AMERICAN UNIVERSITY OF BEIRUT

THE EPIDEMIOLOGY OF ROTAVIRUS AND NOROVIRUS IN THE MIDDLE EAST AND NORTH AFRICA (MENA) REGION: A SYSTEMATIC REVIEW

by
KHALIL ABU BAKR KREIDIEH

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AN ABSTRACT OF THE THESIS OF

Khalil Abu Bakr Kreidieh for Master of Science
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Title: The Epidemiology of Rotavirus and Norovirus in the Middle East and North Africa (MENA) Region: A Systematic Review

Background: According to the 2010 Global Burden of Disease (GBD) Study, diarrheal disorders still mark the second highest burden among all communicable diseases with an estimated disability-adjusted life years (DALYs) equivalent to 89.5 million. Viral infections are the most common causes of diarrheal diseases with rotavirus (RV) and norovirus (NoV) being the leading agents of acute gastroenteritis (AGE). Little is known about the epidemiology of RV and NoV in the MENA region. The aim of this thesis is to assess the distribution of these two viruses in the 25 countries of MENA using a systematic review approach.

Methodology: An extensive systematic literature search was carried out on articles studying RV and NoV in the 25 countries of the MENA region during the past 15 years (2000-2015). The search strategies were developed using the proper Medical Subject Headings (MeSH) terms and keywords related to RV, NoV and the 25 countries. Ten electronic bibliographic databases were used: Medline (OVID), PubMed, EMBASE, COCHRANE, SCOPUS, Web of Science, ProQuest, OpenGrey, IMEMR and AIM. The titles and abstracts of the exported studies were extracted and screened by two independent reviewers for relevance according to the inclusion and exclusion criteria. Full texts of eligible studies were obtained and data was abstracted.

Results: The search strategy identified 2,589 and 816 records on RV and NoV, respectively. After removal of duplicates and as per the inclusion and exclusion criteria, 169 unique records for RV and 39 unique records for NoV were included. The 169 studies reported on RV infection rates in 19 countries of the MENA region. As expected, the majority of these studies were among children presenting with AGE. Regionally, G1[P8] was predominantly reported as the causative agent of AGE among children less than 5 years old. Although RV infection spreads all year round in MENA, winter peaks were the most reported. The 39 studies reported on NoV infection rates in 15 countries of the MENA region. NoV is increasingly being recognized as a causative agent of viral AGE in the MENA region with the majority of peaks during the winter season. GII.4 was commonly reported in the region in compliance with globally circulating genotypes.

Discussion: The extracted data suggests that RV still inflicts a burden in the countries of the MENA region with a 27.39% median percentage of positive RV infection. Similar to RV, NoV imposes a burden of AGE in the MENA region with 15.13% median percentage of positive NoV infection. Our results on both RV and NoV in terms of rates, predominant strains and seasonality are aligned and compatible with published data from different regions of the world. This is the first systematic review that provides an understanding of the burden of these viral infections in the different countries of the MENA region. Based on this review, we advanced several recommendations.

CONTENTS

CHAPTER I

INTRODUCTION

A. Background

According to the 2010 Global Burden of Disease (GBD) Study, diarrheal disorders still mark the second highest burden among all communicable diseases with an estimated disability-adjusted life years (DALYs) equivalent to 89.5 million (1). Diarrheal disorders ranked 11 among the leading causes of DALYs in 2010 in the Middle East and North Africa (MENA) region (1). Worldwide, the proportionate mortality rates due to diarrheal infections reached 17.4% and 11.9% among neonates (age 28-364 days) and children (age 1-4 years) respectively, with an estimated 1.45 million deaths every year (2). The majority (88%) of diarrhea-associated fatalities are caused by the consumption of contaminated food or water and improper hygiene and sanitation (3); predominantly in developing countries (4). Viral infections are the most common causes of diarrheal diseases (5) with rotavirus (RV) and norovirus (NoV) being the leading agents of acute gastroenteritis (AGE) (6). Little is known about the epidemiology of RV and NoV in the MENA region. The aim of this thesis is to assess the distribution of these two viruses in the 25 countries of MENA using a systematic review approach.

B. Rotavirus

1. Overview

Rotavirus is the leading cause of viral gastroenteritis worldwide (7) resulting each year in more than 600,000 deaths among children less than five years of age (8). RV infection leads to hospitalization of 30% of diagnosed cases (9). The annual costs due to RV infection reached 29 million USDs in the United States (US) (10) and 550 million Euros in the European Union (EU) in 2002 (11). In developing countries, RV contributed to 7.1 million episodes of diarrhea, 220,000 annual hospital admissions and 1.8 million healthcare visits among children between 2000 and 2004 (12). Although RV infection can occur at any age, RV is proved to be age-dependent affecting mainly young infants and children (13). Reports suggest that nearly every child is infected with RV by the age of five irrespective of location and/or socioeconomic status (14).

RV is a non-enveloped double-stranded RNA (dsRNA) virus belonging to the family *Reoviridae* (15). It is classified into seven major groups (A through G) based on its capsid antigens (i.e. the protein shell of the virus) (16). Group A is the most common group detected in humans followed by group C (17). The two outer capsid-surface viral proteins VP7 (viral protein 7) or G (glycosylated protein) and VP4 (viral protein 4) or P (protease-cleaved protein) determine the serotypes and genotypes of the virus (18) which can independently assort and segregate into 42 diverse G-P combinations (19). Globally, the most prevalent VP7 serotypes are G1, G2, G3, G4, and G9 whereas the

most common VP4 genotypes are [P4], [P6], and [P8] (20). The diversity and distribution of RV strains differ from year to year and from region to region (18). For instance, G1[P8] is most predominant strain globally except in Taiwan where G2[P4] is the most common (21).

RV is highly contagious and transmitted via the fecal-oral route (15). Contaminated hands, objects (toys, surfaces), food and water can serve as reservoirs for RV (22). In health care settings and day care facilities, RV particles are easily transmitted to susceptible hosts (23). The virus is shed in the human feces with up to 10^{11} particles per gram of stool within 5-10 days of the onset of symptoms (24). Moreover, studies have reported on the aerosol transmission of RV especially in hospitals and day-care settings crowded with children with RV infection (21). Recently, 23.5% of viral outbreaks reported in neonatal intensive care units were attributed to RV (25). In a recent study aiming at identifying the characteristics of child daycare centers in Netherlands, 35.5% of the major enteropathogens were associated with RV along with other bacterial and parasitic pathogens (26).

The incubation period of RV (i.e. before the appearance of signs or symptoms) ranges between two to four days (27). The signs and symptoms start with fever and vomiting, followed by watery diarrhea; the latter can last for three to eight days before final recovery (28). RV symptoms can lead to dehydration, electrolyte imbalance and sometimes convulsions mainly among infants and young children (29). Thus, oral

rehydration with fluids and electrolytes remains the best treatment of RV infections (30). Assessing the degree of dehydration and the severity of gastroenteritis are crucial aspects to guide and monitor the treatment of RV (31). In developing countries, the World Health Organization (WHO) scale is used when assessing dehydration whereas the Gorelick score is used in developed countries (32). The severity of gastroenteritis is usually evaluated using the Vesikari or Clark scores (33). The WHO and Gorelick scores are based on the patient's general appearance and the examination of the eyes, tongue (thirst) and tears; whereas, the Vesikari or Clark scoring systems are based on assessing the degrees and durations of diarrhea, vomiting, fever and dehydration (31). The Vesikari score is mainly used in clinical settings whereby a score of less than 7 is considered mild, between 7 and 10 is considered moderate and above or equal to 11 is labeled as severe gastroenteritis (34).

