Burden of Adenovirus, Astrovirus, Norovirus and Rotavirus Gastroenteritis in Egyptian Children during 2000-2017

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Abstract

Enteric viruses are the leading cause of severe dehydrating diarrhea among children, worldwide. The aim of this review was to estimate the burden of adenovirus (AdV), astrovirus (AstV), norovirus (NoV) and group A rotavirus (RV A) gastroenteritis in Egypt. Literature published in PubMed and other sources (Science direct, google scholar) on the epidemiology and burden of AdV, AstV, NoV and RV among Egyptian children between 2000-2017 were collected. Data from each study was extracted and compared. The search identified 19 studies. AdV, AstV, NoV and RVA gastroenteritis were identified in 2-20%, 0-31%, 2.2-30% and 10.7-76.9%, respectively, with average of 3.6%, 7.2%, 10.5% and 32.5% of all cases of acute gastroenteritis. These viruses were occurred year-around with high detection rates in male and children younger than 12 months. The most common genotypes were HAstV-1 for astrovirus, G1P[8] for rotavirus, GII.4 for norovirus. Children with AdV, AstV, RVA and NoV-positive acute gastroenteritis were more likely to have vomiting, diarrhea, abdominal pain, fever, various degrees of dehydration ranged from mild to severe dehydration. This systematic review documents that enteric viruses, particularly RVA, are significant pathogens of children diarrhea in Egypt. A vaccine covering multiple genotypes may reduce the morbidity and cost burden of AdV, AstV, RVA and NoV gastroenteritis in Egypt.

Keywords: Enteric Virus; Rotavirus; Norovirus; Astrovirus; Adenovirus; Gastroenteritis

Introduction

Acute diarrheal diseases are a major problem for public health, causing approximately 0.8 million deaths per year affecting mostly children < 5 years old [1]. Although the deaths occur mostly in developing countries, diarrheal illness is the main cause of morbidity and mortality in children worldwide [2,3]. Enteric viruses are identified as the most significant causative agent of acute gastroenteritis (AGE) in children, accounting for about 70% of episodes [4]. Four virus families are often associated with AGE in children: adenoviruses (AdV), rotaviruses group A (RVA) and astroviruses (AstV) and noroviruses (NoV) [5].

Rotaviruses, belonging to the Reoviridae family, are classified into 50-P and 35 G-genotypes based on the differences in the nucleotide sequence of VP4 and VP7 genes [6]. RVA with combination of G and P genotypes have been stated in several epidemiological studies [7,8]. The most common five genotype combinations are G1P, G2P, G3P, G4P and G9P, causing about 75% of RVA infections globally [4,8-10]. RVA infections are estimated to cause approximately 453,000 deaths among children below five years of age per year, mostly in developing countries [11].

Noroviruses (NoVs) are identified as the most common cause of AGE in humans, globally [12]. NoVs, within the Caliciviridae family, are small (27-40 nm in diameter) non-enveloped viruses containing a single-stranded RNA genome with a size of approximately 6.5-7.5 kb. NoV can be classified into 6 genogroups GI-GVI [13]. The three genogroups GI, GII and GIV have been recognized to infect human and they are subdivided into approximately 33 genotypes (9 GI, 22 GII and 2 GIV) [14]. The genotype GII.4 are associated with worldwide outbreaks [14].

Adenoviruses, within Adenoviridae family, possess double-stranded non-enveloped DNA genome. AdVs include 57 different serotypes and they can be subdivided into 7 subgenera (A-G). Adenovirus subgenus F, including 40 and 41 serotypes, is called an enteric virus because it associated with AGE. The both 40 and 41 serotypes are responsible for about 1-20% cases of AGE in young children. Also, subgenus A (types 12, 18 and 31), subgenus C (types 1, 2 and 5) and subgenus D (types 28-30, 32, 37 and 43-46) have also been implicated with diarrheal diseases [15,16].

