lineage IV of VP4-P[8] is also called OP354-like, which has been increasingly reported in many countries worldwide [258]. The OP354-like strains from Jordan and Israel showed remarkable differences in the antigenic epitopes compared to the other P[8] lineages. Since the OP354-like strains are genetically divergent from other P[8] lineages, including those of Rotarix and Rotateq, there have been some speculations about the protective effect of the currently used vaccines in this lineage. However, more studies are needed to elucidate if the antigenic properties of lineage IV could cause them to escape neutralization. An interesting remark is that strains from neighboring countries clustered closely together and shared a high genetic similarity, for instance, the strains from Tunisia with Morocco or Libya (G1, G9, P[4], and P[8]) and Saudi Arabia with Iran or Kuwait or Iraq (G1, G9, P[4] and P[8]). These countries share borders, and accordingly, the frequent flow of people

across the border might contribute to the diversity of rotavirus in these countries. A clear data gap remains for determining the alteration in antigenic epitopes of VP4 and VP7 proteins that could lead to escape mutants, this warrants long-term surveillance of the circulating strains, especially in countries with high vaccine coverage.

Rotavirus vaccination is one of the best strategies to decrease vaccine-preventable diarrhea [190]. Four studies showed a significant reduction in rotavirus-positive cases (38.9–64.6 %) with a substantial impact against severe disease in the post-vaccination era with high vaccine coverage. These findings are comparable to those reported in other countries, including high-income countries [255], [259–261]. Indicating that in the MENA region, the vaccine was effective despite the presence of factors that reduce its efficiency, including lower socioeconomic status, hygiene standards, malnutrition, and other diseases. Post-vaccine introduction data showed a sustained dominance of G1P[8] with a parallel increase of G2P[4] and G9P[8] in some countries. Several studies have documented the emergence or re-emergence of G2P[4] and G9P[8] strains post vaccine introduction [262], [250], [213], [263]. The strain shift in the post-vaccination era (G1P[8] to G2P[4] or G9P[8]) has prompted global speculations that this phenomenon is indicative of vaccine-induced selective pressure; however, it was observed in countries with limited vaccine usage and without vaccination over consecutive years [259]. This indicates that the changes in the strain distribution are likely due to the inherent fluctuations of rotavirus or natural reassortment events rather than vaccine pressure. Further evidence on the potential implications and mechanisms of selective vaccine pressure remains to be examined after a long post-vaccination period.

This paper has some limitations. First, the included studies were heterogeneous, making the comparisons between studies difficult. Categorizing the collected data by viral agent, age, method, and reporting countries was an attempt to correct this heterogeneity. In addition, the prevalence data of the different viral agents and genotype diversity of rotavirus and norovirus was non-existent or limited for some countries or periods; thus, the data might limit the ability to assess the true impact of the other agents and their genetic diversity in the whole region. Despite these limitations, this paper is the first attempt at providing a comprehensive overview of the etiological agents of viral AGE in the MENA region. Also, the phylogenetic and antigenic properties of rotavirus strains in the region could provide baseline data for countries that have not yet introduced the vaccine to their NIPs. Lastly, it emphasizes the importance of maintaining and improving surveillance for the viral agents of AGE in order to prioritize their importance on a national basis.

## 5. Conclusion

This paper is the first to provide a comprehensive report on the prevalence of the different enteric viruses that cause AGE among adults and children. In addition, it highlights the genetic diversity of circulating rotavirus genotypes and discusses the availability of rotavirus vaccines in the MENA region. The reported data have shown that viral AGE causes considerable morbidity in the MENA region, especially rotavirus, among children. This paper demonstrated the importance of multiple viral agents of AGE, including rotavirus, norovirus, adenovirus 40/41, astrovirus, and sapovirus detected at varying rates between and within countries. Given that the reported rotavirus genotypes were quite variable among the countries of the MENA region, this denotes the burden of the disease. The comparison of the amino acid motifs of VP7 and VP4 proteins between the circulating rotavirus in the MENA region with the available vaccine strains has revealed multiple antigenic variations that might impact

the vaccine efficacy in the region, highlighting the need for detailed antigenic mapping and continuous monitoring of the prevalent rotavirus genotypes in the MENA region. The results of this paper will be useful as background information for planning and implementing effective vaccination programs and possibly developing new vaccinations. Given the variety and diverse rotavirus types in the region, a vaccine with broad genotype coverage is important to decrease the burden of rotavirus.

## Acknowledgements

Open Access funding provided by the Qatar National Library (QNL).

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2022.09.001.

## References

- [1] Graves NS. Acute gastroenteritis. *Prim Care* 2013;40(3):727–41. <https://doi.org/10.1016/j.pop.2013.05.006>
- [2] Troeger C, et al. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of diarrhoea in 195 countries: a systematic analysis for the global burden of disease study 2016. *Lancet Infect Dis* 2018;18(11):1211–28. [https://doi.org/10.1016/S1473-3099\(18\)30362-1](https://doi.org/10.1016/S1473-3099(18)30362-1)
- [3] “WHO | Diarrhoea: why children are still dying and what can be done,” WHO. ([https://www.who.int/maternal\\_child\\_adolescent/documents/9789241598415/en/](https://www.who.int/maternal_child_adolescent/documents/9789241598415/en/)) (accessed Jul. 27, 2020).
- [4] Kosek M, Bern C, Guerrant RL. The global burden of diarrhoeal disease, as estimated from studies published between 1992 and 2000. *Bull World Health Organ* 2003;81(3):197–204.
- [5] Elliott EJ. Acute gastroenteritis in children. *BMJ* 2007;334(7583):35–40. <https://doi.org/10.1136/bmj.39036.406169.80>
- [6] Stuempfig ND, Seroy J. Viral gastroenteritis. *StatPearls*. Treasure Island (FL): StatPearls Publishing.; 2020 Accessed: Jul. 20, 2020. [Online]. Available: (<http://www.ncbi.nlm.nih.gov/books/NBK518995/>).
- [7] Angel J, Franco MA, Greenberg HB. Rotaviruses. In: Mahy BWJ, Van Regenmortel MHV, editors. *Encyclopedia of Virology* third ed. Oxford: Academic Press; 2008. p. 507–13. <https://doi.org/10.1016/B978-012374410-4.00497-0>
- [8] R. Johnne et al., “Distantly Related Rotaviruses in Common Shrews, Germany, 2004–2014 - Volume 25, Number 12—December 2019 - Emerging Infectious Diseases journal - CDC”, doi: 10.3201/eid2512.191225.
- [9] Tate JE, Burton AH, Boschi-Pinto C, Steele AD, Duque J, Parashar UD. 2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis. *Lancet Infect Dis* 2012;12(2):136–41. [https://doi.org/10.1016/S1473-3099\(11\)70253-5](https://doi.org/10.1016/S1473-3099(11)70253-5)
- [10] Rotavirus Classification Working Group: RCWG. (<https://rega.kuleuven.be/cev/viralmetagenomics/virus-classification/rcwg>) (accessed Apr. 04, 2022).
- [11] Santos N, Hoshino Y. Global distribution of rotavirus serotypes/genotypes and its implication for the development and implementation of an effective rotavirus vaccine. *Rev Med Virol* 2005;15(1):29–56. <https://doi.org/10.1002/rmv.448>
- [12] Chhabra P, et al. Updated classification of norovirus genogroups and genotypes. *J Gen Virol* 2019;100(10):1393–406. <https://doi.org/10.1099/jgv.0.001318>
- [13] Bull RA, Eden J-S, Rawlinson WD, White PA. Rapid evolution of pandemic noroviruses of the GII.4 lineage. *PLOS Pathog* 2010;6(3):e1000831 <https://doi.org/10.1371/journal.ppat.1000831>
- [14] Lindesmith LC, Donaldson EF, Baric RS. Norovirus GII.4 strain antigenic variation. *J Virol* 2011;85(1):231–42. <https://doi.org/10.1128/JVI.01364-10>
- [15] de Graaf M, et al. Emergence of a novel GII.17 norovirus – End of the GII.4 era? *Eurosurveillance* 2015;20(26):21178. <https://doi.org/10.2807/1560-7917.ES2015.20.26.21178>
- [16] Kajon AE, Weinberg JB, Spindler KR. Adenoviruses☆. Reference Module in Biomedical Sciences. Elsevier.; 2019. <https://doi.org/10.1016/B978-0-12-801238-3.00086-6>
- [17] Wood DJ. Adenovirus gastroenteritis. *Br Med J (Clin Res Ed)* 1988;296(6617):229–30. (Jan.).
- [18] Clark B, McKendrick M. A review of viral gastroenteritis. *Curr Opin Infect Dis* 2004;17(5):461–9. <https://doi.org/10.1097/00001432-200410000-00011>
- [19] Bosch A, Pintó RM, Guix S. Human astroviruses. *Clin Microbiol Rev* 2014;27(4):1048–74. <https://doi.org/10.1128/CMR.00013-14>
- [20] Walter JE, Mitchell DK. Astrovirus infection in children. *Curr Opin Infect Dis* 2003;16(3):247–53. <https://doi.org/10.1097/00001432-200306000-00011>
- [21] Coppo P, Scieux C, Ferchal F, Clauvel J, Lassoued K. Astrovirus enteritis in a chronic lymphocytic leukemia patient treated with fludarabine