Two live oral vaccines, Rotarix and Rotateq, are currently available and are highly recommended by WHO (35). Rotarix (GlaxoSmithKline - GSK, UK) is a monovalent vaccine derived from RV serotype G1 (36). Whereas, Rotateq (Merck, USA) is a pentavalent vaccine that represents the most common RV serotypes: G1, G2, G3, G4 and [P8] (37). The genetic and antigenic diversity of RV leads to the generation of new viral variants; the latter is critical for the development of RV vaccines (18).

RV has been associated with distinct seasonality patterns (38). Several studies confirmed RV infection to be year-round in developing countries such as in Latin

America and Asia whereas fall and winter months of industrialized countries, such as in Europe and the US, were associated with peak incidences (39, 40). This pattern has been attributed to the fact that developing countries are located at the tropics where RV activity is higher due to the underlying environmental and geographical variabilities (41). However, during the post-vaccination era, alterations in RV seasonal peaks have been observed (42) as is the case in the US (43), Spain (44) and Belgium (45). The effect of climatic variables on the seasonality pattern changes remains unknown (46). Large-scale studies on the impact of climate factors on the population dynamics of RV are still needed; similar to the ones done on cholera (47) and malaria (48).

2. Diagnostic Methods

A number of commercially available assays, approved by the Food and Drug Administration (FDA), are used for the rapid detection of RV in stool samples as a diagnostic tool in clinical settings. These include: enzyme linked immunosorbent assays (ELISA), enzyme immunoassays (EIA) and immunochromatography (IC) (49). These assays are characterized by 90 to 95% sensitivity and specificity rates (50). Other methods and techniques are also used in research laboratories for the detection of RV infection and these include: electron microscopy (EM), polyacrylamide gel electrophoresis (PAGE), reverse transcription polymerase chain reaction (RT-PCR) and

viral isolation (23). RT-PCR (100% sensitivity and 100% specificity) is widely used in research and clinical laboratories to confirm the RV G-P strains (51).

3. Prevention and Control

Since RV is stable on environmental surfaces, hygienic-sanitary measures such as improving water quality and disinfecting environmental surfaces remain important measures to control RV spread (52). In hospitals settings, infection control guidelines recommend the separation of infected children and following proper hand washing methods after contact with infected children (53). Nevertheless, vaccination remains the most effective method to reduce the burden of RV (54).

Both RV vaccines are safe and have an efficacy rate of more than 85% (54). Rotarix is recommended in two doses given to children at ages 6 and 10 weeks while Rotateq is recommended in three doses given at ages of 6, 10 and 14 weeks (55). About 60 countries worldwide have introduced RV vaccination into their national childhood immunizations programs (NCIPs) (35). According to the WHO vaccine-preventable diseases monitoring system (2016 global summary), RV vaccination in the MENA region is recommended as part of the NCIPs for children in Bahrain, Djibouti, Iraq, Israel, Jordan, Libya, Morocco, Qatar, Saudi Arabia, Sudan, United Arab Emirates (UAE) and Yemen (56).

Rapid and significant decrease in hospitalizations and mortality rates due to RV infection were reported in countries where RV vaccines have been introduced to NCIPs (38). A recent review confirmed a decline of hospitalizations rate by 49% to 92% and an all-cause diarrhea deaths reduction rate by 22% to 50% (57). The yearly reduction rate in RV hospital admissions among children < 5 years reached 58-77% in Belgium (58) and 74% in Austria (59). In the US, RV positivity rate dropped from 43.1% to 10.9% seven years post-vaccine implementation (43).

4. Reporting and Surveillance Systems

In 2002, the WHO and the Centers for Disease Control and Prevention (CDC) established a Global Rotavirus Surveillance Network where hospitals and laboratories report to the national ministries of health the clinical features and RV testing data on hospitalized children with AGE who are less than five years old (60). The surveillance protocol started in Asia (61) and with the help of the Rotavirus Vaccine Program (RVP), it expanded to cover other regions of the world (62). The protocol helps generating data on RV positivity rates and the circulating strains (63). These data are vital to measure vaccine effectiveness and to improve vaccine development based on viral diversity (20). In the US, RV is not a reportable disease but data on RV can be extracted via the CDC National Respiratory and Enteric Virus Surveillance System (NREVSS) and the New Vaccine Surveillance Network (NVSN) (38). Djibouti, Jordan,

Libya, Sudan, Syria and Yemen of the MENA region are part of the WHO Global Rotavirus Sentinel Hospital Surveillance Network (64). The establishment and implementation of surveillance systems lead to continuous collection of data in order to monitor the burden of disease, changing trends and impact of RV vaccination (62).

C. Norovirus

1. Overview

Following RV, NoV is the second leading cause of AGE worldwide (65). NoV infection affects all age groups in both developed and developing countries (66, 67). It is a clinically important diarrheal virus responsible globally for substantial morbidity and mortality rates (68). In the US, NoV contributes to at least 20 million illnesses per year leading to 56,000-71,000 hospitalizations and 570-800 deaths (69). Hospitalization and fatality rates are mainly observed among newborns (70, 71) and elderly (72). NoV infection causes 10-15 % of severe gastroenteritis cases among children less than 5 years of age and 9-15% of mild to moderate diarrhea among all age groups (65, 73). In 2015, the WHO established a Foodborne Disease Burden Epidemiology Reference Group (FERG) that added NoV to the list of diarrheal diseases affecting the global burden of foodborne diseases (74).

NoV is a single-stranded RNA (ssRNA) virus belonging to the family *Caliciviridae.* Similar to RV, NoV is a highly genetically and antigenically diverse virus (68). NoV is

classified into 6 genogroups (GI-GVI) based on the amino acid sequence of its viral proteins (75). Although NoV was first classified as a zoonotic disease; GI, GII and GIV are the most common NoV genogroups that infect humans (76). Based on the capsid sequence, NoV genogroups are further subdivided into genotypes (77). Globally, NoV genorgoup II genotype 4 (GII.4) is the predominant genotype associated with AGE (78).

Histo-blood group antigens (HBGAs) serve as binding receptors for NoV (79). The expression of HBGAs has been associated with susceptibility to NoV infection (80). For instance, NoV GI.1 has been associated with the expression of HBGAs in secretor-positive individuals while NoV GII.4 has been linked to the absence or weak expression of the HBGA motifs in non-secretors (68, 81).

NoV, like RV, is a highly contagious virus transmitted by direct contact from person-to-person (69). The fecal-oral transmission route is well documented since NoV is shed in the human feces with up to 10^{11} viruses per gram and in human vomitus with up to 10^{7} viruses per 30 milliliters (82). Thus, NoV can be easily transmitted through environmental contamination by touching contaminated surfaces or objects (83), by ingesting contaminated food (79) or by drinking contaminated water (84).

NoV incubation period ranges between 1 to 5 days (85). As the case following RV infection, diarrhea, vomiting, nausea and stomach pain are the most common clinical features developed following NoV infection. As reported, these are usually followed by

fever, headache and body aches (86). Recent viral shedding studies documented that NoV infection might be asymptomatic (82).

NoV is a major cause of gastroenteritis outbreaks accounting for at least 50% of the investigated cases (87). NoV outbreaks can cause prolonged morbidity and mortality and considerable economical health burden (88). Outbreaks caused by NoV occur in a variety of settings such as: hospitals (89), schools (90, 91), military training centers (92), nursing homes (93), cruise ships (94), resorts (95) and catered events (95). During the past decade, the major NoV outbreaks were reported in the United Kingdom (UK), Sweden, Germany and France where GII.4 was the most commonly isolated strain (96-99). A review on NoV outbreaks in Japan between 1997 and 2009 highlighted that at least 30 NoV genogroups were detected with GII.4 being the most predominant at a rate of 44.6% (100). A systematic review studying published articles on NoV outbreaks revealed that severe outcomes, such as hospitalizations and deaths, were more likely implicated in outbreaks associated with GII.4 (101).

