Heliyon 6 (2020) e04248

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Prevalence, risk factors, and clinical characteristics of rotavirus and adenovirus among Lebanese hospitalized children with acute gastroenteritis

Rasha Zaraket [a,2], Ali Salami [b,2], Marwan Bahmad [a,3], Ali El Roz [b,3], Batoul Khalaf [b], Ghassan Ghssein [b,c,**], Hisham F. Bahmad [a,d,*,1]

[a] Faculty of Medicine, Beirut Arab University, Beirut, Lebanon
[b] Rammal Hassan Rammal Research Laboratory, Physio-toxicity (PhyTox) Research Group, Lebanese University, Faculty of Sciences (V), Nabatieh, Lebanon
[c] Department of Laboratory Sciences, Faculty of Nursing and Health Sciences, Islamic University of Lebanon, Khalde, Lebanon
[d] Department of Anatomy, Cell Biology, and Physiological Sciences, Faculty of Medicine, American University of Beirut, Beirut, Lebanon

ARTICLE INFO

Keywords:
Gastrointestinal system
Infectious disease
Antibiotic resistant bacteria
Virology
Laboratory medicine
Clinical research
Rotavirus
Adenovirus
Gastroenteritis
Children
Diarrhea
Lebanon

ABSTRACT

Background: Acute gastroenteritis is a very common infectious disease facing all age groups worldwide, especially the pediatric population. Viruses, bacteria, and parasites are all possible causes of infectious gastroenteritis; however, viruses have become more frequently identified with the advances in the ability to diagnose viral infections, particularly rotavirus and adenovirus. We aimed in our study to compare between the prevalence, risk factors, and clinical characteristics of rotavirus and adenovirus among children with viral gastroenteritis in Lebanon.

Materials and methods: A 12-months retrospective study was performed between January 1st and December 31st, 2018 including 308 children aged 1 month to 12 years, who were admitted to three tertiary healthcare centers in South Lebanon. Medical data were retrieved from patients' files, including clinical and laboratory information.

Results: Rotavirus was found in stool of 204 patients (66.23 %), followed by adenovirus in 78 cases (25.32 %), and mixed group (rotavirus and adenovirus) in 26 cases (8.44%). The highest prevalence of rotavirus in our present study was seen among children between 12 and 23 months old, whereas patients infected with adenovirus were mainly aged between 24-35 months or 4–11 months. Majority of patients in the adenovirus and mixed groups had high-grade fever compared to the rotavirus group. Laboratory findings presented significantly higher average of white blood cells (WBCs), absolute neutrophil count (ANC), and C-reactive protein (CRP) in the mixed group compared to the two other groups. Monthly distribution of rotavirus and adenovirus infection revealed a biennial pattern of rotavirus incidence during January and July–August while frequency of adenovirus infection was highest during July–August.

Conclusion: Due to the high prevalence of viral diarrhea among the pediatric age group in our region, particularly rotavirus and adenovirus, along with the associated non-specific signs and symptoms, we highly recommend that medical laboratories be equipped for virus detection. Also, vaccination against rotavirus should be considered as a prevention strategy.

1. Introduction

Acute gastroenteritis is one of the most common infectious diseases facing all age groups worldwide, especially the pediatric population [1]. It represents a major health problem particularly in developing countries. Gastroenteritis is responsible for about 1.5 million doctor visits and 220,000 hospital admissions each year [2]. Although it can be caused by viral, parasitic, or bacterial enteropathogens, viruses remain the most common pathogens causing acute gastroenteritis among children below 5 years of

* Corresponding author.
** Corresponding author.
E-mail addresses: ghassan.ghssein@iul.edu.lb (G. Ghssein), hfbahmad@gmail.com, hfbahmad1@buffs.wtamu.edu (H.F. Bahmad).
[1] Current Address: Arkadi M. Rywlin M.D. Department of Pathology and Laboratory Medicine, Mount Sinai Medical Center, Miami Beach, FL, USA.
[2] These authors also contributed equally to this work as co-first authors.
[3] These authors also contributed equally to this work as co-second authors.

https://doi.org/10.1016/j.heliyon.2020.e04248
Received 22 January 2020; Received in revised form 16 May 2020; Accepted 15 June 2020

age [3]. Acute gastroenteritis is usually acquired by fecal-oral route, as well as through contaminated surfaces and from water sources [4, 5].

In the past, bacteria were thought to be the most common cause of gastroenteritis [6]; however, in the last two decades, viruses have become more frequently identified with the advances in the ability to diagnose viral infections [7]. Among the causative viruses, rotaviruses and adenoviruses represent the leading causing pathogens [8], along with other viruses such as noroviruses and astroviruses [9]. Symptoms of gastroenteritis vary between watery diarrhea, nausea, vomiting, fever, and abdominal pain, among others. These symptoms begin 1–2 days after contracting the infectious agent and may last from 3 up to 8 days in rotavirus [10]. Diarrhea, being the most common symptom, remains a major cause of childhood morbidity and mortality [11]. Reports state that more than 5 billion episodes of diarrhea occur in children below 5 years old of age causing about 2.5 million deaths annually, mainly in tropical regions [12].

The diagnosis of gastroenteritis is usually achieved by correlating the child's symptoms and history of exposure. Although the majority of gastroenteritis cases are self-limiting, it remains a leading cause of morbidity and economic burden [13]. A major cause of childhood morbidity and mortality due to gastroenteritis worldwide is diarrhea. Gastroenteritis caused by bacteria are usually more severe and fatal, having high-grade fever and vomiting as common clinical presentation in most cases, while viral gastroenteritis is usually characterized by watery diarrhea and low-grade fever, along with vomiting and abdominal pain to a lesser extent. Additionally, tachycardia and tachypnea may be present due to fever and dehydration.

Among rotaviruses, the most common strains are G1P[8], G2P[4], G3P[8], G4P[8], and G9P[8] [14,15,16]. Each year, about 111 million episodes of gastroenteritis due to rotavirus are reported in children worldwide, of which 2 million require hospitalizations and 400,000 deaths occur [17], mostly in countries of Asia and Africa [18]. In Lebanon, prevalence of rotavirus has been reported to range between 27.7 and 30.6% [19, 20]. Moreover, a total of United States dollar (USD) 365 million is expended yearly to treat rotavirus gastroenteritis in China alone [21]. Therefore, the use of rotavirus vaccines in routine immunization programs worldwide is now highly recommended by The World Health Organization (WHO) [22].