Human astroviruses, belonging to Astroviridae family, are non-enveloped viruses with a single-stranded RNA genome. HAstV have also been identified as a major cause of viral AGE in immuno-compromised, children and the elderly subjects. HAstV are subdivided into eight serotypes and HAstV-1 is the most prevalent serotype with high seroprevalence rate (~ 90%) in children younger than 5 years [17-23]. Routine diagnostic techniques for viral diarrhea are often based on the detection of most common enteric viruses (AdV, AstV, NoV and RVA) by immunoassays or by molecular methods.

Materials and Methods

Nineteen articles from Egypt were published between January 2000 and December 2017, have been collected from google scholar, science direct and PubMed websites with the keywords “enteric viruses, adenovirus, astrovirus, norovirus and rotavirus gastroenteritis”. All articles published on these websites were collected without specific criteria. Detection of enteric viruses were conducted using a sensitive

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technique such as an enzyme immunoassay (EIA), polymerase chain reaction (PCR) and reverse-transcriptase polymerase chain reaction (RT-PCR). The prevalence, seasonal variation, gender distribution, age distribution, genotyping of enteric viruses and clinical features were extracted from all collected studies and compared.

The prevalence of enteric viruses as well as RVA genotypes were analyzed by two ways:

a. Overall the period of sample collections

b. During different periods according to the years of sample collections.

Results

Studies selected for this review

As depicted in Table 1, we reviewed 19 articles from Egypt contained the following topics: Prevalence of AdV (n=7), AstV (n=8), NoV (n=6) and RVA (n=16); seasonal variation of AdV (n=4), AstV (n=3), NoV (n=3) and RVA (n=10); age distribution of AdV (n=6), AstV (n=4), NoV (n=5) and RVA (n=12); gender distribution of AdV (n=1), AstV (n=2), NoV (n=1) and RVA (n=9); genotype distribution of AdV (n=0), AstV (n=2), NoV (n=2) and RVA (n=10); and disease severity of AdV (n=2), AstV (n=3), NoV (n=2) and RVA (n=7) [24-42].

Prevalence of viral gastroenteritis

Nineteen articles from Egypt contained specimens from 7067 children (6337 < 5 years, 230 < 18 years, 500 < 18 age) with acute gastroenteritis were tested for the occurrence of AdV, AstV, NoV and RVA. Among 7067 stool specimens from patients with acute diarrhea, 2117 (30%) were positive for enteric viruses. Overall the periods of sample collection (1995-2017), the most frequently detected virus was rotavirus (ranged from 10.7% to 76.9%, with average of 32.5%), followed by norovirus (ranged from 2.2% to 30%, with average of 10.5%), astrovirus (ranged from 0% to 31%, with average of 7.2%) and adenovirus (ranged from 2% to 20%, with average of 3.6%). The results are summarized in Table 2. To study the prevalence of enteric viruses during the different periods, data from single and combined studies were extracted according to the years of sample collections as follows: the incidence of AdV gastroenteritis were shown during 2005-2007, 2012-2013, 2013-2015, 2015-2017 with detection rates of 25.2%, 37.4%, 19%, 32%, 42%, 52.7%, 32.8% of all cases, respectively (Figure 1) [24-26,29,30-37,39-42].

The prevalence of RVA was shown during the period 2000-2002, 2004-2007, 2007-2009, 2009-2010, 2010-2013, 2013-2015, 2015-2017 with detection rates of 25.2%, 37.4%, 19%, 32%, 42%, 52.7%, 32.8% of all cases, respectively (Figure 1) [24-26,29,30-37,39-42].

Seasonal distribution of viral gastroenteritis

Eleven published studies from Egypt as shown in Table 2, stated seasonality distribution of AdV, AstV, NoV and RVA [24,28,29,31,34-37,39,40,42]. Ten studies reported that the high incidence of viral gastroenteritis was occurred in the cold and warm seasons [24,28,29,31,34-39]. Other two studies reported that the peak incidence of AdV, AstV, RVA infections were found in spring season [40,42].

