Rotavirus gastroenteritis among hospitalized children under 5 years of age in the Eastern Mediterranean Region: a review

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Abstract

Background: Rotavirus (RV) is one of the primary causes globally of acute diarrhoea in children below 5 years of age.

Aims: This literature research aims to evaluate the rotavirus diarrhoea among hospitalized children < 5 years of age in the Eastern Mediterranean Region from 2010 to 2016. Data from each country were extracted and compared.

Methods: An extensive literature search was carried out using the following databases: PubMed, Google Scholar and Science Direct, with the keyword “Rotavirus”. The search was limited to articles published from January 2010 to December 2016.

Results: The search identified 28 studies. Rotavirus gastroenteritis (RVGE) identification in studies countries ranged from 19%–78.2% of all tested diarrhoeal specimens, primarily in children ≤ 1 year of age. RV occurred throughout the year, with peak incidence during autumn and winter seasons. G1P[8] was the predominant circulating genotype combination followed by G9P[8] and G2P[4]. Out of 28 studies, only one examined the economic burden which ranged from US$ 245 to $345 per hospitalized child due to RV diarrhoea. Moreover, three days were the minimum duration of hospitalization. No available data on the mortality rates due to RVGE among the selected studies.

Conclusions: This research documents that RV is one of the most significant pathogens that cause morbidity and mortality in the paediatric population in Eastern Mediterranean Region countries. The data from this literature research may help public healthcare workers in decreasing mortality and morbidity resulting from RVGE in the region.

Keywords: rotavirus, gastroenteritis, diarrhoea, mortality, vaccine, children

Introduction

Human rotavirus group A (human RV-A) is one of the global environmental risks that causes acute diarrhoea in children aged under five years, and accounts for 527 000 deaths per year, of which 82% occur among the paediatric population in the poorest countries (1,2). Morbidity and death caused by rotavirus occur mainly in low- and middle-income countries, particularly those with poor health care systems (3).

Rotavirus is a non-enveloped virus within the family of Reoviridae. The genome of this virus consist of 11 double-stranded RNA segments and based on the 2 surface capsid segments VP4 and VP7; RV is classified into P and G serotypes, respectively (4). To date, 27-G and 37-P genotypes have been described in humans (5). Several epidemiological studies reported that the G1P[8], G2P[4], G3P[8], G4P[8], G9P[8], and G12P[8] combinations are the major causes of rotavirus gastroenteritis in humans (6,7). Currently, two live-attenuated oral rotavirus vaccines (Rotarix and RotaTeq) were licensed for infants < 6 months old. Rotarix (GlaxoSmithKline, Rixensart, Belgium) contains human G1P[8] serotype while RotaTeq (Vaccines, Whitehouse Station, NJ, USA) contains a mixture of five human serotypes G1–G4 and P[8].

Both vaccines appear to protect against diarrhoeal diseases caused by RV infection (8). This study was designed to update the knowledge of circulating human RV-A G and P genotypes in the Eastern Mediterranean Region, through conducting a comprehensive literature review that assessed the distribution of rotavirus among children younger than 5 years of age with diarrhoea. The data would be beneficial before, during, and after the rotavirus vaccine introduction in populations.

Methods

In order to identify the impact of RV gastroenteritis on the paediatric population under five years of age in the Middle East (Algeria, Bahrain, Egypt, Islamic Republic of Iran, Iraq, Jordan, Kuwait, Libya, Morocco, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Tunisia, United Arab Emirates, Yemen) as well as Turkey for its regional proximity, an extensive literature search was carried out using the following databases: PubMed, Google Scholar and Science Direct, with the keyword “Rotavirus”. The search was limited to articles published in the last seven years (January 2010 to December 2016) that met the following criteria: 1) hospitalized children ≤ 5 years of age with acute diarrhoea; 2) period of sample collection ≥ 12
months; 3) number of tested samples for rotavirus ≥ 100; and 4) detection of RV was performed using a sensitive methods such as an enzyme immunoassay (EIA), latex agglutination (LAT), polyacrylamide gel electrophoresis (PAGE), or reverse-transcriptase polymerase chain reaction (PCR).