As for adenoviruses, gastroenteritis is usually caused by group F strains, of which serotypes 40 and 41 are mainly detected in children [23]. Like rotavirus, adenovirus is spread via fecal–oral route causing diarrhea and fever among other symptoms. A strong association is also noted between adenovirus infection and intussusception [24], as well as increasing incidence of adenoviruses in children following bone marrow transplantation [25]. Since viral gastroenteritis has no definite therapy where symptomatic treatment is the mainstay in managing such cases, it is important to conduct local and regional epidemiological studies comparing between those two common viral infections among children. This is particularly essential for healthcare practitioners and officials to work on developing suitable vaccine programs and implement appropriate infection control measures [26].

Herein, we aimed at comparing between the prevalence, risk factors, and clinical characteristics of rotavirus and adenovirus among children with viral gastroenteritis. We conducted a 12-month study comprising virus testing of fecal specimens collected from hospitalized children under 12 years of age with acute diarrhea in 2018 in Lebanon.

2. Materials and methods

2.1. Study design and setting

During a one-year period, from January 1st, 2018 to December 31st, 2018, children were admitted to the pediatric department of three tertiary healthcare centers located in South Lebanon. Children aged from 1 month to 12 years old and hospitalized for acute gastroenteritis were retrospectively included in the study. We excluded patients with chronic diarrhea, malnutrition, immunodeficiency, or patients with multiple malformations. We also excluded all the non-Lebanese patients.

2.2. Ethical considerations

The experimental protocols followed in our retrospective study were performed in accordance with guidelines and regulations of The Code of Ethics of the World Medical Association (Declaration of Helsinki). The Institutional Review Board (IRB) approval of the Lebanese University (LU) and the Ethics Committee of the healthcare centers were obtained prior to commencement of the study. Written informed consents were obtained from the patients' care givers before random recruitment of the included subjects.

2.3. Clinical variables and specimen collection

Medical data were retrieved from medical files of patients, including clinical and laboratory information following the patients from the admission until discharge. The following data were collected retrospectively:

- Patient demographics: data including the age, sex, family size, breast feeding, and the vaccination history to determine if any dose of Rotavirus vaccines were given.
- Clinical data: this category includes investigation for the presence of fever, vomiting (including its frequency per day and period in days), diarrhea (including its frequency and period in days), dehydration, flu-like signs/symptoms, nausea, abdominal pain, stool texture, antibiotic use prior to hospitalization, and the calculation of the index of severity "Vesikari Score System" [27].
- Laboratory test values: including results of stool analysis, quick identification tests for Adenovirus (CerTest; Biotec, Zaragoza, Spain) and Rotavirus (CerTest), in addition to blood levels of white blood cells (WBCs), hemoglobin (HGB), hematocrit (HCT), absolute neutrophil count (ANC), blood sugar (BS), and C-reactive protein (CRP).

2.4. Viral detection

Fresh stool samples from patients were acquired and analyzed. Samples were received by the laboratory of each tertiary healthcare center and tested within less than 1 h to check for the presence of infectious agents as previously described by our group [28]. Rotavirus and Adenovirus kit tests (CerTest; Biotec, Zaragoza, Spain) were used for viral detection [29] as validated previously [30]. Testing for both viruses was carried out according to the manufacturers' instructions.

2.5. Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA). The level of significance was set at $p < 0.05$ for all statistical analyses. Descriptive analyses were based on frequencies and percentages. The demographic, clinical, and laboratory characteristics among the three study groups (rotavirus, adenovirus, and mixed) were tabulated. Baseline comparisons between groups were performed using Kruskall-Wallis test for continuous variables. The chi-square test was used to assess any significant difference between the categorical variables. Normality was tested using Kolmogorov-Smirnov test.

3. Results

3.1. Socio-demographic and clinical characteristics of patients

During the period between January and December 2018, out of 1,200 Lebanese children admitted to the three healthcare centers with a

diagnosis of acute gastroenteritis (AGE), 308 (25.7%) were diagnosed having rotavirus and/or enteric adenovirus infections. Among those, 135 (43.8%) were females and 173 (56.2%) were males. Patients were divided into seven age groups between 1 month and 12 years (1–3, 4–11, 12–23, 24–35, 36–47, 48–59 and ≥60) as previously described [1, 19]. The mean family size of patients was 4.21; 61.3% of patients were breastfed; and 35.6% of patients have been previously vaccinated with rotavirus vaccine (Table 1).

Rotavirus was found in stool of 204 patients (66.23%), followed by adenovirus in 78 cases (25.32%), and mixed group (rotavirus and adenovirus) in 26 cases (8.44%) (Figure 1). Our results showed a significant difference between patients among the three study groups (rotavirus, adenovirus, and mixed) with respect to their age categories (Table 1). Indeed, distribution of age revealed that majority of patients infected with rotavirus are aged between 12-23 months (31.2%), whereas patients infected with adenovirus were mainly aged between 24-35 months (27.3%) or 4–11 months (26.0%), and those co-infected with both viruses were mainly aged between 4-11 months (46.2%). Henceforth, distribution of age categories among the three patient groups was highly remarkable in children aged between 4 and 35 months ($P = 0.008$) (Figure 2). Concerning the sex distribution and breast feeding status of our patients, no significant association was observed among the three groups of enteropathogens. Yet, and as expected, a significant association was observed between the three study groups regarding the rotavirus vaccination ($P < 0.001$) (Table 1). For instance, majority of patients infected with rotavirus (76.1%) or co-infected with rotavirus/adenovirus (57.7%) have not previously taken the rotavirus vaccine compared to patients in the adenovirus-infected group. Lastly, mean family size was not significantly different between the three patient groups.

3.2. Clinical characteristics of patients

We next sought to compare between the three patient groups regarding their clinical characteristics. Table 2 shows that majority of children had watery stool texture, regardless of the viral infection they got. Majority of patients in the adenovirus and mixed groups had high-grade fever (60.0% and 100.0% respectively) compared to the rotavirus group where majority of patients had low-grade fever (65.9%) with a significance difference between them ($p < 0.003$). Higher number of patients infected with rotavirus or co-infected with rotavirus/adenovirus had abdominal pain (72.2% and 75.0%, respectively) with no statistical significance reported. Almost 90% of patients infected with rotavirus or adenovirus had diarrhea for 1–4 days, and around 60% had 4-5 episodes per day. Besides, vomiting was a common symptom among the three patient groups (70.4%, 62.3%, and 84.6% of the rotavirus, adenovirus, and rotavirus/adenovirus subgroups, respectively) and it lasted mainly for 1 day. Interestingly, flu-like signs/symptoms were highly observed in the rotavirus (56.5%) and adenovirus (100.0%) groups compared to the mixed group (0.0%) ($P = 0.009$).