Age distribution of children with viral gastroenteritis

As shown in Table 2, fifteen studies from Egypt contained data on the age distribution [24,28-40,42]. Among them, eleven studies state that the most viral infections were occurred in children younger than 1 years of age [24,28,31-40,42]. However, five studies found that the most infections with viral gastroenteritis were detected in the age group 12-36 months [30,33,35,38]. Also, one study reported that the most of RVA gastroenteritis was occurred in the age group 6-24 months [29].

Gender distribution of children with viral gastroenteritis

Eleven studies stated data on gender distribution [29,32-34,36-42]. The frequency of AdV, AstV, RVA and NoV diarrhea were higher in males as compared to the females as shown in Table 2 and Figure 2 [29,33,34,36,38,40-42]. However, three studies reported that the most RVA gastroenteritis was found in females as compared to the males [37,39]. An equal distribution of RVA diarrhea in males and females was reported in one study [32].

Distribution of astrovirus genotypes in children with diarrhea

Two studies contained data on astrovirus genotypes [27,38]. Ahmed et al. stated that HaAstV-1 was the most circulating type, was found in 9/16 (56%) of positive samples, followed by HaAstV-MLB1 5/16 (31%) and HaAstV VA2 2/16 (12.5%) [27]. Also, Naficy et al. reported that HaAstV-1 was the most frequent type, it was detected in 36/83 (43.4%) of positive samples, followed by HaAstV-5 13/83 (15.6%), HaAstV-8 10/83 (12%), HaAstV-3 10/83 (12%), HaAstV-6 6/83 (7.2%), HaAstV-4 4/83 (4.8%) and HaAstV-2 3/83 (3.6%) [38].

Distribution of norovirus genotypes in children with diarrhea

Two studies from Egypt contained data on norovirus genotypes. GGII was the most commonly detected genotype; it was identified in 71% of the cases, where GGII.4 was the predominant strain, it was identified in 45% of the cases, followed by GGIIb (22.6%) and GGII.3

| Virus     | Prevalence of viral gastroenteritis | Seasonality | Age distribution | Gender distribution | Genotyping | Disease severity |
|-----------|-----------------------------------|-------------|------------------|---------------------|------------|-----------------|
| Adenovirus | [24,28,30,33,35,40,41]             | [24,28,35,40]| [24,28,30,33,35,40] | [40]       | -           | [33,35]         |
| Astrovirus | [24,26,27,28,33,35,38,41]          | [24,28,35]  | [24,28,33,38]     | [33,38]   | [27,38]     | [33,35,38]       |
| Norovirus  | [24,26,28,30,33,35]                | [24,28,35]  | [24,28,30,33,35]  | [33]       | [24,26]     | [33,35]         |
| Rotavirus  | [24,25,26,29,30,31,32,33,34,35,36,37,39,40,41,42] | [24,29,31,34,35,36,37,39,40,42] | [24,29,30,31,32,33,34,36,37,39,40,42] | [29,33,34,36,37,39,40,41,42] | [24,25,29,31,34,37,39,40,41,42] | [31,32,33,35,36,39,41] |