The proportion of RV infection was extracted from all selected studies and calculated by study and country. In case a single country had several published studies, a pooled average of the proportion of RV diarrhoea among cases of acute diarrhoea was calculated and reported. Also, the percentage of rotaviral genotype combinations among children suffering from RV gastroenteritis was calculated by study. Overall, the mean proportion of RV infection and genotype combinations among hospitalized children under 5 years of age in the MENA region was calculated from a combination of all extracted data. Moreover, age and gender distributions, seasonal variation, genotypes of RV, intravenous rehydration, duration of hospital stay, and medical costs were extracted from the selected studies and compared. Disease severity was measured by using 20-point Vesikari scores, based on the duration of diarrhoea, vomiting, intensity of diarrhoea, fever, and dehydration. A severe disease occurs when a Vesikari score is more than 11 (9).

Results

Studies selected for review

We reviewed 145 articles/abstracts to select a total of 28 that met the inclusion criteria of the current review (Figure 1). The selected studies covered Bahrain (10), Egypt (11,12), Islamic Republic of Iran (13–21), Iraq (22,23), Jordan (24,25), Libya (26), Morocco (27–29), Saudi Arabia (30–32), Tunisia (33), Turkey (34,35), United Arab Emirates (UAE) (36), and Yemen (37). All studies from Algeria, Jordan, Lebanon, Oman, Palestine, and Qatar were excluded because these did not meet our inclusion criteria whereas no studies were available from Kuwait and the Syrian Arab Republic. The included studies in the current review contained the following topics: proportion of RV gastroenteritis (n = 28), seasonal variation (n = 21), age distribution (n = 23), gender distribution (n = 19), genotype distribution (n = 15), and disease severity (n = 13 articles).

Proportion of RV gastroenteritis among hospitalized children

Twenty-eight studies from 12 countries contained data on the proportion of RV gastroenteritis among hospitalized children under five years of age in the Middle East and North Africa region. These studies contained 17,233 diarrhoeal samples and tested for RV gastroenteritis. Of these, 7,366 (42.7%) children had RV infection. By country, the mean percentage of cases caused by rotavirus infection ranged from 316 (22.5%) to 1,885 (63%). Egypt, Tunisia, and Islamic Republic of Iran reported the lowest proportion with 316 (22.5%), 65 (23.3%), and 537 (27.4%), respectively. The highest proportion was observed in Turkey 1,885 (63%), UAE 381 (50.3%), and Saudi Arabia 1,226 (48.7%). The other countries reported a percentage of between 93 (35.8%) and 358 (45.2%) (Figure 2).

Variation in the proportion of RV gastroenteritis over time

Among hospitalized children with acute diarrhoea, the proportion of RV gastroenteritis have fallen in Morocco from 741 (40%) to 89 (26.6%) between 2006 and 2011 (27,29), and in Saudi Arabia from 660 (65.5%) to 171 (31.6%) between 2008 and 2012 (30,32). The proportion of RV gastroenteritis appears to have increased over time in Islamic Republic of Iran from 131 (19%) to 10 (25%) between

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infections was observed in age group ranged from 6–23 months (10, 17, 25, 33), whereas the majority of RV infection occurred in children aged < 12 months in three studies from Egypt and Saudi Arabia (12, 30, 32). A number of studies reported that most RV infections occurred in the age group from 12–24 months (13, 16, 21, 34, 36). Only one study reported that most RV gastroenteritis occurred among children aged 1–6 months (37).

Seasonal distribution of RV gastroenteritis

Twenty-one studies from 12 countries including Bahrain (10), Egypt (12), Islamic Republic of Iran (13, 15–19, 21), Iraq (22), Jordan (25), Libya (26), Morocco (26–28), Saudi Arabia (31, 32), Tunisia (33), Turkey (34), UAE (36) and Yemen (37), reported seasonality distribution (Table 2). Most RV infection was found in winter and autumn. In contrast, three studies from Islamic Republic of Iran, Iraq and Yemen concluded that the peak incidence of rotaviral infection was found in summer (16, 22, 37) (Table 2).