3.3. Laboratory characteristics of patients

Laboratory data of patients were then assessed among the three study groups. Mean Vesikari score was found to be 10.95 ± 1.77 in the rotavirus group, 10.85 ± 2.10 in the adenovirus group, and 11.58 ± 1.54 in the mixed group. Laboratory findings presented significantly higher average of WBCs, ANC and CRP (>50 mg/L of CRP is considered highly positive) in the mixed group ($13.19 \pm 3.82 \times 10^3$ per mm^3, $70.00 \pm 19.79 \times 10^3$ per mm^3, and 158.72 ± 207.39 mg/L for WBCs, ANC and CRP, respectively) compared to the two other groups ($P = 0.017$, $P = 0.018$ and $P = 0.001$, respectively) (Table 3).

3.4. Rotavirus and adenovirus detection rates by age categories and months

We lastly sought to assess the distribution of the three study groups among different age categories of patients. We found that children aged between 4 and 35 months were more prone to be infected by rotavirus and adenovirus. Regarding the monthly distribution, our results showed that rotavirus is more prevalent in January, July and August compared to

Table 1. Socio-demographic characteristics of 308 pediatric patients enrolled in the study.

Demographics	*Rotavirus* n (%)	*Adenovirus* n (%)	Mixed n (%)	Total GE N	P-value
Age (months)*					
1-3	14 (6.9%)	2 (2.6%)	0 (0.0)	16	**0.008**
4-11	41 (20.3%)	20 (26.0%)	12 (46.2)	73	
12-23	63 (31.2%)	18 (23.3%)	5 (19.2)	86	
24-35	34 (16.8%)	21 (27.3%)	1 (3.9)	56	
36-47	25 (12.4%)	11 (14.3%)	2 (7.7)	38	
48-59	6 (3.0%)	2 (2.6%)	3 (11.5)	11	
≥60	19 (9.4%)	3 (3.9%)	3 (11.5)	25	
Total N (%)	202 (100.0%)	77 (100.0%)	26 (100.0%)	305	
Gender					
Female	88 (43.1%)	38 (48.7%)	9 (34.6%)	135	0.429
Male	116 (56.9%)	40 (51.3%)	17 (65.4%)	173	
Total N (%)	204 (100.0%)	78 (100.0%)	26 (100.0%)	308	
Breast feeding*					
No	62 (35.2%)	29 (43.3%)	13 (50.0%)	104	0.126
Yes	114 (64.8%)	38 (56.7%)	13 (50.0%)	165	
Total N (%)	176 (100.0%)	67 (100.0%)	26 (100.0%)	269	
Rota-vaccine*					
No	140 (76.1%)	24 (35.3%)	15 (57.7%)	179	**<0.001**
Yes	44 (23.9%)	44 (64.7%)	11 (42.3%)	99	
Total N (%)	184 (100.0%)	68 (100.0%)	26 (100.0%)	278	
Mean family size	4.33	3.92	4.23	4.21	0.293

* Missing data. Significant p-values are made in bold.

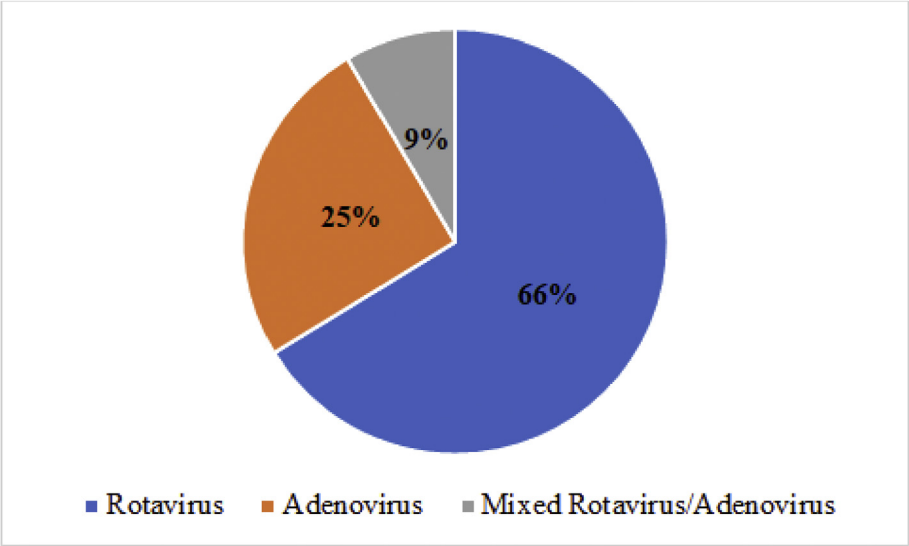

Figure 1. Frequency of rotaviruses and adenoviruses among the study group (n = 308).

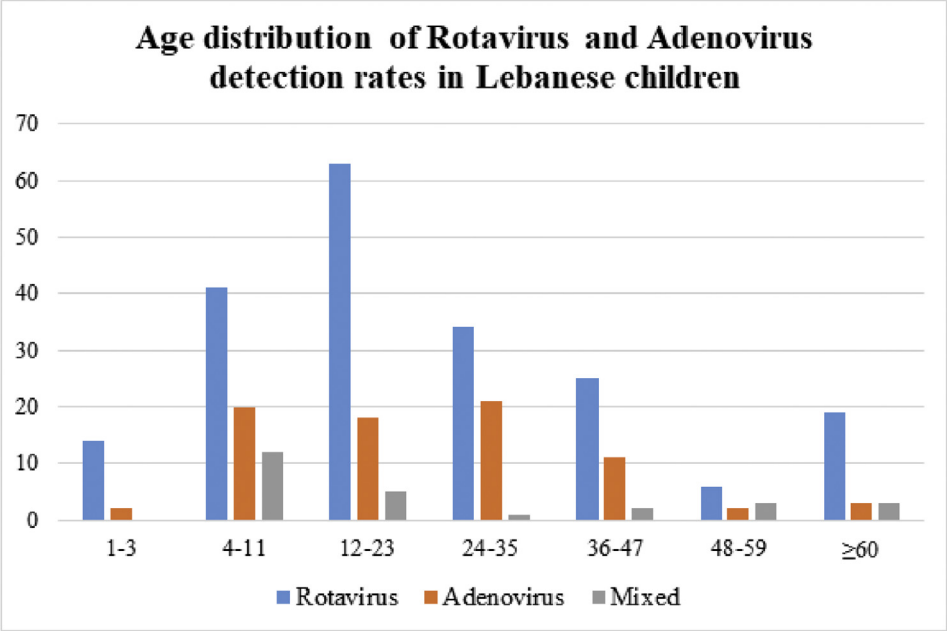

Figure 2. Distribution of rotavirus infection, adenovirus infection and co-infection by the age groups.

other months, whereas adenovirus had prominent peaks in July and August, compared to other months (Figure 3).