Table 1: Literatures of extracted data by virus.
| Reference number | Virus | Study characteristics | Study results |
|------------------|-------|----------------------|---------------|
| [24]             | AdV   | 2006-2007 12 <18 ELISA 230 12(5.2) 2(0.9) 23(10) 76(33) | Cold <12 |
|                  | AstV  | 2007-2009 24 <5 RT-PCR 220 39(17.7) 5(2.2) 72(32.7) | - |
|                  | NoV   | 2006-2007 12 <5 RT-PCR 364 23(6.3) | - |
|                  | RVA   | 2005-2007 24 <5 EIA 2112 34(2) 56(3) 191(9) | Warm <12 |
|                  | RVA   | 2002-2010 12 <5 RT-PCR 450 158(35) M: 92(58.2) F: 66(42) | Cold 6-24 |
| [25]             | RVA   | 2000-2002 24 <5 ELISA 1026 259(25.2) - - - | - |
| [26]             | AstV  | 2007-2009 24 <5 RT-PCR 220 39(17.7) 5(2.2) 72(32.7) | - |
|                  | NoV   | 2007-2009 24 <5 RT-PCR 220 39(17.7) 5(2.2) 72(32.7) | - |
|                  | RVA   | 2002-2010 12 <5 RT-PCR 450 158(35) M: 92(58.2) F: 66(42) | Cold 6-24 |
| [27]             | AstV  | 2000-2001 12 <5 RT-PCR 364 23(6.3) | - |
| [28]             | AdV   | 2005-2007 24 <5 EIA 2112 34(2) 56(3) 191(9) | Warm <12 |
|                  | AstV  | 2005-2007 24 <5 EIA 2112 34(2) 56(3) 191(9) | Warm <12 |
|                  | NoV   | 2005-2007 24 <5 EIA 2112 34(2) 56(3) 191(9) | Warm <12 |
|                  | RVA   | 2002-2010 12 <5 RT-PCR 450 158(35) M: 92(58.2) F: 66(42) | Cold 6-24 |
| [30]             | AstV  | 2006-2007 12 <5 RT-PCR 364 23(6.3) | - |
|                  | NoV   | 2006-2007 12 <5 RT-PCR 364 23(6.3) | - |
|                  | RVA   | 2002-2010 12 <5 RT-PCR 450 158(35) M: 92(58.2) F: 66(42) | Cold 6-24 |
| [31]             | RVA   | 2004-2007 27 <2 EIA 348 140(40) | Warm <12 |
| [32]             | RVA   | 2014-2015 6 <5 qRT-PCR 65 50(76.9) M: 25(50) F: 25(50) | - 6-12 |
| [33]             | AdV   | 2013-2015 18 ≤24 RT-PCR 100 7(7) | 7-12 |
|                  | AstV  | 2013-2015 18 ≤24 RT-PCR 100 7(7) | 7-12 |
|                  | NoV   | 2013-2015 18 ≤24 RT-PCR 100 7(7) | 7-12 |
|                  | RVA   | 2013-2015 18 ≤24 RT-PCR 100 7(7) | 7-12 |
| [34]             | RVA   | 2011-2012 12 <2 EIA 197 77(39.1) M: 50(65) F: 27(35) | Winter <12 |
| [35]             | AdV   | 2015-2017 24 <5 Multiplex RT-PCR 100 20(20) 14(14) 30(30) 44(44) | Winter 12-24 |
|                  | AstV  | 2015-2017 24 <5 Multiplex RT-PCR 100 20(20) 14(14) 30(30) 44(44) | Winter 12-24 |
|                  | NoV   | 2015-2017 24 <5 Multiplex RT-PCR 100 20(20) 14(14) 30(30) 44(44) | Winter 12-24 |
|                  | RVA   | 2015-2017 24 <5 Multiplex RT-PCR 100 20(20) 14(14) 30(30) 44(44) | Winter 12-24 |
| [36]             | RVA   | 2007-2009 24 <5 ELISA 356 38(10.7) M: 27(71) F: 11(29) | Warm ≤6 |
| [37]             | RVA   | 2009-2010 12 <5 RT-PCR 100 19(19) M: 9/19(47.4) F: 10/19(52.6) | Winter 2-6 |
| [38]             | AstV  | 1995-1998 36 <3 ELISA 397 123(31) M: 70/123(56.9) F: 53/123(43) | Warm ≥3 |
| [39]             | RVA   | 2010-2012 17 <5 RT-PCR 92 45(48.9) M: 22(48.9) F: 23(51.1) | Warm 6-12 |
| [40]             | AdV   | 2015-2016 12 <5 ELISA 119 8(6.7) M: 5/7.2 F: 3(6) | Spring <12 |
|                  | RVA   | 2015-2016 12 <5 ELISA 119 8(6.7) M: 5/7.2 F: 3(6) | Spring <12 |
### Table 2: Enteric virus detection among Egyptian children with acute gastroenteritis.