- monophosphate. *Ann Hematol* 2000;79(1):43–5. <https://doi.org/10.1007/s002770050008>
- [22] Iturriza-Gómara M, Cunliffe NA. Chapter 34 – Viral gastroenteritis. In: Ryan ET, Hill DR, Solomon T, Aronson NE, Endy TP, editors. *Hunter's Tropical Medicine and Emerging Infectious Diseases* (Tenth Edition) London: Content Repository Only!; 2020. p. 289–307. <https://doi.org/10.1016/B978-0-323-55512-8.00034-X>
- [23] Hatcher EL, et al. Virus variation resource - improved response to emergent viral outbreaks. *Nucleic Acids Res* 2017;45(D1):D482–90. <https://doi.org/10.1093/nar/gkw1065>
- [24] Kumar S, Stecher G, Li M, Knyaz C, Tamura K. MEGA X: molecular evolutionary genetics analysis across computing platforms. *Mol Biol Evol* 2018;35(6):1547–9. <https://doi.org/10.1093/molbev/msy096>
- [25] Kimura M. A simple method for estimating evolutionary rates of base substitutions through comparative studies of nucleotide sequences. *J Mol Evol* 1980;16(2):111–20. <https://doi.org/10.1007/BF01731581>
- [26] Saitou N, Nei M. The neighbor-joining method: a new method for reconstructing phylogenetic trees. *Mol Biol Evol* 1987;4(4):406–25. <https://doi.org/10.1093/oxfordjournals.molbev.a040454>
- [27] Ismaeel AY, Jamsheer AE, Yousef AQ, Al-Otaibi MA, Botta GA. Causative pathogens of severe diarrhea in children. *Saudi Med J* 2002;23(9):1064–9.
- [28] Al Musawi M, Zainaldeen H, Shafi F, Anis S, DeAntonio R. Rotavirus gastroenteritis in children under 5 years in the Kingdom of Bahrain: hospital-based surveillance. *Clin Epidemiol* 2013;5:269–75. <https://doi.org/10.2147/cep.s46822>
- [29] Naficy AB, et al. Astrovirus Diarrhea in Egyptian Children. *J Infect Dis* 2000;182(3):685–90. <https://doi.org/10.1086/315763>
- [30] Matson DO, et al. Rotavirus Genotypes among Hospitalized Children in Egypt, 2000–2002. *J Infect Dis* 2010;202(Supplement\_1):S263–5. <https://doi.org/10.1086/653581>
- [31] Ahmed SF, et al. Rotavirus genotypes associated with acute diarrhea in Egyptian infants. *Pediatr Infect Dis J* 2014;33:562. <https://doi.org/10.1097/INF.0000000000000052>
- [32] El-Mohammady H, et al. Increase in the detection rate of viral and parasitic enteric pathogens among Egyptian children with acute diarrhea. *J Infect Dev Ctries* 2012;6(11):774–81. <https://doi.org/10.3855/jidc.2349>
- [33] Kamel AH, Ali MA, El-Nady HG, de Rougemont A, Pothier P, Belliot G. Predominance and circulation of enteric viruses in the region of greater Cairo, Egypt. *J Clin Microbiol* 2009;47(4):1037–45. <https://doi.org/10.1128/JCM.01381-08>
- [34] S.F. Ahmed et al., "Novel Astroviruses in Children, Egypt - Volume 12—December 2011 - Emerging Infectious Diseases journal - CDC", doi: 10.3201/eid1712.110909.
- [35] El-Shabrawi M, et al. The burden of different pathogens in acute diarrhoeal episodes among a cohort of Egyptian children less than five years old. *Prz Gastroenterol* 2015;10(3):173–80. <https://doi.org/10.5114/pg.2015.51186>
- [36] El-Senousy W, El-Gamal M, El-Baset AA, Mousa S, El-Sayed E-H, Mohamed S. Prevalence of noroviruses among detected enteric viruses in Egyptian aquatic environment. *World Appl Sci J* 2014;32:2186–205.
- [37] Hashem S, Shoman SA, Mohamed AF. Isolation and molecular genotyping of group A rotavirus strains circulating among Egyptian infants and children. *Egypt J Med Microbiol* 2012;21:11–20. <https://doi.org/10.12816/0004888>
- [38] Shoenb ARS, Hull JJ, Jiang B. Rotavirus G and P types in children with acute diarrhea in Cairo, Egypt, 2011–2012. *J Egypt Public Health Assoc* 2015;90(3):121–4. <https://doi.org/10.1097/01.EPX.0000470849.84604.13>
- [39] Saady N, Elshabrawy WO, Megahed A, Foad MF, Mohamed AF. Genotyping and clinicoepidemiological characterization of rotavirus acute gastroenteritis in Egyptian children. *Pol J Microbiol* 2017;65(4):433–42. <https://doi.org/10.5604/17331331.1227669>
- [40] Zaghoul MZ, El-Sahn SF, Zeinab G. Coinfection of rotavirus group A, norovirus and adenovirus in Egyptian children with gastroenteritis. *Life Sci J* 2013;10(2):848–52. (Jan.).
- [41] W.A.E.-S. El-Mosallamy, M.G. Awadallah, M.D.A. EL-Fattah, A.A. Aboelazm, and M.S. EL-Melouk, "Human Bocavirus among Viral Causes of Infantile Gastroenteritis," 2015, doi: 10.12816/0024929.
- [42] Allayeh AK, Baz RME, Saeed NM, Osman MES. Detection and genotyping of viral gastroenteritis in hospitalized children below five years old in Cairo, Egypt. *Arch Pediatr Infect Dis* 2018;6(3):7.
- [43] El Sayed Zaki M, Abo El Kheir N. Molecular study of astrovirus, adenovirus and norovirus in community acquired diarrhea in children: One Egyptian center study. *Asian Pac J Trop Biomed* 2017;7(11):987–90. <https://doi.org/10.1016/j.apjtb.2017.10.003>
- [44] El-Senousy WM, Abu Senna ASM, Mohsen NA, Hasan SF, Sidkey NM. Clinical and environmental surveillance of rotavirus common genotypes showed high prevalence of common P genotypes in Egypt. *Food Environ Virol* 2020:1–19. <https://doi.org/10.1007/s12560-020-09426-0>
- [45] El Sayed Zaki M, Eid A-R, El Ashry AY, Al-Kasaby NM. Molecular study of norovirus in pediatric patients with gastroenteritis. *Open Microbiol J* 2019;13(1). <https://doi.org/10.2174/187428580191301010324>
- [46] S.R. Roodsari et al., "Detection of Noroviruses Isolated From Children With Acute Gastroenteritis by Rt-PCR in Iran," 2013, doi: 10.5812/PEDINFECT.7619.
- [47] Zarmani AH, Modarres Sh, Jadali F, Sabahi F, Moazzeni SM, Vazirian F. Role of rotaviruses in children with acute diarrhea in Tehran, Iran. *J Clin Virol* 2004;29(3):189–93. [https://doi.org/10.1016/S1386-6532\(03\)00123-9](https://doi.org/10.1016/S1386-6532(03)00123-9)
- [48] Savadkoobi RB, Ahmadpour-Kacho M, Yahyapour Y. Prevalence of viral gastroenteritis in children with acute gastroenteritis in Babol, Iran. *J Pediatr Infect Dis* 2007;02(04):211–4. <https://doi.org/10.1055/s-0035-1557051>
- [49] Samarbafzadeh A, Tehrani EM, Makvandi M, Taremi M. Epidemiological aspects of rotavirus infection in Ahwaz, Iran. *J Health Popul Nutr* 2005;23(3):245–9.