4. Discussion

In our study, out of 1200 hospitalized Lebanese children suffering from AGE, 25.7% were diagnosed having rotavirus and/or enteric adenovirus infections. This is close to a 5-year study by Liu *et al.* where rotavirus and adenovirus were detected in 22.0% and 10.3% of cases, respectively. As noted in almost all studies, rotavirus is always more prevalent than adenovirus. This is true in our study as well with around two thirds of cases diagnosed with rotavirus alone (66%), followed by adenovirus in 25% of cases and mixed rotavirus and adenovirus co-infection in 9% of patients. In a 1-year study by Vesikari *et al.*, rotavirus was found to be present in half of the cases while adenovirus was diagnosed in 11% of patients [31]. As for age group distribution, the highest prevalence of rotavirus in our present study was seen among children between 12 and 23 months old, which is similar to several reports demonstrating high rate of infection between 1 and 2 years of age [32, 33, 34, 35]. Indeed, incidence of rotavirus is greatest during the first 2 years of life [35, 36, 37]. In our study, a small number of patients were reported to have rotavirus infection at the age of 5 years or more. However, it is rarely reported since children have already acquired a natural immunity at this stage of life [38]. For adenovirus, patients were mainly aged between 24-35 months or 4–11 months.

In this study, monthly distribution analysis of rotavirus and adenovirus incidence revealed differential allocation in certain months, where rotavirus alone was highest in January while either of both viruses were found to be highest during July–August. This biennial pattern exhibited in rotavirus epidemiology is consistent with previous studies [39, 40]. Similarly, adenovirus infection being mostly incidental during the months of July and August specifically (wherein the weather is usually

Table 2. Clinical characteristics of 308 pediatric patients enrolled in the study.

Clinical characteristics	*Rotavirus* n (%)	*Adenovirus* n (%)	Mixed n (%)	Total GE	P-value
Stool texture*					
Mucoidal	14 (10.7%)	9 (18.4%)	7 (41.2%)	30	0.053
Watery	111 (84.7%)	39 (79.6%)	10 (58.8%)	160	
Bloody	6 (4.6%)	1 (2.0%)	0 (0.0)	7	
Total N (%)	131 (100.0%)	49 (100.0%)	17 (100.0%)	197	
Fever*					
Low-grade fever	27 (65.9%)	4 (40.0%)	0 (0.0%)	31	0.003
High-grade fever	14 (34.1%)	6 (60.0%)	4 (100.0%)	24	
Total N (%)	41 (100.0%)	10 (100.0%)	4 (100.0%)	86	
Abdominal pain*					
No	15 (27.8%)	4 (50.0%)	1 (25.0%)	20	0.430
Yes	39 (72.2%)	4 (50.0%)	3 (75.0%)	46	
Total N (%)	54 (100.0%)	8 (100.0%)	4 (100.0%)	66	
Diarrhea*					
No	20 (9.9%)	6 (7.8%)	5 (19.2%)	31	0.464
Yes	183 (90.1%)	71 (92.2%)	21 (80.8%)	275	
Total N (%)	203 (100.0%)	77 (100.0%)	26 (100.0%)	306	
Diarrhea episodes per day*					
1-3	14 (34.2%)	4 (40.0%)	0 (0.0%)	18	0.620
4-5	26 (63.4%)	6 (60.0%)	4 (100.0%)	36	
≥6	1 (2.4%)	0 (0.0)	0 (0.0%)	1	
Total N (%)	41 (100.0%)	10 (100.0%)	4 (100.0%)	55	
Diarrhea duration (days)*					
1-4	37 (94.9%)	8 (88.9%)	4 (100.0%)	49	0.688
≥5	2 (5.1%)	1 (11.1%)	0 (0.0%)	3	
Total N (%)	39 (100.0%)	9 (100.0%)	4 (100.0%)	52	
Nausea*					
No	22 (66.7%)	5 (62.5%)	4 (100.0%)	31	0.362
Yes	11 (33.3%)	3 (37.5%)	0 (0.0%)	14	
Total N (%)	33 (100.0%)	8 (100.0%)	4 (100.0%)	45	
Vomiting*					
No	60 (29.6%)	29 (37.7%)	4 (15.4%)	93	0.240
Yes	143 (70.4%)	48 (62.3%)	22 (84.6%)	213	
Total N (%)	203 (100.0%)	77 (100.0%)	26 (100.0%)	306	
Vomiting episodes per day*					
0	8 (19.5%)	4 (40.0%)	0 (0.0%)	12	0.153
1	14 (34.2%)	1 (10.0%)	3 (75.0%)	18	
2-4	19 (46.3%)	5 (50.0%)	1 (25.0%)	25	
Total N (%)	41 (100.0%)	10 (100.0%)	4 (100.0%)	55	
Vomiting duration (days)*					
0	8 (21.0%)	4 (40.0%)	0 (0.0%)	12	0.308
1	25 (65.8%)	6 (60.0%)	4 (100.0%)	35	
2	5 (13.2%)	0 (0.0%)	0 (0.0%)	5	
Total N (%)	38 (100.0%)	10 (100.0%)	4 (100.0%)	52	
Dehydration*					
No	74 (51.7%)	33 (54.1%)	9 (47.4%)	116	0.709
Yes	69 (48.3%)	28 (45.9%)	10 (52.6%)	107	
Total N (%)	143 (100.0%)	61 (100.0%)	19 (100.0%)	223	
Flu-like signs/symptoms*					
No	26 (56.5%)	5 (100.0%)	0 (0.0%)	31	**0.009**
Yes	20 (43.5%)	0 (0.0%)	4 (100.0%)	24	
Total N (%)	46 (100.0%)	5 (100.0%)	4 (100.0%)	55	
Antibiotic prior to hospitalization*					
No	101 (71.6%)	39 (76.5%)	16 (84.2%)	156	0.680
Yes	40 (28.4%)	12 (23.5%)	3 (15.8%)	55	
Total N (%)	141 (100.0%)	51 (100.0%)	19 (100.0%)	211	

* Missing data. Significant p-values are made in bold.