Gender distribution of children with RV gastroenteritis

Nineteen studies from nine countries including Bahrain (10), Islamic Republic of Iran (13, 15–21), Iraq (22), Jordan (25), Morocco (29), Saudi Arabia (30–32), Tunisia (33), Turkey (34, 35), and Yemen (37) contained data on gender distribution. All studies found that the frequency of diarrhoea for Rotavirus was higher in males (Table 2).

Age distribution of children with RV gastroenteritis

Data on age distribution (Table 2) were available in 23 studies from the following countries: Bahrain (10), Egypt (12), Islamic Republic of Iran (13, 15–18, 21), Iraq (22, 23), Jordan (24, 25), Libya (26), Morocco (27–29), Saudi Arabia (30–32), Tunisia (33), Turkey (34), UAE (36), and Yemen (37). Children aged 6–12 months had the highest rate of positive samples for RV (15, 18, 22–24, 26–29, 31). A limited number of studies stated that the peak distribution of RV infections was observed in age group ranged from 6–23 months (10, 17, 25, 33), whereas the majority of RV infection occurred in children aged < 12 months in three studies from Egypt and Saudi Arabia (12, 30, 32). A number of studies reported that most RV infections occurred in the age group from 12–24 months (13, 16, 21, 34, 36). Only one study reported that most RV gastroenteritis occurred among children aged 1–6 months (37).

Distribution of human RV G and P combination in children with gastroenteritis

Out of 28 studies, 15 studies from 11 countries – Bahrain (10), Egypt (11), Islamic Republic of Iran (14), Iraq (23), Jordan (24, 25), Morocco (28, 29), Saudi Arabia (31, 32), Tunisia (33), Turkey (34, 35), UAE (36) and Yemen (37) – studied the human RV G-P combinations in 4070 hospitalized children with RV gastroenteritis. Overall, G1P[8] combination represented the predominant genotype followed by G9P[8] and G2P[4] in the MENA region, in 1535 (37.7%), 916 (22.5%), and 331 (8.1%) of all RV positive samples, respectively. G1P[8] combination was detected in 14 studies from 10 countries (10, 11, 14, 23–25, 28, 29, 31, 32, 34–37). G1P[8] was the most prevalent in 11 of those studies, accounting for between 6 (6%) and 171 (69%) of genotyped RV gastroenteritis samples in those countries. G9P[8] was present in seven countries (Bahrain, Egypt, Jordan, Morocco, Saudi Arabia, Turkey and UAE) where it was the most prevalent genotype in Morocco during 2006–2009 (28), and Turkey during 2006–2014 (34, 35). In addition, G2P[4] was detected in all countries except Islamic Republic of Iran, Tunisia, and UAE. G2P[4] was the highest circulating genotype from November 2006 to February 2008 in Yemen (37) (Figure 3).

Uncommon RV genotype combinations in the MENA region (Figure 3 and Figure 4) were detected in multiple countries and accounted for 5% or less of the
typed RV genotypes were detected in seven studies (11,14,23–25,28,31–33,36–37), respectively. They accounted for 161 (4%) to 68 (1.7%) of all genotypes in the MENA region during 2010–2016, respectively.