- [50] Kargar M, Zare M, Najafi A. Molecular epidemiology of rotavirus strains circulating among children with gastroenteritis in Iran. *Iran J Pediatr* 2012;22(1):63–9.
- [51] Modarees S, et al. *Arch Iran Med* 2011;14(1):39–45. 011141/AIM.009.
- [52] Hamkar R, et al. Prevalence of rotavirus, adenovirus, and astrovirus infections among patients with acute gastroenteritis in, northern Iran. *Iran J Public Health* 2010;39(2):45–51.
- [53] Eesteghamati A, et al. Sentinel hospital-based surveillance of rotavirus diarrhea in Iran. *J Infect Dis* 2009;200:S244–7.
- [54] Sadeghian A, Hamed A, Sadeghian M, Sadeghian H. Incidence of rotavirus diarrhea in children under 6 years referred to the pediatric emergency and clinic of Ghaem Hospital, Mashhad, Iran. *Acta Med Iran* 2010;48(4):263–5. (Aug.).
- [55] Najafi A, Kargar M, Kargar M, Jafarpour T, Jafarpour T, Najafi A. Burden and typing of rotavirus group A in children with acute gastroenteritis in shiraz, southern iran. *Iran Red Crescent Med J* 2012;14(9):531–40.
- [56] Romani S, et al. Prevalence of Norovirus infection in children and adults with acute gastroenteritis, Tehran, Iran, 2008–2009. *Food Environ Virol* 2012;4(1):1–5. <https://doi.org/10.1007/s12560-011-9071-8>
- [57] Shahram J, et al. Relative frequency of norovirus infection in children suffering from gastroenteritis and referred to Aboozar hospital AHVAZ, IRAN. *Jundishapur J Microbiol.* 2011;5(115):355–8. (Jan.).
- [58] Najafi A, Najafi S, Vahdat K, Kargar M, Javdani N. Importance of viral pathogens in children with acute gastroenteritis in the south of Iran. *Ann Saudi Med* 2013;33(2):124–9. <https://doi.org/10.5144/0256-4947.2013.124>
- [59] Motamedifar M, Amini E, Talezadeh Shirazi P. Frequency of rotavirus and adenovirus gastroenteritis among children in Shiraz, Iran. *Iran Red Crescent Med J* 2013;15(8):729–33. <https://doi.org/10.5812/ircmj.4415>
- [60] Kargar M, Akbarzadeh AR. Prevalence and molecular genotyping of group A rotaviruses in Iranian children. *Indian J Virol* 2012;23(1):24–8. <https://doi.org/10.1007/s13337-012-0070-7>
- [61] Kajbaf T, Shamsizadeh A, Kalvandi G, Macvandi M. Relative frequency of rotavirus and adenovirus among children aged 1–60 months hospitalized with acute diarrhoea in South-Western, Iran. *Jundishapur J Microbiol* 2012;6:47–50. <https://doi.org/10.5812/jjm.4072>
- [62] Habibi M, Gilani SM, Rahbarimanes A, Gilani SM. Nosocomial rotavirus gastroenteritis in pediatric patients: A cross sectional study using molecular analysis. *J Pediatr Sci* 2013. <https://doi.org/10.17334/jpvs.56676>
- [63] Khoshdel A, Parvin N, Doosti A, Eshraghi A. Prevalence and molecular characterization of rotaviruses as causes of nosocomial diarrhea in children. *Turk J Pediatr* 2014;56(5):469–74.
- [64] Kargar M, Khodadadi P, Najafi A, Ansari H. Predominance of rotavirus G8 genotype in hospitalized children with acute gastroenteritis in Yasuj, Iran. *Eur Rev Med Pharm Sci* 2014;18(5):699–702.
- [65] Nasab SDM, Sabahi F, Makvandi M, Samiee SM, Nadji SA, Ravanshad M. Epidemiology of rotavirus-norovirus co-infection and determination of norovirus genogrouping among children with acute gastroenteritis in Tehran, Iran. *Iran Biomed J* 2016;20(5):280–6. <https://doi.org/10.22045/ibj.2016.05>
- [66] Farsi M, et al. Prevalence and genetic diversity of norovirus genogroup II in children less than 5 years of age with acute gastroenteritis in Tehran, Iran. *Med Microbiol Immunol* 2018;207(3–4):201–10. <https://doi.org/10.1007/s00430-018-0541-6>
- [67] Azaran A, Makvandi M, Teimoori A, Ebrahimi S, Heydari F, Nikfar R. Distribution of rotavirus genotypes circulating in Ahwaz, Iran in 2016. *Iran Biomed J* 2018;22(2):107–16. <https://doi.org/10.22034/ibj.22.2.107>
- [68] Al-Kaissi EN, Makki M, Al-Khoja M. Aetiology and epidemiology of severe infantile diarrhoea in Baghdad, Iraq. *Eur J Sci Res* 2006;14(3):359–71.
- [69] Hussein AM, Hassan MK. Rotavirus infection among hospitalized children with acute watery diarrhea in Basrah - Iraq. *Bahrain Med Bull* 2000;22(4):170–3.
- [70] Al Marzoki J, Mohammad A, Mohammad AH. Prevalence of rotavirus causing acute diarrhea in children below two years in Babylon governorate in Iraq. *J Arab Board Med Spec* 2008;9(2):36–41.
- [71] Al-Mashhadani MN, et al. Norovirus gastroenteritis among children in Iraqi Kurdistan. *J Med Virol* 2008;80(3):506–9. <https://doi.org/10.1002/jmv.21099>
- [72] Ahmed HM, et al. Molecular characterization of rotavirus gastroenteritis strains, Iraqi Kurdistan. *Emerg Infect Dis* 2006;12(5):824–6. <https://doi.org/10.3201/eid1205.051422>
- [73] Jaff DO, Aziz TAG, Smith NR. The incidence of rotavirus and adenovirus infections among children with diarrhea in Sulaimani Province, Iraq. *J Biosci Med* 2016;4(1):720–6. <https://doi.org/10.4236/jbm.2016.41015>
- [74] Ahmed S, et al. Characterization of human rotaviruses circulating in Iraq in 2008: Atypical G8 and high prevalence of P[6] strains. *Infect, Genet Evol* 2013;16:212–7. <https://doi.org/10.1016/j.meegid.2012.12.003>
- [75] Abood WS, Al-Juboury SA, Al-Rodhan MA. Prevalence and factors associated with rotavirus infection among infants admitted for diarrhea in the region of Mid Iraq. *Al-Qadisiyah Med J* 2014;10(18):24–8.
- [76] Thwiny H. Detection of Norovirus in stool samples by RT-PCR from under five years age children hospitalized for acute gastroenteritis in Basrah, Iraq. *Univ Thi-Qar J Sci* 2015;5(2):47–54.
- [77] AL-Khafaji Younis AR, AL-Jiboury Hawraa J. Detection of rotavirus in diarrhea stool samples of children with acute gastroenteritis in Babylon governorate, Iraq. *Int Res J Microbiol* 2013;4(3):84–8.
- [78] Mohamed N, Al-Jassani MJ, Ahmed NS, Habel KA, Nasser FG. Determination norovirus genotypes in Baghdad children associated with acute gastroenteritis during year 2012–2013. *Iraqi J Biotechnol* 2015;14(2):52–62.