Table 3. Clinical and laboratory data of patients.

Clinical Characteristics	Rotavirus	Adenovirus	Mixed	Total	P-value
Frequency (%)	204 (66.2%)	78 (25.3%)	26 (8.5%)	308 (100.0%)	-
Clinical manifestations					
Vesikari score (Mean ± SD)	10.95 ± 1.77	10.85 ± 2.10	11.58 ± 1.54	10.97 ± 2.12	0.431
Duration of hospitalization per days (Mean ± SD)	3.46 ± 1.53	3.28 ± 1.57	3.40 ± 1.08	3.01 ± 1.53	0.470
Laboratory findings					
WBCs ($\times 10^3$ per mm^3)	9.03 ± 3.09	10.34 ± 3.54	13.19 ± 3.82	11.54 ± 5.00	**0.017**
ANC ($\times 10^3$ per mm^3)	53.85 ± 14.94	43.05 ± 22.67	70.00 ± 19.79	53.16 ± 40.93	**0.018**
HGB (in g/dL; mean ± SD)	11.02 ± 0.99	11.96 ± 1.11	11.18 ± 0.41	11.86 ± 5.08	0.319
HCT (in %; mean ± SD)	32.38 ± 2.67	34.27 ± 5.05	33.54 ± 1.62	33.82 ± 3.81	0.861
BS (in mg/dL; mean ± SD)	76.68 ± 24.78	82.25 ± 17.25	107.20 ± 18.44	88.88 ± 24.67	0.074
CRP (in mg/L; mean ± SD)	22.10 ± 24.84	19.37 ± 54.75	158.72 ± 207.39	42.96 ± 59.59	**0.001**

Abbreviations: ANC: absolute neutrophil count; BS: blood sugar; CRP: C-reactive protein; HCT: hematocrit; HGB: hemoglobin; WBCs: white blood cells. Significant p-values are made in bold.

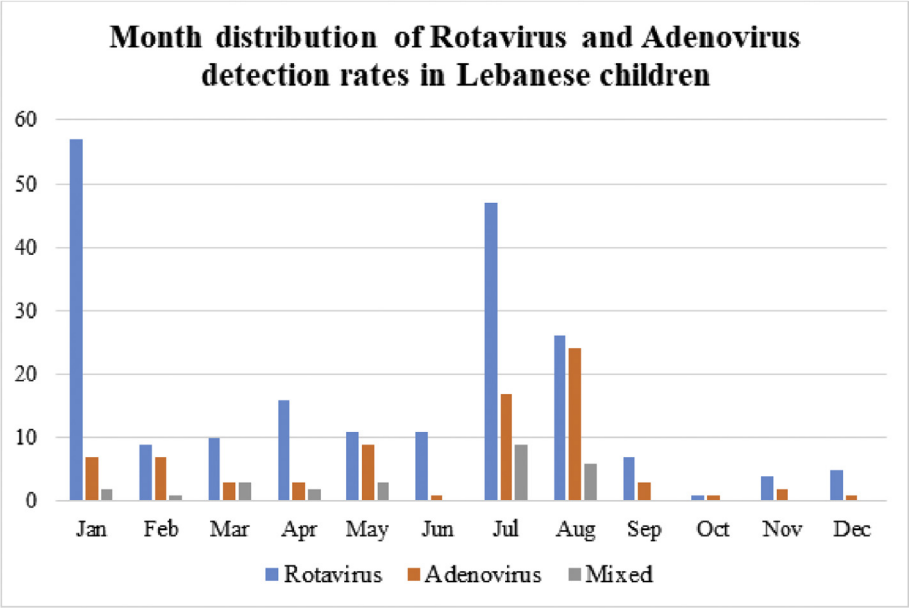

Figure 3. Distribution of rotavirus infection, adenovirus infection and co-infection by months.

hot due to Summer in Lebanon) has been reported in world literature in previous studies as well [41]. This variability might be owing to weather conditions which affect transmission of the viruses more rapidly.

With respect to the associated laboratory findings, significantly higher average of WBC, ANC and CRP were detected among patients co-infected with both rotavirus and adenovirus rather than those in the two other groups alone. In our study, mean CRP level in the rotavirus group of patients was found to be 22 mg/L, which is in consistent with a study by Lausch *et al.* were rotavirus patients had significantly lower CRP level (below 50 mg/L) with non-rotavirus patients [42]. Interestingly, co-infection with both viruses among our patients was associated with a mean CRP of 158 mg/L which is most likely due to severe inflammation accompanying both viruses. A possible explanation of the low CRP levels among patients infected with rotavirus might be the immunosuppressed state accompanying those patients as shown in a study by Lausch *et al.* [42].

Rotavirus, being the most common viral cause of gastroenteritis, is associated with frequent hospitalizations and deaths among children worldwide, and large annual costs for treatment have been reported in many countries [43]. The severity of rotaviruses is seen among babies younger than 11 months old, with the highest mortality rate seen in Africa, Latin America, and Asia, with an estimation of 6% overall mortality among children below 5 years old [44]. With advancement in the medical field, two orally-administered rotavirus vaccines had been licensed and are available worldwide since 2006 [45]. In our study, a significant association was detected between infection with rotavirus and adenovirus on one hand and rotavirus vaccination status on the other side. In fact, patients who previously received the vaccine are less prone to contract rotavirus alone or co-infection with both viruses as shown with a smaller number of patients in those two groups who got the vaccine shot than in those who did not. Nowadays, the wide availability of rotavirus vaccination for children in almost all countries is extremely important and is highly recommended by physicians [46].

We believe our manuscript has several limitations. First, we acknowledge that one-year surveillance data might not be enough to compare between the prevalence, risk factors, and clinical characteristics of rotavirus and adenovirus infections in Lebanon. However, results obtained from our study pave the way for conducting subsequent studies on larger cohorts of patients. Second, some data might have been missing from the medical records of the patients, including details about breastfeeding, rotavirus vaccination, and others.