The development of an effective therapy to treat NoV gastroenteritis is still in progress; nevertheless, alpha interferons and ribavirin have been suggested to be potential treatments (102). Recently, new drugs targeting NoV are being developed including solved crystal structures that inhibit NoV attachment to HBGAs (103). Consequently, oral rehydration, with fluids and electrolytes, remains the best treatment/management strategy to replace the fluid lost through the diarrheal and

vomiting symptoms (68). Currently, a number of randomized clinical trials (RCTs) are being designed to prove if oral human immunoglobulin can treat NoV in immunocompromised (104) and transplant patients (105).

Winter seasonality has been significantly associated with NoV infection that it has been called the "winter vomiting disease" (73) . A recent systematic review conducted to assess the global seasonality of NoV identified that 52.7% of NoV cases and 41.2% of NoV outbreaks occurred during winter months (106). Winter peaks of NoV infection were observed in countries such as France (96), Norway (107), Japan (108) and USA (109). Understanding NoV seasonality remains an important factor in determining changes in viral epidemiology (110). NoV infection, like RV infections, can spread year-round.

2. Diagnostic Methods

NoV viral RNA is mainly detected in human fecal specimens using RT-PCR (111). EIA has been also used for the rapid detection of NoV; even though immunoassays are specific and have been approved by FDA, they remain less sensitive than RT-PCR (112). Recently, rapid and sensitive real-time RT-PCR (rRT-PCR) method is used in clinical and research laboratories to allow the confirmation and quantification of NoV in a single assay (113).

3. Prevention and Control

Since NoV is transmitted through the fecal-oral route, routine screening of contaminated food and water is an essential method used to prevent NoV transmission (114). Moreover, routine screening for NoV among food handlers is necessary to control food contamination particularly that NoV has been detected among asymptomatic food handlers (115). Practicing proper hand hygiene and decontaminating environmental surfaces remain the best ways for the prevention and control of NoV (116).

Studies for the development of a vaccine against NoV are still in progress (117). The incomplete understanding of the immune correlates of protection, the lack of long-term immunity following infection, and the existence of multiple genogroups and genotypes are the main challenges facing scientists and researchers to develop NoV vaccine(s) (68, 117).

4. Reporting and Surveillance Systems

Individual case-reporting of NoV infection is not required in the US; however reporting of NoV is essential during outbreak investigations (87). Health care providers should report any suspected NoV outbreak to the corresponding health department; the latter reports the confirmed cases to the National Outbreak Reporting System (NORS) and CaliciNet (118). In Germany, NoV reporting is part of a larger national infectious

disease surveillance system: SurvNet@RKI that relies on the reporting of nosocomial NoV outbreaks (119). Furthermore, NoroNet is a multinational molecular epidemiologic surveillance system for reporting of NoV strains and monitoring outbreaks by scientists and researchers from Europe, Asia and Australia (120). NoroNet reports on NoV sequences and monitors outbreak activity. In Europe, the Food-Borne Viruses in Europe Network (FBVE) identify NoV cases as part of the centralized European system for monitoring foodborne outbreaks (121). Recently, a new surveillance system for outbreaks of NoV was developed in England: the hospital norovirus outbreak reporting system (HNORS). To our knowledge, there are no surveillance systems monitoring NoV activity in the MENA region. Implementing NoV surveillance systems will help in monitoring NoV transmission, identifying any NoV outbreak and assessing the predominant circulating strains to support vaccine development (122).

CHAPTER II

AIMS AND OBJECTIVES

Several viral infections have been associated with AGE including RV and NoV (123). The global burden of these infections have been studied in most developed and some developing countries (124).To our knowledge, there are no systematic reviews summarizing the current status of RV and NoV infections in the MENA region in relation to geographical distribution, outbreaks reporting, diagnostic and reporting methods, predominant circulating strains, age groups affected by these viruses, and seasonality. Thus, the aim of this thesis is to systematically review the literature for studies on the rates of RV and NoV infections and their roles as causative agents of acute gastroenteritis in the MENA region. The objectives of this systematic review are to:

- Extract and report from the included studies: the overall rates of RV and NoV infections, the associated country-specific burden, the predominant circulating strains, the age groups tested, populations studied, seasonality and record of reported outbreaks (if any).

- Review and report on the detection methods used to detect these viruses as causative agents of AGE in MENA countries to reflect on the sensitivity and the specificity of the reported data.

- To qualitatively analyze the published data and advance recommendations at the research, policy and practice levels to enhance the prevention and control of RV and NoV in the MENA region.

CHAPTER III

METHODLOGY

A. Literature Search

The methods and reporting of this systematic review were set according to the 2015 preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) (125) and based on the elements from the international prospective register of systematic reviews (PROSPERO) (126). An extensive systematic literature search was carried out on articles studying RV and NoV in the 25 countries of the MENA region during the past 15 years (2000-2015). These countries include: Algeria, Bahrain, Cyprus, Djibouti, Egypt, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Libya, Mauritania, Morocco, Oman, Palestine, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, Turkey, UAE and Yemen. The search strategies were developed using the proper Medical Subject Headings (MeSH) terms and keywords related to RV, NoV and the 25 countries listed above. To ensure the comprehensiveness and completeness of the search (127), six electronic bibliographic databases were used: Medline (OVID), PubMed, EMBASE, COCHRANE, SCOPUS and Web of Science. Moreover, in order to rule out any source of bias to the selected studies and in order to account for hard to reach material, unpublished literature in theses, dissertations and grey literature were screened through ProQuest and OpenGrey databases. The Global Health Library

(GHL) was used to retrieve studies published on the regional databases namely: Index Medicus for the Eastern Mediterranean Region (IMEMR) and African Index Medicus (AIM). Appendix III includes the search strategies mentioned above.

B. Selection Process

Our search included studies published between January 01, 2000 and December 31, 2015. The search was limited to the past 15 years; a decade after FDA approval of RV vaccination and around two decades after the introduction of molecular assays to detect NoV. Consequently, published data during 2000-2015 will capture the changes in the infection rates following vaccination against RV and will also highlight the increased knowledge related to identification of NoV. All relevant studies were sent to the citation manager Endnote (version X7.1) where duplicates were removed. The titles and abstracts of the exported studies were extracted and screened by two independent reviewers for relevance according to the inclusion and exclusion criteria. Disagreements were resolved by consensus of a third reviewer.

C. Eligibility Criteria

We included studies meeting the following criteria:

a. assessed detected/reported either rotavirus, norovirus or both

b. conducted in at least one of the 25 countries of the MENA region

c. published between 2000 and 2015

d. included the total number of samples tested along with positive occurrences for either RV or NoV

e. used standardized laboratory techniques for the detection of the viruses including:

i. EIA
ii. ELISA
iii. EM
iv. gold immuno-assay (GA)
v. IC
vi. indirect immunofluorescence (IF)
vii. latex agglutination (LA)
viii. PAGE
ix. RT-PCR
x. rRT-PCR
xi. sequencing
xii. viral isolation

We excluded review articles, case studies, clinical trials, animal and environmental studies and articles published in a non-English language; the latter were in Turkish and

Persian languages. When studies did not report the number of participants, the number of positive cases or the percentages that allowed these raw numbers to be calculated were also excluded. Similarly, studies that didn't use standardized laboratory techniques for the detection of the RV or NoV were also excluded.