- [79] Mero WMS, Jameel AY, Amidy KSK. Microorganisms and viruses causing diarrhea in infants and primary school children and their relation with age and sex in Zakhko city, Kurdistan Region, Iraq. *Int J Res Med Sci* 2017;3(11):3266–73. <https://doi.org/10.18203/2320-6012.ijrms20151174>
- [80] Yassin BAG, et al. A trend of seasonality of enteric adenoviral gastroenteritis in pediatric patients less than five years from Baghdad. *J Res Med Dent Sci* 2018;6(4):18–23.
- [81] Azeez SS, Alsakee HM. <em> Cryptosporidium </em> spp. and rotavirus gastroenteritis and change of incidence after rotavirus vaccination among children in Raparin Pediatrics Hospital, Erbil, Iraq. *Med J Indones* 2017;26(3):190–7. <https://doi.org/10.13181/mji.v26i3.1957>
- [82] Al-Shuwaikh AMA. Frequency of rotavirus, adenovirus and astrovirus among patients with acute diarrhea by chromatographic immunoassay and enzyme linked immunosorbent assay. *J Biotechnol Res Cent* 2016;10(2):58–64.
- [83] Sameh Arif H, Hassan Hadi AM, Thaher Al-Marsome H, Salman Hassan J. Diagnosis of noroviruses in Iraqi children suffering from gastroenteritis by enzyme linked assay and conventional PCR. *Med J Basrah Univ* 2016;34(1):42–9. <https://doi.org/10.33762/mjbu.2016.111187>
- [84] Alsadawi AA, Al-Ammar M, Tuwaij NS. Viral agent that causing diarrhoea among children in AL-NAJAF Province, IRAQ. *World J Pharm Res* 2017;6(8):1–11. <https://doi.org/10.20959/wjpr20178-8947>
- [85] Mohamed NS, Maarof MN, Hussein HK. Determination of Human Sapovirus Genotypes Causing Gastroenteritis in Children under Five Years in Baghdad. *Al-Nahrain J Sci* 2017;20(3):121–6.
- [86] Harb A, Abraham S, Rusdi B, Laird T, O'Dea M, Habib I. Molecular detection and epidemiological features of selected bacterial, viral, and parasitic enteropathogens in stool specimens from children with acute diarrhea in Thi-Qar Governorate, Iraq. *Int J Environ Res Public Health* 2019;16(9). <https://doi.org/10.3390/ijerph16091573>
- [87] Hussein AA, Hussein RA, Shaker MJ. Enteric viruses co-infection with giardiasis among diarrheal children in Diyala Province – Iraq. *J Pure Appl Microbiol* 2018;12(2):793–799ya.
- [88] F. & et AL. “Molecular detection of astrovirus using reverse transcriptase quantitative polymerase chain reaction technique.” *Iraqi Journal of Agricultural Sciences*, vol. 51, no. Special, Art. no. Special, Jan. 2020, doi: 10.36103/ijas.v51i1Special.897.
- [89] Tuky HSH, Semender BA. Assessing risk factors and causative organisms of acute diarrhea in children under 5 years in AL-Hindiya, Karbala, Iraq. *Med J Babylon* 2019;16(4):357. [https://doi.org/10.4103/MJBL.MJBL\\_58\\_19](https://doi.org/10.4103/MJBL.MJBL_58_19)
- [90] Mohammed Hadi A, Al-Rubaey N, Al-Zamily Y. Detection of rotavirus, norovirus and astrovirus among children with acute gastroenteritis in BABYLON GOVERNORATE, IRAQ. *Biochem Cell Arch* 2020;20:3295.
- [91] Moussawi DKA-, Chelab RL, Jarullah BAH. Genotyping and phylogenetic of norovirus as main cause of children gastritis in Thi-Qar province. *J THI-QAR Sci* 2018;6(4) Accessed: Dec. 24, 2020. [Online]. Available: (<https://www.iasj.net/iasj/article/150858>).
- [92] Perl S, Goldman M, Berkovitch M, Kozer E. Characteristics of rotavirus gastroenteritis in hospitalized children in Israel. *Isr Med Assoc J* 2011;13(5):274–7. (May).
- [93] Givon-Lavi N, Greenberg D, Dagan R. Comparison between two severity scoring scales commonly used in the evaluation of rotavirus gastroenteritis in children. *Vaccine* 2008;26(46):5798–801. <https://doi.org/10.1016/j.vaccine.2008.08.030>
- [94] Stein M, et al. The burden and cost of ambulatory cases of rotavirus gastroenteritis in central Israel. *Isr Med Assoc J* 2010;12(3):168–71.
- [95] Muhsen K, et al. Incidence, characteristics, and economic burden of rotavirus gastroenteritis associated with hospitalization of Israeli children <5 years of age, 2007–2008. *J Infect Dis* 2009;200(Suppl 1):S254–63. <https://doi.org/10.1086/605425>
- [96] Muhsen K, et al. Incidence and characteristics of sporadic norovirus gastroenteritis associated with hospitalization of children less than 5 years of age in Israel. *Pediatr Infect Dis J* 2013;32(6):688–90. <https://doi.org/10.1097/INF.0b013e318287fc81>
- [97] Givon-Lavi N, Ben-Shimol S, Cohen R, Greenberg D, Dagan R. Rapid impact of rotavirus vaccine introduction to the National Immunization plan in southern Israel: comparison between 2 distinct populations. *Vaccine* 2015;33(16):1934–40. <https://doi.org/10.1016/j.vaccine.2015.02.062>
- [98] Leshem E, Givon-Lavi N, Vinjé J, Gregoricus N, Parashar U, Dagan R. Differences in norovirus-associated hospital visits between Jewish and Bedouin children in Southern Israel. *Pediatr Infect Dis J* 2015;34(9):1036–8. <https://doi.org/10.1097/INF.0000000000000786>
- [99] Muhsen K, et al. A significant and consistent reduction in rotavirus gastroenteritis hospitalization of children under 5 years of age, following the introduction of universal rotavirus immunization in Israel. *Hum Vaccin Immunother* 2015;11(10):2475–82. <https://doi.org/10.1080/21645515.2015.1056951>
- [100] Meqdam MM, Youssef MT, Nimri LF, Shurman AA, Rawashdeh MO, al-Khdour MS. Viral gastroenteritis among young children in northern Jordan. *J Trop Pediatr* 1997;43(6):349–52. <https://doi.org/10.1093/tropej/43.6.349>
- [101] Nimri LF, Hijazi S. Rotavirus-associated diarrhoea in children in a refugee camp in Jordan. *J Diarrhoeal Dis Res* 1996;14(1):1–4.
- [102] Youssef M, Shurman A, Bougnoux M-E, Rawashdeh M, Bretagne S, Strockbine N. Bacterial, viral and parasitic enteric pathogens associated with acute diarrhea in hospitalized children from northern Jordan. *FEMS Immunol Med Microbiol* 2000;28(3):257–63. <https://doi.org/10.1111/j.1574-695X.2000.tb01485.x>
- [103] Battikhi MNG. Epidemiological study on Jordanian patients suffering from diarrhoea. *N Microbiol* 2002;25(4):405–12.