5. Conclusions

In conclusion, our results indicated that rotavirus infection is much more frequent (66.23%) than adenovirus infection (25.32%) among Lebanese children, with the majority of patients contracting both viruses between 4 and 35 months of age. The larger portion of patients infected with rotavirus (76.1%) or co-infected with rotavirus/adenovirus (57.7%) were found not to be previously vaccinated against rotavirus, which reflects the importance of implementing vaccination programs to raise public awareness on the importance of vaccination in South Lebanon. Such campaigns need to be implemented during periods of the year where viral infections mostly occur. In our study, monthly distribution analysis revealed biennial pattern of rotavirus infection (during January and July–August months) among Lebanese children whereas adenovirus infection mainly occurred during the months of July–August only. Also, it is highly recommended to improve the laboratory detection of gastroenteric viruses using specific viral panels. More specifically, rotavirus and adenovirus antigens should be investigated on a routine basis in fresh stool samples to reach an accurate diagnosis and treatment of gastroenteritis among children.

Declarations

Author contribution statement

R. Zaraket, A. Salami and G. Ghssein: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

M. Bahmad and A. El Roz: Analyzed and interpreted the data; Wrote the paper.

B. Khalaf: Performed the experiments; Analyzed and interpreted the data.

H. Bahmad: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

Acknowledgements

We would like to thank first all the parents of children who were enrolled in this study and accepted to give us the requested information. Secondly, we would like to express our gratitude thanks to the healthcare centers and LU for their support in the conduction of this study.

References

[1] A. Salami, H. Fakih, M. Chakkour, L. Salloum, H.F. Bahmad, G. Ghssein, Prevalence, risk factors and seasonal variations of different Enteropathogens in Lebanese hospitalized children with acute gastroenteritis, BMC Pediatr. 19 (2019) 137.

[2] C.K. King, R. Glass, J.S. Bresee, C. Duggan, Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. MMWR. Recommendations and reports : morbidity and mortality weekly report, Recommendations and reports 52 (2003) 1–16.

[3] P. Chhabra, D.C. Payne, P.G. Szilagyi, K.M. Edwards, M.A. Staat, S.H. Shirley, M. Wikswo, W.A. Nix, X. Lu, U.D. Parashar, J. Vinjé, Etiology of viral gastroenteritis in children <5 Years of age in the United States, 2008–2009, J. Infect. Dis. 208 (2013) 790–800.

[4] W.X. Cheng, Y. Jin, Z.J. Duan, Z.Q. Xu, H.M. Qi, Q. Zhang, J.M. Yu, L. Zhu, M. Jin, N. Liu, S.X. Cui, H.Y. Li, Z.Y. Fang, Human bocavirus in children hospitalized for acute gastroenteritis: a case-control study, Clin. Infect. Dis. : Offl. Publ. Infect. Dis. Soc. Am. 47 (2008) 161–167.

[5] P.H. Dennehy, Infectious gastroenteritis, in: J. Domachowske (Ed.), Introduction to Clinical Infectious Diseases: A Problem-Based Approach, Springer International Publishing, Cham, 2019, pp. 157–168.

[6] J. Barrett, C.N. Fhogartaigh, Bacterial gastroenteritis, Medicine 45 (2017) 683–689.

[7] Y.S. Malik, A.K. Verma, N. Kumar, N. Touil, K. Karthik, R. Tiwari, D.P. Bora, K. Dhama, S. Ghosh, M.G. Hemida, A.S. Abdel-Moneim, K. Bányai, A.N. Vlasova, N. Kobayashi, R.K. Singh, Advances in diagnostic approaches for viral etiologies of diarrhea: from the lab to the field, Front. Microbiol. 10 (2019).

[8] U.S.Ş. Coşkun, T. Kasap, Frequency of rotavirus and adenovirus in pediatric patients with acute gastroenteritis, J. Contemp. Med. 9 (2019) 85–88.

[9] U.D. Parashar, J.S. Bresee, J.R. Gentsch, R.I. Glass, Rotavirus. Emerging infectious diseases 4 (1998) 561–570.

[10] M.V. Yates, Rotavirus, in: S.L. Percival, M.V. Yates, D.W. Williams, R.M. Chalmers, N.F. Gray (Eds.), Microbiology of Waterborne Diseases: Microbiological Aspects and Risks, second ed., Elsevier, Amsterdam, Netherlands, 2014, pp. 523–527.

[11] M. Mokomane, I. Kasvosve, E. de Melo, J.M. Pernica, D.M. Goldfarb, The global problem of childhood diarrhoeal diseases: emerging strategies in prevention and management, Ther. Adv. Respir. Dis. 5 (2018) 29–43.

[12] M.K. Bhan, Accelerated progress to reduce under-5 mortality in India. The Lancet, Global health 1 (2013) e172–173.

[13] S. Hoffman, B. Maculloch, M. Batz, Economic burden of Major Foodborne Illnesses Acquired in the United States, 2015.

[14] R. Durmaz, A.T. Kalaycioglu, S. Acar, Z. Bakkaloglu, A. Karagoz, G. Korukluoglu, M. Ertek, M.A. Torunoglu, Prevalence of rotavirus genotypes in children younger than 5 years of age before the introduction of a universal rotavirus vaccination program: report of rotavirus surveillance in Turkey, PloS One 9 (2014), e113674.

[15] H.K. Oh, S.H. Hong, B.Y. Ahn, H.K. Min, Phylogenetic analysis of the rotavirus genotypes originated from children < 5 Years of age in 16 cities in South Korea, between 2000 and 2004, Osong public health and research perspectives 3 (2012) 36–42.

[16] L. da Silva Soares, S. de Fatima Dos Santos Guerra, A. do Socorro Lima de Oliveira, F. da Silva Dos Santos, E.M. de Fatima Costa de Menezes, J. Mascarenhas, A.C. Linhares, Diversity of rotavirus strains circulating in Northern Brazil after introduction of a rotavirus vaccine: high prevalence of G3P[6] genotype, J. Med. Virol. 86 (2014) 1065–1072.

[17] U.D. Parashar, E.G. Hummelman, J.S. Bresee, M.A. Miller, R.I. Glass, Global illness and deaths caused by rotavirus disease in children, Emerg. Infect. Dis. 9 (2003) 565–572.