**Clinical features and disease severity**

Thirteen studies from the studied region provided data on clinical manifestations caused by RV gastroenteritis in the following countries: Bahrain (10), Egypt (12), Islamic Republic of Iran (15,16), Iraq (22), Libya (26), Morocco (27,29), Saudi Arabia (31,32), Tunisia (33), UAE (36) and Yemen (37). In most cases, RV-positive children suffered from vomiting (10,12,15,16,22,26,27,28,31–33,36,37), dehydration (10,26,27,29,31–33,36,37), and fever (12,15,16,22,31,33,36,37). Convulsion was reported in two studies from Islamic Republic of Iran (3) and Iraq (4) (22). Disease severity was measured by the Vesikari scale in two studies from Morocco with a mean score of 86.4 (11.66%, $P = 0.13$) vs. 126.6 (11.51%) of non-RV gastroenteritis (27) and 11.5 (14.74%, $P < 0.0001$) vs. 23.6 (12.3%) of non-RV gastroenteritis (29), which increased to 16.5 (17.8%, $P = 0.001$) vs. 26.2 (15.7%) of RV gastroenteritis and 102 (25%, $P = 0.0005$) vs. 133 (23.4%) of non-RV gastroenteritis in Libya (26) and Saudi Arabia (31) during hospitalization, respectively. The higher severity score was identified in a study from UAE with 161 (42.3%, $P = 0.0031$ vs. 117 (31%) of non-RV gastroenteritis (36). No deaths were reported in all included studies.

**Intravenous rehydration**

Seven studies from Bahrain (10), Libya (26), Morocco (27), Saudi Arabia (31), Tunisia (33), UAE (36) and Yemen (37) reported that 106 (99.6%), 93 (100%), 627 (84.5%), 387 (98%), 28 (77.7%), 337 (99%) and 421 (53.0%) of all hospitalized...
children with RV diarrhoea received Intravenous rehydration therapy, respectively.

**Duration of hospital stay**

The mean (± SD) duration of hospitalized children with RV diarrhoea was 4.1 (± 2.41), 3, and 4.0 (± 1.8) days in three studies from Bahrain (10), Morocco (27), and Saudi Arabia (31), respectively. Health care utilization and economic burden resulted from RV gastroenteritis. One study from Tunisia contained data on healthcare resource use with a mean cost ranging from US$ 245 to $345 per hospitalized child with RV diarrhoea (33).

**Discussion**

Rotavirus is a major cause of gastroenteritis in humans in both low- and middle-income countries as well as high-income countries. A continuous survey to identify the most common RV strains responsible for severe gastroenteritis is an important tool for vaccine selection and production to prevent rotavirus infection in the Eastern Mediterranean Region. Based on collected data from 28 studies in studied countries, our analysis revealed that RV is a major cause of diarrhoeal disease in children under 5 years of age in all included countries.

The detection rates of RV were different between these countries and can be explained by the differing conditions of these studies, such as geographical area, number of collected samples, RV antigen concentration in the collected samples, season of sample collection, and the sampling methods. In the studied region (2010–2016), RV infections were responsible for 42.7% of all diarrhoeal cases in children < 5 years of age. This finding is close to studies published by Centers for Disease Control and Prevention (CDC), where 40% was the median RV detection rate in the Eastern Mediterranean Region during 2001–2008 (38). Forster et al. (39) reported that RV gastroenteritis accounted for 43.4% of diarrhoeal cases in European children < 5 years of age from February 2005 to August 2006.

According to our survey, the majority of RV gastroenteritis was detected in children aged 6–23 months, which is in agreement with previous reports on the epidemiological profile of RV infection (40–42). This may be explained by the protection that was given by maternal antibodies in the first six months of the child’s life rather than the immunity acquired after two years of age due to repeated exposure (43). Based on this explanation, preventive strategies should occur during infancy. Moreover, RV infection was detected in all seasons but primarily during cooler months, as reported by McNulty (44) who found RV tends to be more common in winter than summer. It has been suggested that the low humidity of these seasons and combination of rainfall with drying soils might lead to an increase in the aerial transportation of dried and faecal contaminated materials (45,46). Moreover, the prevalence of acute gastroenteritis due to RV infection was higher in males than in females. This finding is similar to other studies conducted in Lebanon, Japan, and Nepal (41,47,48).

In this survey, G1P[8] genotype combination was the most common in MENA countries during 2010–2016. G9P[8] was second in frequency; however, it was the predominant genotype in Turkey during 2012–2014 (34). In spite of the presence of G2P[4] at low levels (median
La gastro-entérite à rotavirus chez les enfants hospitalisés de moins de 5 ans dans la Région de la Méditerranée orientale : analyse

Résumé

Contexte : Le rotavirus est l’une des principales causes mondiales de diarrhée aiguë chez les enfants de moins de 5 ans.