D. Data Abstraction Process

Based on the pre-defined inclusion and exclusion criteria, the full-texts of potentially eligible titles and abstracts were obtained. Using a standardized data sheet, two reviewers (an MPH holder, MSc candidate) extracted the data independently from each eligible study The abstracted information were checked by a third reviewer (PhD holder, Associate Professor) and included the following: virus detected, first author, article title, journal name, year of publication, country of study, study start date, study end date, population studied, number of cases tested, number of positive cases, positive rate, mean age of participants, sample type, detection method used, serotypes, strains, genogroups or genotype and their rates, and seasonal pattern. Later, the study period was calculated in months, the population studied was recoded into participants' setting ("community" if samples obtained from the general population, "outpatients" if samples obtained from outpatient clinics or "inpatients" if samples obtained from hospitalized or admitted patients) and if the positive rates were not mentioned, they were calculated

according to the sample size and the number of positive cases on each on RV and NoV separately.

E. Risk of Bias Assessment

Risk bias analysis was performed on studies reporting on NoV in the MENA countries; the tool used was developed for prevalence studies by Hoy et al. (128). The tool assesses the domains of selection, nonresponse, measurement and analysis biases. It focuses on identifying whether the studies had attempted to minimize bias but it doesn't directly measure the presence or absence of bias. Risk bias analysis on studies reporting on RV was not performed as part of this proposal.

F. Statistical Analysis

Descriptive statistics, such as rates, ranges and medians, were carried out using Statistical Package for the Social Sciences (SPSS) version 23 (IBM, USA). Figures were built using Microsoft Office Excel 2010.

CHAPTER IV

RESULTS

The search strategy identified 2,589 and 816 records on RV and NoV, respectively. Consequently and for ease of interpretation, the results from countries of the MENA region are separately presented to those collected/extracted on RV and those on NoV.

A. Rotavirus

The literature search on RV in the MENA region between 2000 and 2015 yielded 2,589 citations. After removal of duplicates, we assessed the eligibility of 671 citations based on their titles and abstracts. Figure 1 presents the flow diagram of study selection on RV in MENA countries; 169 unique records were included following exclusion of non-eligible studies as per the inclusion and exclusion criteria described under methods.

Studies on RV have been reported in 19 out of the 25 countries of the MENA region. Our search did not identify any reported studies on RV in Algeria, Cyprus, Djibouti, Mauritania, Somalia and Syria. A wide range of RV infection rates was reported in the MENA region. Reported rates ranged between 0.60% (129) and 78.21% (130) with a 27.39% median percentage of positive RV. Table 1 summarizes the number of studies reporting on RV infection in the different countries, the range of rates and median per country. Turkey leads in the MENA region in terms of the number of

publications on RV followed by Iran, Saudi Arabia and Egypt. Only one publication on RV originated from Kuwait and Qatar.

The collected data from the eligible 169 RV studies conducted in MENA between 2000 and 2015 were tabulated and sorted by country and descending year of publication. Table 2 summarizes the data extracted from the literature on the studied populations, participants' setting, study period, detection method(s) used, number of recruited participants, RV positive rates, seasonal peaks and predominant serotypes or genotypes.

The majority of studies reporting on RV infection rates were clinical observational studies. In 162 out of the 169 studies, the study participants were recruited either from hospitals or outpatient clinics. These patients presented with signs and symptoms of AGE and consequently were recruited in order to test for RV infection. Moreover, 108 studies were conducted among children less than 5 years of age whereas the remaining ones reported on RV association with gastroenteritis among other age groups and rarely adults. Study periods ranged from 2 months to 19 years. The latter was a retrospective study originating from Tunisia that assessed the rates of RV by reviewing medical charts over 19 years.

In an attempt to assess the accuracy of the laboratory methods (clinical or research) used to report on RV in stool of infected patients, we found that the majority of studies utilized rapid detection methods for the detection of RV such as EIA, IC, LA and

ELISA. These methods are characterized by 90 to 95% sensitivity and specificity rates. RT-PCR was the method of choice for the characterization of RV genotypes in the majority of these studies, with 100% sensitivity and 100% specificity, used in order to report on the molecular characteristics of RV (Table 2).

We next determined the predominant reported RV strains associated with gastroenteritis reported in MENA countries between 2000 and 2015 (Table 2). The following genotypes were reported (Figure 2): G1[P8] (37 studies, 55.2%) followed by G2[P4] (6 studies, 9.0%), G9[P8] (6 studies, 9.0%), G3[P8] (5 studies, 7.5%), G4[P8] (4 studies, 6.0%) and G2[P6] (1 study, 1.5%). Some studies reported only on the predominant G serotype: G1 (n=6, 9.0%), G2 (n=1, 1.5%), G4 (n=2, 3.0%), G8 (n=1, 1.5%) and G9 (n=1, 1.5%). Thus, the predominant RV strain in MENA is G1[P8] followed by G2[P4] and G9[P8]. The data from the region is similar to those reported worldwide whereby G1[P8] has been predominantly associated with AGE (21).

When assessing the seasonal patterns of RV infection in the region, we detected 95 studies reporting on the seasonality of RV infections. Regionally, RV infection spreads all year round with detectable winter peaks in Egypt, Iran, Israel, Jordan, Lebanon, Libya, Morocco, Oman, Saudi Arabia, Sudan, Tunisia, Turkey and UAE (62 studies). Fall peaks were also reported in Egypt, Iran, Jordan, Libya, Morocco, Saudi Arabia, Sudan, Tunisia, Turkey and Yemen (27 studies). Interestingly, summer peaks were reported along with fall peaks in Egypt, Iran, Iraq, Jordan, Saudi Arabia, Turkey and

Yemen (13 studies) . Figure 3 shows the number of studies reporting seasonal peaks in RV across years in MENA countries.

Below is a summary of the results on RV by country following the extraction of data reported on RV between 2000 and 2015 in the region (Table 2).

The majority of studies conducted in Egypt were among in- and outpatients children where RV infection rates ranged between 8.10% and 76.92% (131-147). Studies that used RT-PCR as a detection method reported that G1[P8] (136, 142), G3[P8] (131) and G2[P4] (144) to be predominant among their study groups.

Iran ranks the second country after Turkey in terms of the number of publications on RV (n=31) where RV infection rates ranged between 15.34% and 67.65% (148-177). Most of the studied populations were in- or outpatient children except for one community study among adults living in Tehran (165). The other studies were conducted in different southern Iranian regions and provinces. Almost 50% of the studies relied only on rapid detection methods to identify RV. Studies that relied on molecular assays for genotypic characterization showed that the predominant G serotypes in Iran includes: G1 (150, 155, 161, 162, 172, 174, 177), G2 (159), G4 (159, 160, 167), G8 (151) and G9 (150) with few reporting the genotypic viral variant being G1[P8] as causative agent of viral diarrhea among children.

Seven studies were conducted in Iraq where RV infection rate ranged from 5.79% to 43.28% among Iraqi children populations (178-184) . When genotypic characterization

was performed, G2[P6] (179) and G1[P8] (183) were associated with AGE among children less than 5 years old. Consequently, the predominance of a circulating viral variant cannot be judged. Similarly, 9 studies described RV rates in Israel where RV rate ranged between 16.05% and 48.97% (185-193). Among these studies, two confirmed a significant and consistent reduction in RV gastroenteritis after the introduction of RV immunization in 2010 (186, 188) and one study confirmed the reduction in clinic visits for RV gastroenteritis in young children (192). One study detected the rate of nosocomial rotavirus gastroenteritis to be 0.99% (191). It is worth noting that the Israeli studies had long study periods and highest sample sizes. In a study of 412 children < 5 years of age assessing RV serotypes, G1[P8] (49.1%) was the most common strain followed by G1[P4] (11.1%), G9[P8] (9.3%) and G3[P8] (8.3%) (192).