[18] H. Wang, C.A. Liddell, M.M. Coates, M.D. Mooney, C.E. Levitz, A.E. Schumacher, H. Apfel, M. Iannarone, B. Phillips, K.T. Lofgren, L. Sandar, R.E. Dorrington, I. Rakovac, T.A. Jacobs, X. Liang, M. Zhou, J. Zhu, G. Yang, Y. Wang, S. Liu, Y. Li, A.A. Ozgoren, S.F. Abera, I. Abubakar, T. Achoki, A. Adelekan, Z. Ademi, Z.A. Alemu, P.J. Allen, M.A. AlMazroa, E. Alvarez, A.A. Amankwaa, A.T. Amare, W. Ammar, P. Anwari, S.A. Cunningham, M.M. Asad, R. Assadi, A. Banerjee, S. Basu, N. Bedi, T. Bekele, M.L. Bell, Z. Bhutta, J.D. Blore, B.B. Basara, S. Boufous, N. Breitborde, N.G. Bruce, L.N. Bui, J.R. Carapetis, R. Cardenas, D.O. Carpenter, V. Caso, R.E. Castro, F. Catala-Lopez, A. Cavlin, X. Che, P.P. Chiang, R. Chowdhury, C.A. Christophi, T.W. Chuang, M. Cirillo, I. da Costa Leite, K.J. Courville, L. Dandona, R. Dandona, A. Davis, A. Dayama, K. Deribe, S.D. Dharmaratne, M.K. Dherani, U. Dilmen, E.L. Ding, K.M. Edmond, S.P. Ermakov, F. Farzadfar, S.M. Fereshtehnejad, D.O. Fijabi, N. Foigt, M.H. Forouzanfar, A.C. Garcia, J.M. Geleijnse, B.D. Gessner, K. Goginashvili, P. Gona, A. Goto, H.N. Gouda, M.A. Green, K.F. Greenwell, H.C. Gugnani, R. Gupta, R.R. Hamadeh, M. Hammami, H.L. Harb, S. Hay, M.T. Hedayati, H.D. Hosgood, D.G. Hoy, B.T. Idrisov, F. Islami, S. Ismayilova, V. Jha, G. Jiang, J.B. Jonas, K. Juel, E.K. Kabagambe, D.S. Kazi, A.P. Kengne, M. Kereselidze, Y.S. Khader, S.E. Khalifa, Y.H. Khang, D. Kim, Y. Kinfu, J.M. Kinge, Y. Kokubo, S. Kosen, B.K. Defo, G.A. Kumar, K. Kumar, R.B. Kumar, T. Lai, Q. Lan, A. Larsson, J.T. Lee, M. Leinsalu, S.S. Lim, S.E. Lipshultz, G. Logroscino, P.A. Lotufo, R. Lunevicius, R.A. Lyons, S. Ma, A.A. Mahdi, M.B. Marzan, M.T. Mashal, T.T. Mazorodze, J.J. McGrath, Z.A. Memish, W. Mendoza, G.A. Mensah, A. Meretoja, T.R. Miller, E.J. Mills, K.A. Mohammad, A.H. Mokdad, L. Monasta, M. Montico, A.R. Moore, J. Moschandreas, W.T. Msemburi, U.O. Mueller, M.M. Muszynska, M. Naghavi, K.S. Naidoo, K.M. Narayan, C. Nejjari, M. Ng, J. de Dieu Ngirabega, M.J. Nieuwenhuijsen, L. Nyakarahuka, T. Ohkubo, S.B. Omer, A.J. Caicedo, V. Pillay-van Wyk, D. Pope, F. Pourmalek, D. Prabhakaran, S.U. Rahman, S.M. Rana, R.Q. Reilly, D. Rojas-Rueda, L. Ronfani, L. Rushton, M.Y. Saeedi, J.A. Salomon, U. Sampson, I.S. Santos, M. Sawhney, J.C. Schmidt, M. Shakh-Nazarova, J. She, S. Sheikhbahaei, K. Shibuya, H.H. Shin, K. Shishani, I. Shiue, I.D. Sigfusdottir, J.A. Singh, V. Skirbekk, K. Sliwa, S.S. Soshnikov, L.A. Sposato, V.K. Stathopoulou, K. Stroumpoulis, K.M. Tabb, R.T. Talongwa, C.M. Teixeira, A.S. Terkawi, A.J. Thomson, A.L. Thorne-Lyman, H. Toyoshima, Z.T. Dimbuene, P. Uwaliraye, S.B. Uzun, T.J. Vasankari, A.M. Vasconcelos, V.V. Vlassov, S.E. Vollset, S. Waller, X. Wan, S. Weichenthal, E. Weiderpass, R.G. Weintraub, R. Westerman, J.D. Wilkinson, H.C. Williams, Y.C. Yang, G.K. Yentur, P. Yip, N. Yonemoto, M. Younis, C. Yu, K.Y. Jin, M. El Sayed Zaki, S. Zhu, T. Vos, A.D. Lopez, C.J. Murray, Global, regional, and national levels of neonatal, infant, and under-5 mortality during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013, Lancet 384 (2014) 957–979.

[19] G. Dbaibo, M. Rajab, A. Inati, R. Mikhael, E. Choueiry, M. Al-Tannir, O. Salam, G. Ramakrishnan, R. DeAntonio, Hospital-based surveillance study of rotavirus