- [104] Khuri-Bulos N, Khatib MAI. Importance of rotavirus as a cause of gastroenteritis in Jordan: a hospital based study. *Scand J Infect Dis* 2006;38(8):639–44. <https://doi.org/10.1080/00365540600606515>
- [105] Kaplan NM, et al. Detection and molecular characterisation of rotavirus and norovirus infections in Jordanian children with acute gastroenteritis. *Arch Virol* 2011;156(8):1477–80. <https://doi.org/10.1007/s00705-011-0996-x>
- [106] Salem K, Bdour S, Zeller M, Van Ranst M, Matthijssens J. Genotypes of rotavirus strains circulating in Amman, Jordan, in 2006/07 and their significance for the potential effectiveness of future rotavirus vaccination. *Arch Virol* 2011;156(9):1543–50. <https://doi.org/10.1007/s00705-011-1028-6>
- [107] Nafi O. Rotavirus gastroenteritis among children aged under 5 years in Al Karak, Jordan. *East Mediterr Health J* 2010;16(10):1064–9.
- [108] Khuffash FA, Majeed HA, Sethi SK, Al-Nakib W. Gastroenteritis in a regional hospital in Kuwait: some aspects of the disease. *Ann Trop Paediatr* 1982;2(3):123–8. <https://doi.org/10.1080/02724936.1982.11748243>
- [109] Sethi SK, Khuffash FA, al-Nakib W. Microbial etiology of acute gastroenteritis in hospitalized children in Kuwait. *Pediatr Infect Dis J* 1989;8(9):593–7. <https://doi.org/10.1097/00006454-198909000-00005>
- [110] MARMASH RW, et al. Genotypic characterization of rotaviruses and prevalence of serotype-specific serum antibodies in children in Kuwait. *Epidemiol Infect* 2007;135(8):1331–7. <https://doi.org/10.1017/S0950268807007868>
- [111] Al-Rashidi A, Chehadeh W, Szücs GG, Albert MJ. Different norovirus genotypes in patients with gastroenteritis in Kuwait. *J Med Virol* 2013;85(9):1611–8. <https://doi.org/10.1002/jmv.23645>
- [112] Albert MJ, Rotimi VO, Iqbal J, Chehadeh W. Evaluation of the xTAG Gastrointestinal Pathogen Panel Assay for the Detection of Enteric Pathogens in Kuwait. *Med Princ Pract* 2016;25(5):472–6. <https://doi.org/10.1159/000447698>
- [113] Mohammad HA, Madi NM, Al-Nakib W. Analysis of viral diversity in stool samples from infants and children with acute gastroenteritis in Kuwait using Metagenomics approach. *Virol J* 2020;17(1):10. <https://doi.org/10.1186/s12985-020-1287-5>
- [114] Dbaibo G, et al. Hospital-based surveillance study of rotavirus gastroenteritis in children under 5 years of age in Lebanon. *Trials Vaccinol* 2013;2:25–30. <https://doi.org/10.1016/j.trivac.2013.08.002>
- [115] Naous A, Naja Z, Zaatari N, Kamel R, Rajab M. Intestinal amebiasis: a concerning cause of acute gastroenteritis among hospitalized Lebanese children. *N Am J Med Sci* 2013;5(12):689–98. <https://doi.org/10.4103/1947-2714.123253>
- [116] Al-Ali RM, Chehadeh W, Hamze M, Dabboussi F, Hlais S, Mallat H. First description of gastroenteritis viruses in Lebanese children: a pilot study. *J Infect Public Health* 2011;4(2):59–64. <https://doi.org/10.1016/j.jiph.2011.01.002>
- [117] Melhem NM, et al. Clinical and epidemiological characteristics of norovirus gastroenteritis among hospitalized children in Lebanon. *World J Gastroenterol* 2016;22(48):10557–65. <https://doi.org/10.3748/wjg.v22.i48.10557>
- [118] Ali Z, et al. Rotavirus Genotypes and Vaccine Effectiveness from a Sentinel, Hospital-Based, Surveillance Study for Three Consecutive Rotavirus Seasons in Lebanon. *PLOS One* 2016;11(8):e0161345 <https://doi.org/10.1371/journal.pone.0161345>
- [119] Ghsein G, Salami A, Salloum L, Chedid P, Joumaa WH, Fakhir H. Surveillance study of acute gastroenteritis etiologies in hospitalized children in south Lebanon (SAGE study). *Pediatr Gastroenterol Hepatol Nutr* 2018;21(3):176–83. <https://doi.org/10.5223/pghn.2018.21.3.176>
- [120] Salami A, Fakhir H, Chakkour M, Salloum L, Bahmad HF, Ghsein G. Prevalence, risk factors and seasonal variations of different Enteropathogens in Lebanese hospitalized children with acute gastroenteritis. *BMC Pediatr* 2019;19(1):137. <https://doi.org/10.1186/s12887-019-1513-8>
- [121] Zaraket R, et al. Prevalence, risk factors, and clinical characteristics of rotavirus and adenovirus among Lebanese hospitalized children with acute gastroenteritis. *Heliyon* 2020;6(6):e04248 <https://doi.org/10.1016/j.heliyon.2020.e04248>
- [122] Ali MB, Ghenghesh KS, Aissa RB, Abuhalfia A, Dufani M. Etiology of childhood diarrhea in Zliten, Libya. *Saudi Med J* 2005;26(11):1759–65. (Nov).
- [123] Cunliffe NA, et al. Expanding global distribution of rotavirus serotype G9: detection in Libya, Kenya, and Cuba. *Emerg Infect Dis* 2001;7(5):890–2.
- [124] Abugalia M, et al. Clinical features and molecular epidemiology of rotavirus and norovirus infections in Libyan children. *J Med Virol* 2011;83(10):1849–56. <https://doi.org/10.1002/jmv.22141>
- [125] Rahouma A, et al. Enteric pathogens associated with childhood diarrhea in Tripoli-Libya. *Am J Trop Med Hyg* 2011;84(6):886–91. <https://doi.org/10.4269/ajtmh.2011.11-0116>
- [126] Kalaf RN, Elahmer OR, Zorgani AA, Ghenghesh KS. Rotavirus in children with diarrhea in Tripoli, Libya. *Libyan J Med* 2011;6. <https://doi.org/10.3402/ljm.v6i0.6041>
- [127] Miftah A, Alkoshi SIM, Ernst KC, Nagib SM. Frequency of rota virus infection among children in North-eastern region of Libya: a hospital-based study from Almarj. *Libyan J Med Sci* 2017;1(3):76. [https://doi.org/10.4103/LJMS.LJMS\\_17\\_17](https://doi.org/10.4103/LJMS.LJMS_17_17)
- [128] alkoshi S, ernst K, maimaiti N, dahlui M. Rota viral infection: a significant disease burden to Libya. *Iran J Public Health* 2014;43(10):1356–63. (Oct.).
- [129] Alkoshi S, Leshem E, Parashar UD, Dahlui M. Anticipating rotavirus vaccines—a pre-vaccine assessment of incidence and economic burden of rotavirus hospitalizations among children <5 year of age in Libya, 2012–13. *BMC Public Health* 2015;15:26. <https://doi.org/10.1186/s12889-015-1400-7>
- [130] Benhafid M, et al. Diversity of rotavirus strains circulating in children under 5 years of age admitted to hospital for acute gastroenteritis in morocco, june 2006 to may 2009. *J Med Virol* 2013;85(2):354–62. <https://doi.org/10.1002/jmv.23445>