| Year   | AdV | AstV | RVA  | NoV | Methods     | Positive | Gender | Seizure |
|--------|-----|------|------|-----|-------------|----------|--------|---------|
| 2012   | 4   | < 5  | 93   | 4   | ELISA       | 4 (4.3)  | -      | -       |
| 2015-16| 12  | < 5  | 198  | 56  | ELISA       | 53 (57)  | M: 29 (54.7) | F: 24 (45.3) |

*EIA: Enzyme Immunoassay; ELISA: Enzyme-Linked Immunosorbent Assay; RT-PCR: Reverse Transcriptase Polymerase Chain Reaction; Qr RT-PCR, Quantitative Real Time RT-PCR; M= Male; F= Female.*

(13%). In the same study, *GGI* was detected in 29% of all positive samples while *GGI.1* and *GGI.9* were detected in 9.7% of all positive samples while *GGI.3, GGI.4, GGI.5* and *GGI.15* were detected in 3.2% of all positive samples [24]. In the second study, *GGI* was detected in five of 220 (2.2%) diarrheal samples while *GGII* was not detected [26].

### Distribution of rotavirus genotypes in children with diarrhea

Three studies from Egypt contained data on G types in 233 stool samples from children with acute diarrhea [29,37,42]. *RVA G1* was the most common strain (93/233) followed by *G3* (46/233), *G9* (26/233), *G4* (19/233), mixed G types (15/233), *G10* (4/233), Non-type G (3/233).
and G2 (2/233). Moreover, seven studies contained 665 diarrheal samples determined RVA G-P combination [24,25,31,34,39,40,41]. G1P[8], G2P[4], G3P[8] were the most frequently detected in tested samples with median 233/665, 124/665, 63/665, respectively. G1P[8] combination was the only genotype detected in all seven studies with a proportion ranged from 6/223 to 136/223 of the given specimens. Also, Uncommon RVA genotype combinations such as G1P[4], G1P[6], G2P[8], G3[6], G4P[8], G9P[8], G9P[6], G9P[8] and G12P[6] were detected in multiple articles with a median prevalence of lower than 5%. Rare RVA genotype combinations including G2P[6], G3P[4], G4P[4], G8P[14], G9P[4] and G12P[4] in multiple articles with a median prevalence of lower than ≤ 0.4% have also been detected (Figure 3).

In another way for data analysis, studies contained data on RVA G-P combinations were classified according to years of sample collection into four periods (2000-2002, 2004-2007, 2010-2012, 2015-2017). The periods of 2000-2002 represent one study, 2004-2007 represent pooling of two studies, 2010-2012 represent pooling of three studies, 2015-2017 represent one study [24,25,31,34,39-41]. G1P[8] and G1P[6] genotypes were the only genotypes detected through the four periods. G2P[4] and mixed genotypes were detected in all periods except 2015-2017 of sample collection. G3P[6] and G9P[8] genotypes were detected only during 2000-2007, whereas G3P[6], G4P[4] and G8P[14] genotypes were detected only during 2010-2015 and they did not detect in the other periods of sample collection. G3P[8] and G9P[8] genotypes did not detect during 2000-2002 but they were detected in the other three periods 2000-2002, 2004-2007, 2010-2012 of sample collection. G2P[8], G9P[8] and partially genotypes were found only during the first two periods 2000-2002 and 2004-2007 of sample collection. G3P[4], G4P[8], G9P[6] and non-type genotypes were detected only during the periods 2000-2002 and 2010-2015 of sample collection. G1P[4] genotype appeared in all period of sample collection except 2004-2007 of sample collection. G12P[6] genotype was detected during the period of 2004-2007 and 2010-2012 of sample collection. The results are summarized in Figure 4.