gastroenteritis in children under 5 years of age in Lebanon, Trials in Vaccinology 2 (2013) 25–30.
[20] A. Naous, Z. Naja, N. Zaatari, R. Kamel, M. Rajab, Intestinal amebiasis: a concerning cause of acute gastroenteritis among hospitalized lebanese children, N. Am. J. Med. Sci. 5 (2013) 689–698.
[21] K. Kawai, M.A. O'Brien, M.G. Goveia, T.C. Mast, A.C. El Khoury, Burden of rotavirus gastroenteritis and distribution of rotavirus strains in Asia: a systematic review, Vaccine 30 (2012) 1244–1254.
[22] The World Health Organization, Introduction of Rotavirus Vaccines: Information for Policy Makers, Programme Managers, and Health Workers, World Health Organization, Geneva, Switzerland, 2013.
[23] M.V. Yates, Adenovirus, in: S.L. Percival, M.V. Yates, D.W. Williams, R.M. Chalmers, N.F. Gray (Eds.), Microbiology of Waterborne Diseases: Microbiological Aspects and Risks, second ed., Elsevier, Amsterdam, Netherlands, 2014, pp. 471–477.
[24] J.E. Bines, N.T. Liem, F.A. Justice, T.N. Son, C.D. Kirkwood, M. de Campo, P. Barnett, R.F. Bishop, R. Robins-Browne, J.B. Carlin, Risk factors for intussusception in infants in Vietnam and Australia: adenovirus implicated, but not rotavirus, J. Pediatr. 149 (2006) 452–460.
[25] T. Walls, A.G. Shankar, D. Shingadia, Adenovirus: an increasingly important pathogen in paediatric bone marrow transplant patients, Lancet Infect. Dis. 3 (2003) 79–86.
[26] B. Clark, M. McKendrick, A review of viral gastroenteritis, Curr. Opin. Infect. Dis. 17 (2004) 461–469.
[27] T. Ruuska, T. Vesikari, Rotavirus disease in Finnish children: use of numerical scores for clinical severity of diarrhoeal episodes, Scand. J. Infect. Dis. 22 (1990) 259–267.
[28] G. Ghssein, A. Salami, L. Salloum, P. Chedid, W.H. Joumaa, H. Fakih, Surveillance study of acute gastroenteritis etiologies in hospitalized children in South Lebanon (SAGE study), Pediatr. Gastroenterol., Hepatol. Nutr. 21 (2018) 176–183.
[29] Rotavirus + Adenovirus Detection Kit, Combo Cards, CerTest; Biotec, Zaragoza, Spain, 2018.
[30] H. Akan, G. Izbirak, Y. Gurol, S. Sarikaya, T.S. Gunduz, G. Yilmaz, O. Hayran, A. Vitrinel, Rotavirus and adenovirus frequency among patients with acute gastroenteritis and their relationship to clinical parameters: a retrospective study in Turkey, Asia Pac. Fam. Med. 8 (2009) 8.
[31] T. Vesikari, M. Maki, H.K. Sarkkinen, P.P. Arstila, P.E. Halonen, Rotavirus, adenovirus, and non-viral enteropathogens in diarrhoea, Arch. Dis. Child. 56 (1981) 264–270.
[32] H. Chen, T. Hu, Y. Yao, Y. Huang, N. Xiao, X. Liu, Y. Xiao, Q. Chen, S. Yu, Etiological and epidemic characterization of viral diarrhea in children under the age of 5 years in Guangzhou City, Chin. J. Dis. Control Prev. 18 (2014) 336–339.
[33] J. Wu, Y. Yan, Analysis on detection results of rotavirus and adenovirus in children with diarrhea, Chin. J. Microecol. 26 (2014) 1069–1071.
[34] J.-h. Li, S. Zhou, Y. Liu, Z. Deng, W. Huang, D. Li, F. Zhang, Z. Yao, D. Yuan, F. Liu, Etiological study on viral diarrhea among infants and young children in surveillance hospitals of Hunan Province from 2009 to 2010, Pract. Prev. Med. 19 (2012) 337–341.
[35] L. Liu, Y. Qian, Y. Zhang, L. Zhao, L. Jia, H. Dong, Epidemiological aspects of rotavirus and adenovirus in hospitalized children with diarrhea: a 5-year survey in Beijing, BMC Infect. Dis. 16 (2016) 508.
[36] Y. Jin, W.-x. Cheng, X.-m. Yang, M. Jin, Q. Zhang, Z.-q. Xu, J.-m. Yu, L. Zhu, S.-h. Yang, N. Liu, Viral agents associated with acute gastroenteritis in children hospitalized with diarrhea in Lanzhou, China, J. Clin. Virol. 44 (2009) 238–241.
[37] Z.J. Duan, N. Liu, S.H. Yang, J. Zhang, L.W. Sun, J.Y. Tang, Y. Jin, Z.Q. Du, J. Xu, Q.B. Wu, Z.L. Tong, S.T. Gong, Y. Qian, J.M. Ma, X.C. Liao, M.A. Widdowson, B. Jiang, Z.Y. Fang, Hospital-based surveillance of rotavirus diarrhea in the people's Republic of China, August 2003-July 2007, J. Infect. Dis. 200 (Suppl 1) (2009) S167–173.
[38] B. Standaert, D. Strens, A. Alwan, M. Raes, Medium- to long-term impact of rotavirus vaccination on hospital care in Belgium: a 7-year follow-up of the rotavirus Belgium impact study (RotaBIS), Infect. Dis. Ther. 5 (2016) 31–44.
[39] M.P. Shah, R.M. Dahl, U.D. Parashar, B.A. Lopman, Annual changes in rotavirus hospitalization rates before and after rotavirus vaccine implementation in the United States, PloS One 13 (2018), e0191429.
[40] K. Ureña-Castro, S. Ávila, M. Gutierrez, E.N. Naumova, R. Ulloa-Gutierrez, A. Mora-Guevara, Seasonality of rotavirus hospitalizations at Costa Rica's National Children's Hospital in 2010–2015, Int. J. Environ. Res. Publ. Health 16 (2019) 2321.
[41] M.R. Vetter, R. Staggemeier, A. Dalla Vecchia, A. Henzel, C. Rigotto, F.R. Spilki, Seasonal variation on the presence of adenoviruses in stools from non-diarrheic patients, Braz. J. Microbiol.: Publ. Brazilian Soc. Microbiol. 46 (2015) 749–752.
[42] K.R. Lausch, L. Westh, L.H. Kristensen, J. Lindberg, B. Tarp, C.S. Larsen, Rotavirus is frequent among adults hospitalised for acute gastroenteritis, Danish Med. J. 64 (2017).
[43] I. Rudan, S. El Arifeen, R.E. Black, H. Campbell, Childhood pneumonia and diarrhoea: setting our priorities right, Lancet Infect. Dis. 7 (2007) 56–61.
[44] S.M. Cook, R.I. Glass, C.W. LeBaron, M.S. Ho, Global seasonality of rotavirus infections, Bull. World Health Organ. 68 (1990) 171–177.
[45] P.H. Dennehy, Rotavirus vaccines: an overview, Clin. Microbiol. Rev. 21 (2008) 198–208.
[46] H. Szajewska, P. Dziechciarz, Gastrointestinal infections in the pediatric population, Curr. Opin. Gastroenterol. 26 (2010) 36–44.