The rate of RV infection in Jordan ranged between 26.64% and 49.46% in 7 published studies (194-200). All studies included hospitalized patients from different age groups. G1[P8] was confirmed to be the predominant genotype followed by G2[P4] and G9[P8] in 2 studies using molecular assays (195, 196). Similarly, the studies conducted in Libya (n=8), reported rates of RV infection ranging between 13.39% and 58.29% (201-208) among children from in- or outpatient settings. There was a shift in the predominant circulating strains in Libya in 2001; the most predominant RV was

G1[P8] followed by G9[P8] (208). Whereas in 2011 the predominant strain was G9[P8] followed by G1[P8] (205).

Among the 169 included studies, 19 were conducted in Saudi Arabia where the range of RV infection was between 4.51% and 65.54% (209-227). 17 out of 19 studies reported on data from children less than 5 years presenting to hospitals with AGE (214, 223). Detection methods differed among studies; those using molecular techniques such as PAGE and RT-PCR confirmed that the most common RV strain associated with AGE in Saudi Arabia is G1[P8] (209-212, 215, 221-223).

In MENA, Tunisia had the longest study periods among the published studies on RV in hospitals where some reached 10 (an epidemiological hospital-based survey), 13 (an epidemiological survey) and 19 (a retrospective study from medical charts) years. The rate of RV infection in Tunisia ranged between 17.33% and 28.28% in 13 conducted studies (228-240). The predominant strains varied across studies and years where G1[P8] was the most common in 5 studies (233-235, 238, 240), G3[P8] in 4 studies (228, 231, 232, 237), G9[P8] (229) and G2[P4] (230) in one study each. Turkey ranked the first country in MENA in terms of the number of publications on RV between 2000 and 2015 (n=32). Studies were conducted on several age groups presenting to hospitals with AGE-associated symptoms. The reported rates of infection associated with RV ranged between 0.60% and 78.21% (129, 130, 241-270) with a 20.19% median percentage of positive RV. The diagnosis of RV among hospitalized

children relied on rapid detection methods. 12 out of 32 studies reported on RV strains associated with diarrhea whereby RT-PCR was used as a confirmatory tool. The RV genotypes reported in the Turkish studies include most frequently G9[P8] (130, 242, 245, 253), G1[P8] (252, 261, 262, 264), G2[P4] (251, 258) and G4[P8] (268). G9[P8] was predominantly reported in 2015 (n=3 studies) and G1[P8] (n=4 studies) between 2008 and 2009 which reflects a temporal change in the predominant circulating strains.

Few studies on RV were conducted in Bahrain (n=2) (271, 272), Kuwait (n=1) (273), Lebanon (n=3) (274-276), Morocco (n=5) (277-281), Oman (n=2) (282, 283), Palestine (n=2) (284, 285), Qatar (n=1) (286), Sudan (n=4) (287-290), UAE (n=3) (291-293) and Yemen (n=3) (294-296). G1[P8] was the predominant strain in these countries except for Lebanon where G4[P8] was reported to be predominant (275). Studies from Bahrain, Palestine, Qatar and Sudan didn't conduct any molecular studies and consequently there is lack of data on the genotype associated RV-viral diarrhea as reported. One of the studies in Sudan aimed at establishing a baseline burden of RV in the country using ELISA as a diagnostic method; this study included a large sample size of 10,910 children less than 5 years old (216). RV rate was reported to be 36.27% with infection peaks reported during March to May (spring) and November to December (fall).

When we screened the literature for reports on outbreaks on RV in the MENA region, our search yielded one article reporting on a waterborne diarrheal outbreak

(group A RV) in Malatya, Turkey during fall 2005. This study did not report on the genotyping data. 9,907 citizens suffered from symptoms of diarrhea, abdominal cramps, fever and vomiting (297).

In conclusion, 169 studies reported on RV infection rates in 19 countries of the MENA region. As expected, the majority of these studies were among children presenting with AGE. Regionally, G1[P8] was predominantly reported as the causative agent of AGE among children less than 5 years old. Although RV infection spreads all year round in MENA, winter peaks were mostly reported.

B. Norovirus

We followed the same pattern outlined above in reporting the results of NoV-associated AGE in the region. Our literature search on NoV yielded 816 citations between 2000 and 2015. After removal of duplicates, we assessed the eligibility of 217 citations based on their titles and abstracts. Figure 4 presents the flow diagram of study selection on NoV in MENA whereby 39 unique records were included following exclusion of non-eligible studies.

Studies on NoV have been conducted in 15 out of the 25 countries of the MENA region (total of 39 studies). Algeria, Cyprus, Mauritania, Somalia and Syria lacked studies on both NoV and RV. No studies on NoV were reported from Bahrain, Oman, Palestine, Sudan and UAE. It is worth mentioning that 18 studies have been conducted

on both RV and NoV using the same stool samples where in the majority of the studies (15/18) RV rate was higher than NoV. The reported NoV infection rates in MENA ranged between 0.38% (213) to 36.84% (298) with a 15.13% median percentage of positive NoV (Table 3). These numbers represent almost half of those reported for RV (27.39% median percentage of positive) in the region. As RV, Turkey is also the leader in the region in terms of the number of publications on NoV followed by Iran and Tunisia.

We tabulated NoV studies reporting on NoV (n=39) conducted in MENA between 2000 and 2015. Data were sorted by country and descending year of publication (Table 4). As the case with studies on RV, the majority of studies on NoV in MENA were clinical observational studies aiming at assessing NoV rates among children with three studies from Djibouti, Iran and Qatar that included adults specifically or all ages. Participants were recruited from hospitals or outpatient clinics with study periods extending from two months to 7 years. Moreover, the majority of studies relied on RT-PCR as a tool to detect NoV and to identify its genogroups or genotypes. Few studies utilized rapid detection methods to detect NoV in stool of patients. 25 out of the 39 extracted studies reported on the predominant NoV genogroup/genotype particularly since RT-PCR was used. In MENA, GII was the most predominant genogroup reported in all the 25 studies. GII.4 was the predominant genotype detected in stool of patients as reported by 16 studies (64%) from Egypt, Iran, Iraq, Israel, Kuwait, Libya, Morocco,

Tunisia, Turkey and Yemen followed by GII.3 (n=4, 16.0%) reported in Jordan and Tunisia (Figure 5).

Figure 6 shows the number of studies reporting NoV seasonal peaks across years. It was noted that NoV infection spreads all year round with detectable winter peaks in Egypt, Morocco, Tunisia and Turkey as the case for RV with reported fall-winter seasonality. However, summer peaks of NoV infections were also reported in Egypt, Libya, Morocco, Tunisia and Turkey. This variability requires further investigation due to the narrow time frame during which hospitalization due to diarrhea was reported and stool tested.

Between 2000 and 2015, the lowest numbers of studies were conducted in Djibouti (n=1), Iraq (n=1), Israel (n=2), Jordan (n=1), Kuwait (n=1), Lebanon (n=1), Libya (n=2), Morocco (n=2), Qatar (n=1), Saudi Arabia (n=3) and Yemen (n=1). The study conducted in Djibouti aimed at detecting and characterizing human caliciviruses among adults with sporadic acute diarrhea where 25.33% of the tested stool samples were NoV positive with GII.14 predominantly reported (299). In Iraq, NoV was detected in 30.00% of the tested stool samples with GII.4 being the predominant genotype (65.5%) followed by GI.4 (10.4%) (300). In Southern Israel, NoV infection was detected at a rate of 9.95% (301) compared to 17.28% in the North (302) in two separate studies. The 2 studies confirmed that the predominant circulating genotype in Israel is again GII.4 followed by GII.3. NoV infection rate was 11.41% in Jordan (196), 8.23% in Kuwait

(303) and 6.32% in Lebanon (276). GII.3 and GII.4 are the predominantly reported genotypes in Jordan (196) and Kuwait (303) while GII was the only reported genogroup in Lebanon without further characterization (276). In Libya and Morocco, NoV infection rate ranged from 15.48% to 17.50% (203, 205) and from 0.82 to 16.20% (277, 304) respectively. GII.4 was the most common genotype reported in both countries. In Qatar, one study was conducted among 288 patients visiting a Qatari hospital using rRT-PCR with 28.47% reported as NoV-positive (286). According to our systematic review, Saudi Arabia has the lowest rates of reported NoV infection compared to other countries in the region. Three studies revealed that the NoV infection rates in Saudi Arabia range between 0.38% and 4.58% (213, 221, 224). In Yemen, NoV infection reached 10.35% with more than 10 NoV genotypes reported and GII.4 being predominant (296).