- [131] El Qazoui M, et al. Rotavirus and Norovirus infections among acute gastroenteritis children in Morocco. *BMC Infect Dis* 2014;14:300. <https://doi.org/10.1186/1471-2334-14-300>
- [132] Benmessaud R, et al. Aetiology, epidemiology and clinical characteristics of acute moderate-to-severe diarrhoea in children under 5 years of age hospitalized in a referral paediatric hospital in Rabat, Morocco. *J Med Microbiol* 2015;64(Pt 1):84–92. <https://doi.org/10.1099/jmm.0.079830-0>
- [133] Benhafid M, et al. Effect of monovalent rotavirus vaccine on rotavirus disease burden and circulating rotavirus strains among children in Morocco. *J Med Virol* 2015;87(6):944–53. <https://doi.org/10.1002/jmv.24122>
- [134] Aithala G, Al Dhahry SH, Saha A, Elbualy MS. Epidemiological and clinical features of rotavirus gastroenteritis in Oman. *J Trop Pediatr* 1996;42(1):54–7. <https://doi.org/10.1093/tropej/42.1.54>
- [135] Al Baqlani S, et al. Molecular characterization of rotavirus strains circulating in Oman in 2005. *J Infect Dis* 2010;202(Suppl):S258–62. <https://doi.org/10.1086/653582>
- [136] Al Awaidy SA, et al. Considerations for introduction of a rotavirus vaccine in Oman: rotavirus disease and economic burden. *J Infect Dis* 2009;200(Supplement\_1):S248–53. <https://doi.org/10.1086/605339>
- [137] Baqlani S. Molecular characterization of group A rotavirus genotypes circulating in Oman between 2009 and 2013. *J Virol Emerg Dis* 2016;2. <https://doi.org/10.1696/2471-822X.113>
- [138] Abu-Elamreen FH, Abed AA, Sharif FA. Viral, bacterial and parasitic etiology of pediatric diarrhea in Gaza, Palestine. *Med Princ Pract* 2008;17(4):296–301. <https://doi.org/10.1159/000129609>
- [139] Al-Thani A, Baris M, Al-Lawati N, Al-Dhahry S. Characterising the aetiology of severe acute gastroenteritis among patients visiting a hospital in Qatar using real-time polymerase chain reaction. *BMC Infect Dis* 2013;13:329. <https://doi.org/10.1186/1471-2334-13-329>
- [140] Humphrey JM, et al. Multiplex polymerase chain reaction for detection of gastrointestinal pathogens in migrant workers in Qatar. *Am J Trop Med Hyg* 2016;95(6):1330–7. <https://doi.org/10.4269/ajtmh.16-0464>
- [141] Mathew S, Alansari K, Smatti MK, Zaraket H, Al Thani AA, Yassine HM. Epidemiological, molecular, and clinical features of norovirus infections among pediatric patients in Qatar. *Viruses* 2019;11(5):400. <https://doi.org/10.3390/v11050400>
- [142] Mathew S, Al Ansari K, Al Thani AA, Zaraket H, Yassine HM. Epidemiological, molecular, and clinical features of rotavirus infections among pediatrics in Qatar. *Eur J Clin Microbiol Infect Dis* 2021. <https://doi.org/10.1007/s10096-020-04108-y>
- [143] Akhter J, Qadri SM, Myint SH. Gastrointestinal adenovirus infections in a tertiary referral centre in Saudi Arabia. *Eur J Clin Microbiol Infect Dis* 1995;14(8):707–10. <https://doi.org/10.1007/BF01690880>
- [144] el-Sheikh SM, el-Assouli SM. Prevalence of viral, bacterial and parasitic enteropathogens among young children with acute diarrhoea in Jeddah, Saudi Arabia. *J Health Popul Nutr* 2001;19(1):25–30.
- [145] Arif M, El-Hazmi MM. Viral gastroenteritis in Saudi children. *Saudi Med J* 2005;26(6):1017–8.
- [146] Tayeb HT, Dela Cruz DM, Al-Qahtani A, Al-Ahdal MN, Carter MJ. Enteric viruses in pediatric diarrhea in Saudi Arabia. *J Med Virol* 2008;80(11):1919–29. <https://doi.org/10.1002/jmv.21291>
- [147] Ghazi HO, Khan MA, Telmesani AM, Idress B, Mahomed MF. Rotavirus infection in infants and young children in Makkah, Saudi Arabia. *J Pak Med Assoc* 2005;55(6):231–4.
- [148] Kheyami AM, Nakagomi T, Nakagomi O, Dove W, Hart CA, Cunliffe NA. Molecular epidemiology of rotavirus diarrhea among children in Saudi Arabia: first detection of G9 and G12 strains. *J Clin Microbiol* 2008;46(4):1185–91. <https://doi.org/10.1128/JCM.02244-07>
- [149] Kheyami AM, Areeshi MY, Dove W, Nakagomi O, Cunliffe NA, Anthony Hart C. Characterization of rotavirus strains detected among children and adults with acute gastroenteritis in Gizan, Saudi Arabia. *Saudi Med J* 2008;29(1):90–3. (Jan.).
- [150] Meqdam MM. Prevalence of group A rotavirus, enteric adenovirus, norovirus and astrovirus infections among children with acute gastroenteritis in al-qassim, Saudi Arabia. *Pak J Med Sci* 2007;39(30):551–5.
- [151] Khalil M, et al. Gastroenteritis attributable to rotavirus in hospitalized Saudi Arabian children in the period 2007–2008. *Clin Epidemiol* 2015;7:129–37. <https://doi.org/10.2147/CLEP.S69502>
- [152] Obeid OE. Characterization of human rotavirus subgroups and serotypes in children under five with acute gastroenteritis in a Saudi Hospital. *J Fam Community Med* 2011;18(1):22–5. <https://doi.org/10.4103/1319-1683.78634>
- [153] Johargy A, Ghazi H, Mumenah A. Frequency of viral, bacterial and parasitic enteropathogens among young children with acute diarrhoea in Saudi Arabia. *J Pak Med Assoc* 2010;60(6):456–9.
- [154] Tayeb HT, Balkhy HH, Aljuhani SM, Elbanyan E, Alalola S, Alshaalan M. Increased prevalence of rotavirus among children associated gastroenteritis in Riyadh Saudi Arabia. *Virol J* 2011;8:548. <https://doi.org/10.1186/1743-422X-8-548>
- [155] Affi R, Nabih M. The burden of Rotavirus gastroenteritis among hospitalized pediatric patients in a tertiary referral hospital in Jeddah. *Ann Saudi Med* 2013;33(3):241–6. <https://doi.org/10.5144/0256-4947.2013.241>
- [156] Ashshi AM. Is rotavirus infection still responsible for acute gastroenteritis and severe diarrhea among children in holy Makkah? *Res J Med Sci* 2012;6(4):170–4. <https://doi.org/10.3923/rjmsci.2012.170.174>
- [157] Aly M, Al Khairy A, Al Johani S, Balkhy H. Unusual rotavirus genotypes among children with acute diarrhea in Saudi Arabia. *BMC Infect Dis* 2015;15:192. <https://doi.org/10.1186/s12879-015-0923-y>
- [158] Sabra S. Research report; study the process of rotavirus infection for children which affecting the community public health with reference to the epidemic, incidence of morbidity and mortality at Al-Taif, KSA. *World Appl Sci J* 2014;29(1):80–8.
- [159] Hegazi MA, et al. Is rotavirus still a major cause for diarrheal illness in hospitalized pediatric patients after rotavirus vaccine introduction in the Saudi national immunization program? *Medicine* 2017;96(15):e6574. <https://doi.org/10.1097/MD.00000000000006574>
- [160] Zaki A, Abousekkien M, Alkholly UM, Eid A. Effectiveness and impact of rotavirus vaccines in Saudi Arabia: a single hospital-based study. *Arab J Gastroenterol* 2017;18(3):140–3. <https://doi.org/10.1016/j.ajg.2017.09.008>
- [161] Hawash YA, Ismail KA, Almeahdi M. High frequency of enteric protozoan, viral, and bacterial potential pathogens in community-acquired acute diarrheal episodes: evidence based on results of luminex gastrointestinal pathogen panel assay. *Korean J Parasitol* 2017;55(5):513–21. <https://doi.org/10.3347/kjp.2017.55.5.513>
- [162] Elhag WI, Saeed HA, Omer EFE, Ali AS. Prevalence of rotavirus and adenovirus associated with diarrhea among displaced communities in Khartoum, Sudan. *BMC Infect Dis* 2013;13(1):209. <https://doi.org/10.1186/1471-2334-13-209>
- [163] Mustafa A, et al. Baseline burden of rotavirus disease in Sudan to monitor the impact of vaccination. *Pediatr Infect Dis J* 2014;33:S23. <https://doi.org/10.1097/INF.0000000000000095>
- [164] Magzoub MA, Bilal NE, Bilal JA, Alzohairy MA, Elamin BK, Gasim GI. Detection and sequencing of rotavirus among sudanese children. *Pan Afr Med J* 2017;28. <https://doi.org/10.11604/pamj.2017.28.87.11008>
- [165] Abdalla AE, Nagi AM, Elawa HE. Frequency of rotavirus infection among children with diarrhea in omdurman pediatric hospital, Sudan. *Sudan J Med Sci* 2013;8(4):163–8. <https://doi.org/10.4314/sjms.v8i4>
- [166] Saeed A, Abd H, Sandstrom G. Microbial aetiology of acute diarrhoea in children under five years of age in Khartoum, Sudan. *J Med Microbiol* 2015;64(Pt 4):432–7. <https://doi.org/10.1099/jmm.0.000043>
- [167] Adam MA, et al. Molecular survey of viral and bacterial causes of childhood diarrhea in Khartoum State, Sudan. *Front Microbiol* 2018;9. <https://doi.org/10.3389/fmicb.2018.00112>
- [168] Mohamed EE, Hussein ARME, Mustafa MO, Elkhidir IM, Enan KA. Molecular detection of rotavirus (A and B) and astrovirus in children less than 5 years with gastroenteritis in Khartoum and Aljazeera States, Sudan. *Int J Sci Res Sci, Eng Technol* 2018;4(10):07–13. <https://doi.org/10.32628/IJSRSET184473>
- [169] Trabelsi A, Peenze I, Pager C, Jeddi M, Steele D. Distribution of rotavirus VP7 serotypes and VP4 genotypes circulating in Soussa, Tunisia, from 1995 to 1999: emergence of natural human reassortants. *J Clin Microbiol* 2000;38(9):3415–9.
- [170] Chouikha A, et al. Group A rotavirus strains circulating in the eastern center of Tunisia during a ten-year period (1995–2004). *J Med Virol* 2007;79(7):1002–8. <https://doi.org/10.1002/jmv.20919>
- [171] Al-Gallas N, Bahri O, Bouratbeen A, Ben Haasen A, Ben Aissa R. Etiology of acute diarrhea in children and adults in Tunisia, Tunisia, with emphasis on diarrheagenic *Escherichia coli*: prevalence, phenotyping, and molecular epidemiology. *Am J Trop Med Hyg* 2007;77(3):571–82.
- [172] Fodha I, et al. Identification of viral agents causing diarrhea among children in the Eastern Center of Tunisia. *J Med Virol* 2006;78(9):1198–203. <https://doi.org/10.1002/jmv.20681>
- [173] Sdiri-Loulizi K, et al. Acute infantile gastroenteritis associated with human enteric viruses in Tunisia. *J Clin Microbiol* 2008;46(4):1349–55. <https://doi.org/10.1128/JCM.02438-07>
- [174] Hassine-Zaafrane M, et al. Prevalence and genetic diversity of norovirus infection in Tunisian children (2007–2010). *J Med Virol* 2013;85(6):1100–10. <https://doi.org/10.1002/jmv.23552>
- [175] Hassine-Zaafrane M, et al. The molecular epidemiology of circulating rotaviruses: three-year surveillance in the region of Monastir, Tunisia. *BMC Infect Dis* 2011;11:266. <https://doi.org/10.1186/1471-2334-11-266>
- [176] Soltani MS, et al. Epidemiology and medical cost of hospitalization due to rotavirus gastroenteritis among children under 5 years of age in the central-east of Tunisia. *East Mediterr Health J* 2015;21(8):584–90. <https://doi.org/10.26719/2015.21.8.584>
- [177] Moussa A, et al. Distribution of rotavirus VP7 and VP4 genotypes circulating in Tunisia from 2009 to 2014: Emergence of the genotype G12. *J Med Microbiol* 2016;65(9):1028–37. <https://doi.org/10.1099/jmm.0.000305>
- [178] Ayouni S, et al. Relationship between GII.3 norovirus infections and blood group antigens in young children in Tunisia. *Clin Microbiol Infect* 2015;21(9). <https://doi.org/10.1016/j.cmi.2015.05.015>
- [179] Bennour H, et al. Molecular characterization of group A rotavirus among children aged under 5 years in Tunisia, 2015–2017. *J Med Microbiol* 2019;68(8):1240–3. <https://doi.org/10.1099/jmm.0.001031>
- [180] Ijaz MK, et al. Seasonality and prevalence of rotavirus in Al-Ain, United Arab Emirates. *Clin Diagn Virol* 1994;2(6):323–9. [https://doi.org/10.1016/0928-0197\(94\)90002-7](https://doi.org/10.1016/0928-0197(94)90002-7)
- [181] Howidi M, Balhaj G, Yaseen H, Gopala K, Van Doorn LJ, DeAntonio R. Burden and genotyping of rotavirus disease in the United Arab Emirates. *Hum Vaccin Immunother* 2014;10(8):2284–9. <https://doi.org/10.1016/hv.29386>
- [182] Alsuwaidi AR, et al. Etiology of diarrhea by multiplex polymerase chain reaction among young children in the United Arab Emirates: a case-control study. *BMC Infect Dis* 2021;21(1):7. <https://doi.org/10.1186/s12879-020-05693-1>
- [183] Al-Badani A, Al-Areqi L, Majily A, AL-Sallami S, AL-Madhagi A, Amood AL-Kamarany M. Rotavirus diarrhea among children in Taiz, Yemen: prevalence – risk factors and detection of genotypes. *Int J Pediatr* 2014;2014. <https://doi.org/10.1155/2014/928529>