Objectifs : La présente recherche documentaire vise à évaluer la gastro-entérite à rotavirus chez les enfants hospitalisés de moins de 5 ans dans la Région de la Méditerranée orientale entre 2010 et 2016. Les données de chaque pays ont été extraites et comparées.


Conclusion

Data on mortality and medical costs is limited to the studied countries. However, the available data showed that RV diarrhoea is a common disease in the Eastern Mediterranean Region, affecting the paediatric population health. Currently, two or three genotype combinations, including G1P[8], G9P[8] and G2P[4] are predominant in the region. Thus, the current Rotarix vaccine might be suitable to reduce the rates of morbidity and mortality caused by RV infection. However, new vaccines rather than Rotarix are desired to contain the other predominant genotypes of RV such as G9P[8] and G2P[4] in the region.

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Competing interests: None declared.
التهاب المعدة والأمعاء الناشئ عن الإصابة بالفيروسة العجلية بين الأطفال دون الخامسة داخل المستشفيات في إقليم شرق المتوسط: دراسة مراجعة
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الخلاصة
تُعَدُ الفيروسة العجلية أحد الأسباب الأساسية التي تسبب الإسهال الحاد عند الأطفال دون الخامسة على مستوى العالم.

الخلفية:
هدف هذا البحث هو تقييم الإسهال الناشئ عن الإصابة بالفيروسة العجلية بين الأطفال دون الخامسة داخل المستشفيات في إقليم شرق المتوسط.

الأهداف:
1. وتم استخراج البيانات من كل بلد ومقارنتها.
2. وتم استخراج البيانات من كل بلد ومقارنتها.

طرق البحث:
- أُجري بحث موَّسع في المواد المنشورة باستخدام قواعد البيانات التالية: ScienceDirect، Google Scholar، PubMed.
- وتم استخدام الكلمة الأساسية "Rotavirus" في البحث.

النتائج:
- في دراسة، تم تحديد التهاب المعدة والأمعاء الناشئ عن الإصابة بالفيروسة العجلية بنسبة 28% من جميع عينات الإسهال الداخلة، بينما في الأطفال الذين بلغ عمرهم عامًا واحدًا أو أقل، وحدثت الإصابة بالفيروسة العجلية في مدار العام، وتكون ذروة وقوع الإصابة في فصل الخريف والشتاء. وكانت مجموعة النمط الجيني الدائرة والسائدة هي G2P[4] وG1P[8]، وليليها.
- دراسة، بحثت دراسة واحدة العبء الاقتصادي الذي تراوح بين 245 و 345 دولارًا أمريكيًا لكل طفل أُدخل إلى المستشفى بسبب الإسهال.
- وتم تحديد الفقرة الناتجة عن الإصابة بالفيروسة العجلية في الدراسات المحددة.

الاستنتاجات:
يُوقَّر هذا البحث أن الإسهال الناشئ عن الإصابة بالفيروسة العجلية هو أحد أكبر الممرضات الجسيمة التي تؤدي إلى المرضة والوفاة بين الأطفال في بلدان شرق المتوسط. وقد تساعد البيانات المستخرجة من هذا البحث في المواد المنشورة العامة في مجال الرعاية الصحية العامة على تخفيف اللواء والمراضة الناتجة عن التهاب المعدة والأمعاء الناشئ عن الإصابة بالفيروسة العجلية في الأسر.

References

Conclusions: Cette recherche montre que le rotavirus est l’un des agents pathogènes les plus significatifs à l’origine d’une morbidité et d’une mortalité dans la population pédiatrique des pays de la Région de la Méditerranée orientale. Les données produites par cette recherche documentaire pourraient aider les agents de santé publique à réduire la mortalité et la morbidité associées à la gastro-entérite à rotavirus dans la Région.