In Egypt, four studies have been conducted to assess the rate of NoV infection among children from in- and outpatient settings with rates ranging from 13.48% to 26.00%. Samples were collected from patients in urbanized cities of Egypt (Cairo and Nile Delta) presenting with diarrhea with NoV GII being the predominant genogroup (137, 144, 305, 306). Six studies have been conducted in Iran mainly targeting hospitalized inpatients from different age groups: infants, children and adults. The rate of NoV infection in Iran ranged from 4.14% to 32.92% (148, 307-311) with GII.4 being the most common genotype associated with diarrhea followed by GII.6, GII.3, GII.7 and

GI.4 (309). While Tunisia had the highest rate of NoV infection reported in the MENA region reaching 36.84% in one of the five studies conducted (298), GII.3 was reported in studies conducted between 2013 and 2015 (230, 298, 312) and GII.4 was reported between 2008 and 2009 (237, 313).

GII.4 was again detected as the causative agent of NoV-associated diarrhea (251, 257, 314, 315) in Turkey as reported in 8 studies published between 2000 and 2015 (244, 251, 257, 314-318). These studies reported detection rates of NoV ranging between 9.81% and 27.7% which are comparable/close to those observed in studies originating from Egypt.

Our search yielded 8 studies that reported on NoV outbreaks in the MENA region between 2000 and 2015 specifically in Turkey, Iraq and Israel. In Turkey, two outbreaks were community outbreaks in Erzurum (319) and Tokat (320) and one was among US military personnel caused by NoV GII (321). In Iraq, the outbreak took place among British Troops (322). The four outbreaks in Israel were among nursing homes residents (323, 324) and among army recruits in the military (325, 326) attributed to NoV GII.

Taken together, this systematic review shows that NoV is increasingly being recognized as a causative agent of viral AGE in the MENA region. GII.4 was commonly reported in the region in compliance with globally circulating genotypes.

C. Variability and Heterogeneity of NoV Included Studies

There was a variability among the included studies on NoV in terms of population studied, study periods, detection methods, sample sizes, seasonal peaks and predominant genogroups and genotypes (Table 4). Only studies that selected molecular detection methods such as RT-PCR and rRT-PCR reported on the predominant circulating genogroups and genotypes (25 studies). Similarly, studies where the study periods extended over 12 months or more were able to report on the seasonal peaks of NoV (15 studies).

When reviewing the populations studied, studies that selected participants of less than five years old reported higher NoV rates than studies that selected participants of older ages. This trend was clearly seen in the Egyptian studies where studies with children less than 5 years had NoV infection rates of 25.58% and 26.00% compared to 13.48% and 16.00% in studies with children less than 18 years (137, 144, 305, 306). A similar trend was observed in Iran where the study that included infants less than 1 year had the highest NoV rate (32.92%) compared to the other studies (148). This could be attributed to the fact that NoV infection is more common among children less that the age of 5.

The studies from Israel recruited children of similar age groups and participants' settings and detected NoV using rRT-PCR. Thus, these studies could be considered comparable. The difference in NoV rates between the two studies (9.95% versus

17.28%) could be attributed to the different study periods (7 versus 3 years, respectively); however we cannot confirm this variability (301, 302).

While checking the variability in the laboratory method used for the detection of NoV, studies reporting rRT-PCR results showed higher rates compared to studies relying on multiplex RT-PCR. This was confirmed in studies from Morocco (16.12% versus 0.82%) (277, 304) and Tunisia (36.84% versus 8.99%) (230, 298). The rates from Saudi Arabia (0.38%, 3.56% and 4.58%) could be also underestimated since the conducted studies on NoV used rapid detection methods (EM, ELISA and EIA) which are considered less sensitive and specific compared to RT- PCR (213, 221, 224). Similar findings were detected in Libya where EIA was used (203) and in Turkey where IC was used as detection methods (lowest rates) (316, 317) compared to RT-PCR.

We couldn't assess heterogeneity in studies from Iraq, Jordan Kuwait, Lebanon Qatar and Yemen since only one study on NoV was reported in each of these countries.

D. Risk of Bias Assessment: NoV Studies

Assessing the risk of bias is important in the interpretation of systematic reviews. Consequently, we attempted to assess qualitatively the risk of bias in the NoV reported studies published in the region. Based on the tool used (Appendix

IV), we reported on risks encountered through the study's target population as a close representation of the national population, the sampling frame as a true or close representation of the target population, random selection, response rate, subjects, case definition, reliability and validity of the instrument used, mode of data collection, length of the shortest prevalence period and if numerator(s) and denominator(s) for the parameter of interest is appropriate. The majority of studies had moderate risk of bias as described by Hot et al. This finding infers that further research is likely to have an important impact on our confidence in the estimate of NoV and might change the estimate. The main risk of bias was that the study's target population was not a close representation of the national population in relation to relevant variables. Moreover, some internal validity biases were found in terms of the study instrument used that measured NoV. Appendix IV shows the detailed table of the risk of bias assessment for each study.

CHAPTER V

DISCUSSION

This systematic review provides a summary on the epidemiology of RV and NoV in the 25 countries of the MENA region. RV has been recognized as the leading cause of viral AGE worldwide followed by NoV. AGE is responsible for substantial rates of morbidity and mortality predominantly among young children living in developing countries (327). Annually, more than 2.5 billion cases of childhood diarrhea occurs worldwide (328). The significant health outcomes and risk factors of diarrheal diseases were systematically incorporated in the GBD Study (329). As of 2015, WHO included NoV as part of the global estimates of the burden of foodborne diseases (74).

While the status of RV and NoV infections have been reported in many regions of the world, little is known about these infections in the countries of MENA region. Nevertheless, over the past 15 years (2000-2015) several studies described the rates, seasonal peaks/variation and predominant circulating strains of RV and/or NoV in the region. To our knowledge, there are no systematic reviews providing a mapping of the current status of RV and NoV as viral agents of diarrhea in the region. This review highlights the burden exerted by RV and NoV. Both viruses are still the leading causes of viral diarrheal diseases worldwide a decade after FDA approval of RV vaccination and two decades after the introduction of molecular assays to detect NoV.

The extracted data suggests that RV still inflicts a burden in the countries of the MENA region, particularly among children less than five years old. Among the 169 included RV studies, 108 studies were conducted among children less than 5 years where RV infection rates ranged between 5.63% (242) and 78.21% (130). Our results show that the median percentage of positive RV infection among this age group is 28.44% in 18 MENA counties. This number is lower than that reported in the 2009 WHO global RV-surveillance report where the median percentage of positive RV infection was 38% in 10 MENA countries (330).