**Clinical features, disease severity and Intravenous rehydration**

Eight studies from Egypt provided us data on clinical features of gastroenteritis caused by enteric viruses [31-33,35,36,38,39,41]. The common clinical features resulted from the infections by these viruses were vomiting, diarrhea, abdominal pain, fever, various degrees of dehydration ranged from mild to severe dehydration. Children who received oral solution, oral solution packets to take at home and medication due to RVA infections was reported in one study by El-Shabrawi et al. (2015) [36]. In the same study, convulsions and bloody diarrhea was found in 5% and 20% of children infected with RVA, respectively [36]. The median durations of diarrhea due to RVA infection were 3.7 and 3 ± 2 days [36,39]. On the other hand, two studies reported that 94.4% and 18% of dehydrated children due to RVA gastroenteritis were received Intravenous fluid therapy [36,39]. No deaths were occurred among infected children with viral diarrhea in the all included studies.

**Discussion**

Acute Diarrhea is one of the major cause of deaths in infant and young children worldwide, particularly in developing countries [43]. To increase our knowledge about the impact of viral intestinal infections on children, a comprehensive survey on various enteric viruses was carried out in Egypt. This study included commercial EIA, PCR and RT-PCR to detect the most common enteric viruses associated with diarrhea. Our study demonstrated that RVA is the main enteric virus associated with diarrhea in children, followed by norovirus, astrovirus and adenovirus. The frequency distribution in this survey agrees with results reported from study conducted in Saudi Arabia [44]. As reported by other investigators RVA was recorded as the principal cause for children diarrhea [45-49]. Furthermore, this survey supports the notion that NoV is the second most viral pathogen of diarrhea in children seeking medical attention [50,51]. Also, this survey supports other study that AstV, AdV are rarely implicated in children gastroenteritis [52].

Although the collected articles in this survey were published between 2000-2018, the sample collections were started from 1995 for astrovirus detection [38]. When we classified this survey into different periods according to the years of sample collections, we found that the higher prevalence of AdV was 12.8% during the recent years (2015-2017) of sample collection while the higher prevalence of AstV, NoV,
As the difference in the location of sample collection, number of tested samples, season of sample collection, concentration of viral antigens in the collected samples and the sampling methods.

The higher rates of AdV, AstV, NoV and RV antigens in the present survey were found in children ≤ 12 years of age. This observation may be resulted from the protection which acquired by maternal antibodies during the first year of child life then by the immunity which given after two years of life due to repeated infections [63]. Based on this finding, preventive strategies should be carried out during infancy. Furthermore, most of the included studies in this survey reported that males were more sensitive than females for infection with enteric viruses. Similar results were reported in studies from Jordan, Tunisia, Indonesia and Gabon [64-67]. In the current survey, enteric viral infections were found thought the year including cold, warm, spring seasons and this was reported in other studies [50,52,56,60,62]. The main symptoms of AdV, AstV, NoV and RVA gastroenteritis were vomiting, diarrhea, abdominal pain, fever and dehydration. These symptoms were reported in several reports conducted in Venezuela, Indonesia, Japan and France [51,66,68,69]. Study limitations are worth mentioning. The included articles in this survey are contained little data mentioning. The included articles in this survey are contained little data on AstV and NoV genotyping whereas no data was available on AdV genotyping. Moreover, no data was available on the burden of these viruses in terms of diarrhea duration, mortality, economic burden and healthcare resource utilization [24,26-28].

Conclusion

Enteric viruses, especially RVA, gastroenteritis is a common illness associated with significant morbidity in Egyptian children. The results of this study provide useful data to public health. Furthermore, this genetic diversity of AstV, NoV, RVA types in Egypt have been reported in this survey and based on these data updating vaccine formulation, covering the most common serotypes may help to decrease the burden of gastroenteritis resulted from the infections by these viruses in the Egypt.

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