- [184] Kirby A, et al. Rotavirus and norovirus infections in children in Sana'a, Yemen. *Trop Med Int Health* 2011;16(6):680–4. <https://doi.org/10.1111/j.1365-3156.2011.02756.x>
- [185] Banajeh SM, Abu-Asba BA. The epidemiology of all-cause and rotavirus acute gastroenteritis and the characteristics of rotavirus circulating strains before and after rotavirus vaccine introduction in Yemen: analysis of hospital-based surveillance data. *BMC Infect Dis* 2015;15:418. <https://doi.org/10.1186/s12879-015-1165-8>
- [186] Amod AL-Kamarany M, Al-Areqi L, Mujally A, Alkashy F, Nasser A, Jumaan AO. Diarrheal diseases hospitalization in Yemen before and after rotavirus vaccination. *Scientifica* 2016;2016. <https://doi.org/10.1155/2016/8485417>
- [187] Sadiq A, et al. Molecular characterization of human group A rotavirus genotypes circulating in Rawalpindi, Islamabad, Pakistan during 2015–2016. *PLOS One* 2019;14(7):e0220387. <https://doi.org/10.1371/journal.pone.0220387>
- [188] Aoki ST, Trask SD, Coulson BS, Greenberg HB, Dormitzer PR, Harrison SC. Cross-linking of rotavirus outer capsid protein VP7 by antibodies or disulfides inhibits viral entry. *J Virol* 2011;85(20):10509–17. <https://doi.org/10.1128/JVI.00234-11>
- [189] Monnier N, Higo-Moriguchi K, Sun Z-Y, Prasad BVV, Taniguchi K, Dormitzer PR. High-resolution molecular and antigen structure of the VP8\* core of a sialic acid-independent human rotavirus strain. *J Virol* 2006;80(3):1513–23. <https://doi.org/10.1128/JVI.80.3.1513-1523.2006>
- [190] Walker CLF, et al. Global burden of childhood pneumonia and diarrhoea. *Lancet* 2013;381(9875):1405–16. [https://doi.org/10.1016/S0140-6736\(13\)60222-6](https://doi.org/10.1016/S0140-6736(13)60222-6)
- [191] Dennehy PH. Rotavirus vaccines: an overview. *Clin Microbiol Rev* 2008;21(1):198–208. <https://doi.org/10.1128/CMR.00029-07>
- [192] Bhandari N, et al. Efficacy of a monovalent human-bovine (116E) rotavirus vaccine in Indian infants: a randomised double blind placebo controlled trial. *Lancet* 2014;383(9935):2136–43. [https://doi.org/10.1016/S0140-6736\(13\)62630-6](https://doi.org/10.1016/S0140-6736(13)62630-6)
- [193] Riddle MS, Chen WH, Kirkwood CD, MacLennan CA. Update on vaccines for enteric pathogens. *Clin Microbiol Infect* 2018;24(10):1039–45. <https://doi.org/10.1016/j.cmi.2018.06.023>
- [194] J.H. Bloomberg, "VIEW-hub report: global vaccine introduction and implementation," 2021.
- [195] Muhsen K, et al. Incidence of rotavirus gastroenteritis hospitalizations and genotypes, before and five years after introducing universal immunization in Israel. *Vaccine* 2016;34(48):5916–22. <https://doi.org/10.1016/j.vaccine.2016.10.021>
- [196] Al-Ayed MSZ, Asaad AM, Qureshi MA, Hawan AA. Epidemiology of group A rotavirus infection after the introduction of monovalent vaccine in the national immunization program of Saudi Arabia. *J Med Virol* 2017;89(3):429–34. <https://doi.org/10.1002/jmv.24664>
- [197] Debellut F, et al. Introduction of rotavirus vaccination in Palestine: an evaluation of the costs, impact, and cost-effectiveness of ROTARIX and ROTAVAC. *PLOS One* 2020;15(2):e0228506. <https://doi.org/10.1371/journal.pone.0228506>
- [198] Cunliffe NA, et al. Healthcare-associated viral gastroenteritis among children in a large pediatric hospital, United Kingdom. *Emerg Infect Dis* 2010;16(1):55–62. <https://doi.org/10.3201/eid1601.090401>
- [199] Wang L-P, et al. Etiological, epidemiological, and clinical features of acute diarrhea in China. *Nat Commun* 2021;12(1). <https://doi.org/10.1038/s41467-021-22551-z>
- [200] Podkolzin AT, et al. Hospital-based surveillance of rotavirus and other viral agents of diarrhea in children and adults in Russia, 2005–2007. *J Infect Dis* 2009;200(Suppl 1):S228–33. <https://doi.org/10.1086/605054>
- [201] Tran A, et al. Prevalence of rotavirus, adenovirus, norovirus, and astrovirus infections and coinfections among hospitalized children in Northern France. *J Clin Microbiol* 2010;48(5):1943–6. <https://doi.org/10.1128/JCM.02181-09>
- [202] Rossouw E, Brauer M, Meyer P, du Plessis NM, Avenant T, Mans J. Virus etiology, diversity and clinical characteristics in South African children hospitalised with gastroenteritis. *Viruses* 2021;13(2). <https://doi.org/10.3390/v13020215>
- [203] Amaral MSC, et al. The prevalence of norovirus, astrovirus and adenovirus infections among hospitalised children with acute gastroenteritis in Porto Velho, state of Rondônia, western Brazilian Amazon. *Mem Inst Oswaldo Cruz* 2015;110(2):215–21. <https://doi.org/10.1590/0074-02760140381>
- [204] G. 2015 M, C. of D. Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the global burden of disease study 2015. *Lancet* 2016;388(10053):1459. [https://doi.org/10.1016/S0140-6736\(16\)31012-1](https://doi.org/10.1016/S0140-6736(16)31012-1)
- [205] Robilotti E, Deresinski S, Pinsky BA. Norovirus. *Clin Microbiol Rev* 2015;28(1):134–64. <https://doi.org/10.1128/CMR.00075-14>
- [206] Magwalivha M, Kabue J-P, Traore AN, Potgieter N. Prevalence of human sapovirus in low and middle income countries. *Adv Virol* 2018;2018:5986549. <https://doi.org/10.1155/2018/5986549>
- [207] Phan TG, et al. Genetic heterogeneity, evolution, and recombination in noroviruses. *J Med Virol* 2007;79(9):1388–400. <https://doi.org/10.1002/jmv.20924>
- [208] Sidoti F, Rittà M, Costa C, Cavallo R. Diagnosis of viral gastroenteritis: limits and potential of currently available procedures. *J Infect Dev Ctries* 2015;9(6):551–61. <https://doi.org/10.3855/jidc.7051>
- [209] Wilhelmi I, Roman E, Sanchez-Fauquier A. Viruses causing gastroenteritis. *Clin Microbiol Infect* 2003;9(4):247–62. <https://doi.org/10.1046/j.1469-0691.2003.00560.x>
- [210] Fletcher SM, McLaws M-L, Ellis JT. Prevalence of gastrointestinal pathogens in developed and developing countries: systematic review and meta-analysis. *J Public Health Res* 2013;2(1):42–53. <https://doi.org/10.4081/jphr.2013.e9>
- [211] Bányai K, et al. Systematic review of regional and temporal trends in global rotavirus strain diversity in the pre rotavirus vaccine era: insights for understanding the impact of rotavirus vaccination programs. *Vaccine* 2012;30(Suppl 1):A122–30. <https://doi.org/10.1016/j.vaccine.2011.09.111>
- [212] Dóró R, et al. Review of global rotavirus strain prevalence data from six years post vaccine licensure surveillance: is there evidence of strain selection from vaccine pressure? *Infect Genet Evol* 2014;28:446–61. <https://doi.org/10.1016/j.meegid.2014.08.017>
- [213] Lestari FB, Vongpunsawad S, Wanlapakorn N, Poovorawan Y. Rotavirus infection in children in Southeast Asia 2008–2018: disease burden, genotype distribution, seasonality, and vaccination. *J Biomed Sci* 2020;27:66. <https://doi.org/10.1186/s12929-020-00649-8>
- [214] Seheri LM, et al. Rotavirus strain diversity in Eastern and Southern African countries before and after vaccine introduction. *Vaccine* 2018;36(47):7222–30. <https://doi.org/10.1016/j.vaccine.2017.11.068>
- [215] Kawai K, O'Brien MA, Goveia MG, Mast TC, El Khoury AC. Burden of rotavirus gastroenteritis and distribution of rotavirus strains in Asia: a systematic review. *Vaccine* 2012;30(7):1244–54. <https://doi.org/10.1016/j.vaccine.2011.12.092>
- [216] Gentsch JR, et al. G and P types of circulating rotavirus strains in the United States during 1996–2005: nine years of prevaccine data. *J Infect Dis* 2009;200(Supplement\_1):S99–109. <https://doi.org/10.1086/605038>
- [217] Ogilvie I, Khoury H, Goetghebeur MM, El Khoury AC, Giaquinto C. Burden of community-acquired and nosocomial rotavirus gastroenteritis in the pediatric population of Western Europe: a scoping review. *BMC Infect Dis* 2012;12:62. <https://doi.org/10.1186/1471-2334-12-62>
- [218] Parra GI, Espinola EE. Nucleotide mismatches between the VP7 gene and the primer are associated with genotyping failure of a specific lineage from G1 rotavirus strains. *Virol J* 2006;3:35. <https://doi.org/10.1186/1743-422X-3-35>
- [219] Rahman M, et al. Typing of human rotaviruses: nucleotide mismatches between the VP7 gene and primer are associated with genotyping failure. *Virol J* 2005;2:24. <https://doi.org/10.1186/1743-422X-2-24>
- [220] Espinola EE, Parra GI, Russomando G, Arbiza J. Genetic diversity of the VP4 and VP7 genes affects the genotyping of rotaviruses: analysis of Paraguayan strains. *Infect Genet Evol* 2008;8(1):94–9. <https://doi.org/10.1016/j.meegid.2007.08.003>
- [221] Mitui MT, et al. Inaccurate identification of rotavirus genotype G9 as genotype G3 strains due to primer mismatch. *Virol J* 2012;9:144. <https://doi.org/10.1186/1743-422X-9-144>
- [222] Kambhampati A, Payne DC, Costantini V, Lopman BA. Host genetic susceptibility to enteric viruses: a systematic review and meta-analysis. *Clin Infect Dis* 2016;62(1):11–8. <https://doi.org/10.1093/cid/civ873>
- [223] Cannon JL, et al. Global trends in norovirus genotype distribution among children with acute gastroenteritis. *Emerg Infect Dis* 2021;27(5):1438–45. <https://doi.org/10.3201/eid2705.204756>
- [224] Mans J. Norovirus infections and disease in lower-middle- and low-income countries, 1997–2018. *Viruses* 2019;11(4):4. <https://doi.org/10.3390/v11040341>
- [225] Lindesmith LC, et al. Mechanisms of GII.4 norovirus persistence in human populations. *PLOS Med* 2008;5(2):e31. <https://doi.org/10.1371/journal.pmed.0050031>
- [226] Aoki ST, Settembre EC, Trask SD, Greenberg HB, Harrison SC, Dormitzer PR. Structure of rotavirus outer-layer protein VP7 bound with a neutralizing Fab. *Science* 2009;324(5933):1444–7. <https://doi.org/10.1126/science.1170481>
- [227] Espinola EE, Amarilla A, Arbiza J, Parra GI. Sequence and phylogenetic analysis of the VP4 gene of human rotaviruses isolated in Paraguay. *Arch Virol* 2008;153(6):1067–73. <https://doi.org/10.1007/s00705-008-0096-8>
- [228] Zeller M, et al. Genetic analyses reveal differences in the VP7 and VP4 Antigenic Epitopes between Human Rotaviruses Circulating in Belgium and rotaviruses in Rotarix and RotaTeq. *J Clin Microbiol* 2012;50(3):966–76. <https://doi.org/10.1128/JCM.05590-11>
- [229] Maranhão AG, Vianez-Júnior JLSG, Benati FJ, Bisch PM, Santos N. Polymorphism of rotavirus genotype G1 in Brazil: In silico analysis of variant strains circulating in Rio de Janeiro from 1996 to 2004. *Infect, Genet Evol* 2012;12(7):1397–404. <https://doi.org/10.1016/j.meegid.2012.04.018>
- [230] Mladenova Z, Iturriza-Gomara M, Esona MD, Gray J, Korsun N. Genetic characterization of Bulgarian rotavirus isolates and detection of rotavirus variants: challenges for the rotavirus vaccine program? *J Med Virol* 2011;83(2):348–56. <https://doi.org/10.1002/jmv.21919>
- [231] Cashman O, et al. Molecular characterization of group A rotaviruses detected in children with gastroenteritis in Ireland in 2006–2009. *Epidemiol Infect* 2012;140(2):247–59. <https://doi.org/10.1017/S0950268811000306>
- [232] Pietsch C, Schuster V, Liebert UG. A hospital based study on inter- and intra-genotypic diversity of human rotavirus A VP4 and VP7 gene segments, Germany. *J Clin Virol* 2011;50(2):136–41. <https://doi.org/10.1016/j.jcv.2010.10.013>
- [233] László B, et al. Surveillance of human rotaviruses in 2007–2011, Hungary: exploring the genetic relatedness between vaccine and field strains. *J Clin Virol* 2012;55(2):140–6. <https://doi.org/10.1016/j.jcv.2012.06.016>
- [234] Chan-it W, et al. Detection and genetic characterization of rotavirus infections in non-hospitalized children with acute gastroenteritis in Japan, 2007–2009. *Infect, Genet Evol* 2011;11(2):415–22. <https://doi.org/10.1016/j.meegid.2010.11.018>
- [235] Nakagomi T, et al. Molecular characterization of rotavirus strains detected during a clinical trial of a human rotavirus vaccine in Blantyre, Malawi. *Vaccine* 2012;30:A140–51. <https://doi.org/10.1016/j.vaccine.2011.09.119>
- [236] Khananurak K, Vutithanachot V, Simakachorn N, Theamboonlers A, Chongsrisawat V, Poovorawan Y. Prevalence and phylogenetic analysis of rotavirus genotypes in Thailand between 2007 and 2009. *Infect, Genet Evol* 2010;10(4):537–45. <https://doi.org/10.1016/j.meegid.2010.02.003>