As of 2016, only 12 countries in the MENA region recommend RV vaccination for infants (56). Rotarix is recommended in two doses in Bahrain, Iraq, Qatar, Saudi Arabia and UAE at ages of 2 and 4 months and in Djibouti, Sudan and Yemen at ages of 6 and 10 weeks. Rotateq is recommended in three doses in Jordan at ages of 3, 4 and 5 months, in Israel and Libya at 2, 4 and 6 months and in Morocco at 2, 3 and 4 months. According to the WHO vaccine-preventable diseases monitoring system, RV vaccination is not included in the NCIPs of the following MENA countries: Algeria, Cyprus, Egypt, Iran, Kuwait, Lebanon, Mauritania, Oman, Palestine, Somalia, Syria, Tunisia and Turkey (56). This however does not refute the fact that RV vaccination is offered in some of these countries yet without being incorporated in the NCIPs. Based on our review, Egypt, Iran, Tunisia and Turkey have significant RV infection rates with median percentages of positive RV infection equivalent to 25.24%, 30.00%, 26.21%

and 20.19%, respectively. These numbers reflect on the existing burden of RV on young age groups. The introduction of RV vaccination in the NCIPs of these countries is suggested in an attempt to reduce the corresponding burden of diarrhea (331). The introduction of RV vaccination will however need to be associated with studies taking into consideration the variability between countries in terms of the potential cost of illness, morbidity and mortality rates.

Similar to RV, NoV imposes a burden of AGE in the MENA region among children less than 5 years old. Seventeen studies were conducted where the median percentage of positive NoV infection was 11.41%. The rate of NoV in these studies ranged between 0.82% (332) and 32.92% (148). These results are compatible with similar recent reviews conducted in Latin America and Africa whereby infection rates ranged between 2.2%-43% (333) and 0.58%-22.0% (334), respectively.

While RV and NoV are associated with AGE among children, recent studies showed that other age groups and elderly are considered at high risk due to the viral mode of transmission and severity of symptoms (335). Only 14 studies on RV and 3 studies on NoV were conducted among all age groups in the MENA region. Consequently, more studies are needed to assess the burden of viral AGE among these age groups as well as elderly and immunosuppressed patients especially due to recent evidence associating NoV among these populations with risk from several complications (336, 337). Moreover, most of the studies included in this systematic

review were conducted among in- and outpatients from hospitals or clinics settings. Thus more community studies are needed to assess the community prevalence rates of both RV and NoV infections. Due to living in suboptimal conditions of hygiene and sanitation, community studies to assess RV or NoV infection among displaced populations nowadays are also important (338, 339).

Several studies and reviews have assessed the molecular epidemiology of RV and NoV circulating strains in the different regions of the world. G1[P8] is the most prevalent RV group causing diarrhea in North America (73%), Australia (82%), Europe (72%), South America (34%) and Asia (34%) (21, 340). While G1[P8] is the predominantly circulating strain globally, other RV groups have been also reported to co-circulate including G2[P4], G3[P8], G4[P8] and G9 in addition to mixed RV infections occurrences (21). Our review confirmed that G1[P8] is also the predominant RV strain in MENA as per the published data. The MENA region is similar to the other parts of the world whereby G2[P4], G2[P6], G3[P8], G4[P8] and G9[P8] were also reported along with G1[P8]. There is lack of data on sequence homologies between isolated reports in countries of the MENA region. The annual variation of RV strains within and between countries and the genetic strain evolution still require further investigation (341).

Rotateq has a 98% protection rate against severe RV gastroenteritis as compared to 85% exerted by Rotarix (85%) (36, 37). Moreover, Rotateq showed 96% reduction in

rate of rotavirus-associated hospitalization compared to Rotarix (85%) (36, 37). While the diversity of the detected RV strains in MENA allows us to safely suggest the use of the commercially available pentavalent vaccine Rotateq (including serotypes G1-4 and [P8]), it is important to understand the dynamics of viral evolution as a result of vaccination; data that are lacking in the region. Active surveillance systems should be implemented in MENA countries for the continuous monitoring of circulating and newly emerging serotypes. This is critical for the assessment of vaccine efficacy in the region and for implementing RV immunization in NCIPs.

The Global Rotavirus Sentinel Hospital Surveillance Network includes 68 countries with only 6 MENA countries being part of this network: Djibouti, Jordan, Libya, Sudan, Syria and Yemen (64). The estimates reported by the WHO are regional ones rather than single country median. Accordingly, it is difficult to compare our country-specific extracted data. This clearly identifies a huge gap in the development of targeted prevention and control strategies in the region. Surveillance systems are legally mandated sources of information that aid in monitoring infectious diseases, detecting epidemics, estimating the magnitude of the disease burden, reporting outbreaks and assessing the geographic and demographic distribution of health events (342). Our results infer a burden of RV in MENA countries; consequently, we recommend adding RV to the surveillance systems in these countries. Moreover, monitoring of RV infection and associated outbreaks and further molecular characterization of RV strain

prevalence will enhance the selection and implementation of vaccines (341). Cost-effectiveness studies on RV immunization such as the ones conducted in the US (343) and Europe (331), are urgently needed in our region.

Our systematic review showed that NoV genogoup GII and genotype GII.4 are predominant in the MENA region. These results are aligned with data from the Americas, Europe, Asia and Africa where GII.4 is also the predominant genotype (344). Our review highlights the molecular epidemiology of NoV in the MENA region and the predominant genotypes in the region, a topic that has been neglected in recent reviews (344, 345).

Challenges and limitations still exist to develop an effective NoV vaccine (346). However, understanding the epidemiology of the virus and its circulating predominant strains remain a key factor in the rapid development of a NoV vaccine. This could be primarily possible if NoV testing, using the most sensitive and specific detection methods, becomes included as part of the clinical/laboratory diagnostic tests in our region. Importantly, including NoV-associated AGE as part of the surveillance systems in the MENA countries would be instrumental in assessing the burden of the virus.

When assessing the seasonal pattern of RV and NoV, our results confirmed that both viruses spread all year round in MENA countries with predominant detected seasonal peaks. The most detectable RV peaks were during the winter season (55.36% of included studies), followed by fall (24.11% of included studies). Our results are

compatible with globally reported RV seasonality studies in Europe, North America and Oceania where RV peaks during winter months (347). In MENA, NoV was mostly detected during winter season in 40% of the included studies followed by fall and summer (25% each). This is also aligned with global seasonality trends where NoV peaks in winter in the Northern Hemisphere where geographically MENA countries are located (106). Nevertheless, and due to the inconsistent seasonal pattern of reports, we suggest further investigational studies on the seasonality of RV and NoV infections in the MENA region; a region impacted by changes in the environmental conditions, humidity, temperature cycles, rain patterns and winds suggested to impact RV and NoV transmission (110). This could be further enhanced when both viruses are included in the surveillance systems of MENA counties.

Diarrheal diseases are indicators of the development scale of countries. The availability of and access to safe drinking water and sanitation are key indicators of diarrheal morbidity and mortality and determinants of integral prevention measures to reduce the burden of RV and/or NoV infections, two major viral agents of public health concern (31, 348). Our results reflect a lack of data on the impact of hygienic practices and access to safe drinking water in relation to RV and NoV propagation. Thus, further studies are needed to help in designing environmental risk assessments for the MENA region.

When assessing qualitatively the variability among the included NoV studies and the risk of bias, the majority of studies couldn't be generalized to the population level. This requires further studies where the target population is a close representation of the national population in relation to relevant variables. Moreover, studies on NoV should rely more on molecular techniques as detection methods of choice and as reliable and valid instruments measuring the parameter of interest.

While we attempted to qualitatively address the risk of bias among NoV included studies, using the Hoy et al., we found that this tool is recently developed and it is not widely used as is the case of all tools advanced for observational studies; specifically among clinical virological studies. Further qualitative analysis will be performed to address the variability, heterogeneity and risk of bias in studies reporting RV-associated AGE in the MENA region. Moreover, one limitation of this systematic review was not performing meta-analysis and pooled prevalence due to the encountered variability among the included studies.