- [237] Afrad MH, et al. Changing profile of rotavirus genotypes in Bangladesh, 2006–2012. *BMC Infect Dis* 2013;13(1):320. <https://doi.org/10.1186/1471-2334-13-320>
- [238] Karafillakis E, Hassounah S, Atchison C. Effectiveness and impact of rotavirus vaccines in Europe, 2006–2014. *Vaccine* 2015;33(18):2097–107. <https://doi.org/10.1016/j.vaccine.2015.03.016>
- [239] de Oliveira LH, Camacho LAB, Coutinho ESF, Ruiz-Matus C, Leite JPG. Rotavirus vaccine effectiveness in Latin American and Caribbean countries: a systematic review and meta-analysis. *Vaccine* 2015;33(Suppl 1):A248–54. <https://doi.org/10.1016/j.vaccine.2014.11.060>
- [240] Rha B, et al. Effectiveness and impact of rotavirus vaccines in the United States – 2006–2012. *Expert Rev Vaccin* 2014;13(3):365–76. <https://doi.org/10.1586/14760584.2014.877846>
- [241] Linhares AC, et al. Efficacy and safety of an oral live attenuated human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in Latin American infants: a randomised, double-blind, placebo-controlled phase III study. *Lancet* 2008;371(9619):1181–9. [https://doi.org/10.1016/S0140-6736\(08\)60524-3](https://doi.org/10.1016/S0140-6736(08)60524-3)
- [242] Vesikari T, et al. Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study. *Lancet* 2007;370(9601):1757–63. [https://doi.org/10.1016/S0140-6736\(07\)61744-9](https://doi.org/10.1016/S0140-6736(07)61744-9)
- [243] Trinh QD, et al. Sequence analysis of the VP7 gene of human rotaviruses G2 and G4 isolated in Japan, China, Thailand, and Vietnam during 2001–2003. *J Med Virol* 2010;82(5):878–85. <https://doi.org/10.1002/jmv.21630>
- [244] Doan YH, Nakagomi T, Cunliffe NA, Pandey BD, Sherchand JB, Nakagomi O. The occurrence of amino acid substitutions D96N and S242N in VP7 of emergent G2P[4] rotaviruses in Nepal in 2004–2005: a global and evolutionary perspective. *Arch Virol* 2011;156(11):1969–78. <https://doi.org/10.1007/s00705-011-1083-z>
- [245] Do LP, Nakagomi T, Doan YH, Kitahori Y, Nakagomi O. Molecular evolution of the VP7 gene of Japanese G2 rotaviruses before vaccine introduction. *Arch Virol* 2014;159(2):315–9. <https://doi.org/10.1007/s00705-013-1804-6>
- [246] Ahmed K, et al. Molecular characterization of VP7 gene of human rotaviruses from Bangladesh. *Virus Genes* 2010;40(3):347–56. <https://doi.org/10.1007/s11262-010-0463-x>
- [247] Thanh HD, Tran VT, Lim I, Kim W. Emergence of human G2P[4] rotaviruses in the post-vaccination era in South Korea: footprints of multiple interspecies reassortment events. *Sci Rep* 2018;8(1):1. <https://doi.org/10.1038/s41598-018-24511-y>
- [248] Ciarlet M, Reggeti F, Piña CI, Liprandi F. Equine rotaviruses with G14 serotype specificity circulate among Venezuelan horses. *J Clin Microbiol* 1994;32(10):2609–12. (Oct.).
- [249] Ciarlet M, Hoshino Y, Liprandi F. Single point mutations may affect the serotype reactivity of serotype G11 porcine rotavirus strains: a widening spectrum? *J Virol* 1997;71(11):8213–20. (Nov.).
- [250] Roczo-Farkas S, et al. The impact of rotavirus vaccines on genotype diversity: a comprehensive analysis of 2 decades of Australian surveillance data. *J Infect Dis* 2018;218(4):546–54. <https://doi.org/10.1093/infdis/jiy197>
- [251] Lartey BL, et al. Rotavirus strain distribution in Ghana pre- and post- rotavirus vaccine introduction. *Vaccine* 2018;36(47):7238–42. <https://doi.org/10.1016/j.vaccine.2018.01.010>
- [252] Arana A, et al. Molecular epidemiology of G12 rotavirus strains during eight consecutive epidemic seasons in the Basque Country (North of Spain), 2010–2018. *Infect, Genet Evol* 2019;71:67–75. <https://doi.org/10.1016/j.meegid.2019.03.016>
- [253] Wylie KM, Stanley KM, TeKippe EM, Mihindukulasuriya K, Storch GA. Resurgence of rotavirus genotype G12 in St. Louis during the 2014–2015 rotavirus season. *J Pediatr Infect Dis Soc* 2017;6(4):346–51. <https://doi.org/10.1093/jpids/piw065>
- [254] Rakau KG, et al. Genetic characterization of G12P[6] and G12P[8] rotavirus strains collected in six African countries between 2010 and 2014. *BMC Infect Dis* 2021;21(1):107. <https://doi.org/10.1186/s12879-020-05745-6>
- [255] Jiang V, Jiang B, Tate J, Parashar UD, Patel MM. Performance of rotavirus vaccines in developed and developing countries. *Hum Vaccin* 2010;6(7):532–42. <https://doi.org/10.4161/hv.6.7.11278>
- [256] Velasquez DE, Jiang B. Evolution of P[8], P[4], and P[6] VP8\* genes of human rotaviruses globally reported during 1974 and 2017: possible implications for rotavirus vaccines in development. *Hum Vaccin Immunother* 2019;15(12):3003–8. <https://doi.org/10.1080/21645515.2019.1619400>
- [257] Dormitzer PR, Sun Z-Y, Wagner G, Harrison SC. The rhesus rotavirus VP4 sialic acid binding domain has a galectin fold with a novel carbohydrate binding site. *EMBO J* 2002;21(5):885–97. <https://doi.org/10.1093/emboj/21.5.885>
- [258] Zeller M, et al. Emerging OP354-like P[8] rotaviruses have rapidly dispersed from Asia to other continents. *Mol Biol Evol* 2015;32(8):2060–71. <https://doi.org/10.1093/molbev/msv088>
- [259] Atchison C, et al. Reduction in rotavirus disease due to the infant immunisation programme in England; evidence from national surveillance. *J Infect* 2015;71(1):128–31. <https://doi.org/10.1016/j.jinf.2015.01.007>
- [260] Sun Z-W, et al. Association of rotavirus vaccines with reduction in rotavirus gastroenteritis in children younger than 5 years: a systematic review and meta-analysis of randomized clinical trials and observational studies. *JAMA Pediatr* 2021;175(7):e210347. <https://doi.org/10.1001/jamapediatrics.2021.0347>
- [261] Patel MM, Glass R, Desai R, Tate JE, Parashar UD. Fulfilling the promise of rotavirus vaccines: how far have we come since licensure? *Lancet Infect Dis* 2012;12(7):561–70. [https://doi.org/10.1016/S1473-3099\(12\)70029-4](https://doi.org/10.1016/S1473-3099(12)70029-4)
- [262] Santos VS, Marques DP, Martins-Filho PRS, Cuevas LE, Gurgel RQ. Effectiveness of rotavirus vaccines against rotavirus infection and hospitalization in Latin America: systematic review and meta-analysis. *Infect Dis Poverty* 2016;5:83. <https://doi.org/10.1186/s40249-016-0173-2>
- [263] Mwanga MJ, et al. Rotavirus group A genotype circulation patterns across Kenya before and after nationwide vaccine introduction, 2010–2018. *BMC Infect Dis* 2020;20(1):504. <https://doi.org/10.1186/s12879-020-05230-0>