In conclusion, this is the first systematic review that provides an understanding of the burden of RV and NoV in the different countries of the MENA region. Based on this review, we advance the following recommendations:

The median percentage of positive RV and NoV in MENA were 27.39% and 15.13% respectively, thus we recommend to advance a policy in adding RV and NoV in the active surveillance systems of the MENA countries including all age groups and

mainly among children less than the five years of age: this will help detecting RV or NoV epidemics, estimating the magnitude of the disease burden, reporting outbreaks and assessing the geographic and demographic distribution of both viruses. Moreover, it will aid in developing targeted prevention and control strategies against RV and NoV.

Since limited number of studies reported on the predominant circulating strains of RV and NoV in MENA, further research is urgently needed to investigate the molecular characteristics of the circulating RV and NoV strains/genotypes: this is critical to determine the sequence homology of viral variants circulating in the region compared to other areas of the world. The data will feed into the selection and enhancement of RV vaccines in the region and it will allow understanding the transmission dynamics across the region. Moreover, since our data showed a lack of community studies, we recommend researchers to conduct community studies to assess the community prevalence rates of both RV and NoV: this is especially needed among vulnerable populations and communities such as elderly, transplant patients, immunocompromised patients and refugees. Our results reflected that not all of the included studies reported on the seasonality of RV and NoV in MENA, therefore we recommend researchers to further investigate the seasonality of these viruses in MENA region: this is important due to the inconsistent seasonal patterns of RV and NoV in the region. The continuous monitoring of these viruses will allow better inference in relation to seasonality.

RV vaccination is not part of the NCIPs in several MENA countries, we consequently recommend a policy and practice to include RV immunization in the NCIPs of MENA countries where the median percentage of positive RV infection is high: Studies on the impact and cost-effectiveness of RV immunization are urgently needed in the region as measures of the economical and health burdens of RV. And since NoV testing is not introduced in clinical diagnostic laboratories in MENA countries, we recommend such practice: this is especially important due to the clinical impact of the virus which has been recently acknowledged in the GBD study.

APPENDIX I

FIGURES

Figure 1. Flow diagram of RV study selection in MENA countries, 2000-2015

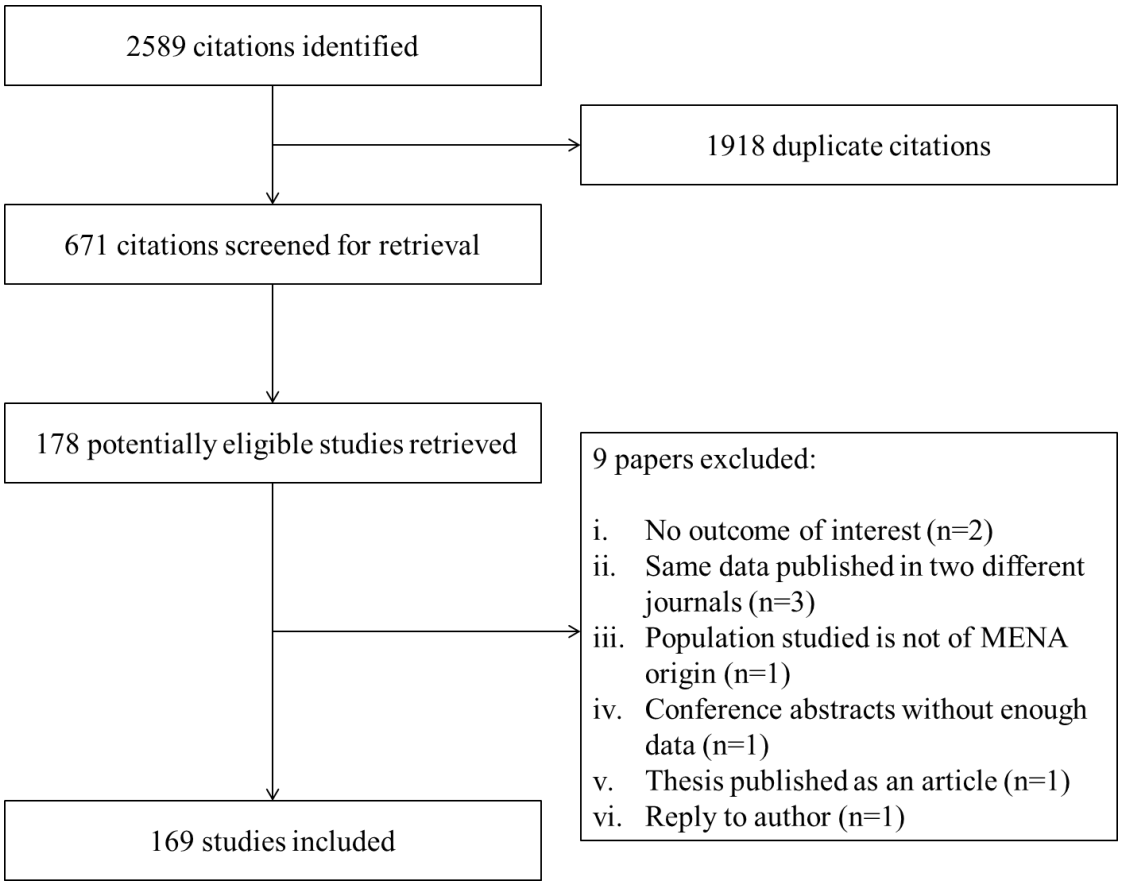
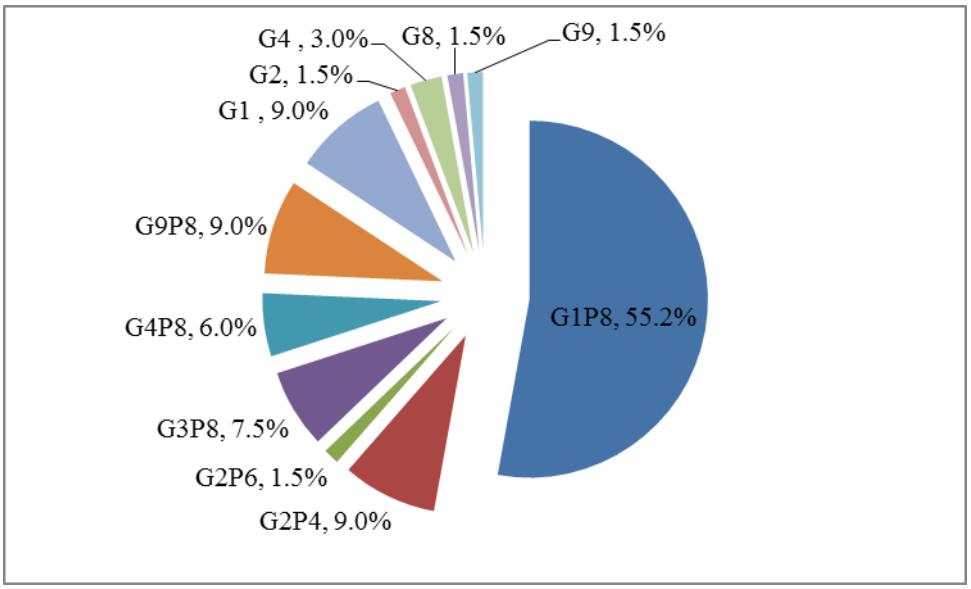


Figure 2. Rotavirus genotypes reported in the MENA region between 2000 and 2015



The percentages are distributed against the number of studies where each strain or genotype was the predominant.

Figure 3. Number of studies reporting seasonal peaks of RV infection in MENA countries between 2000 and 2015

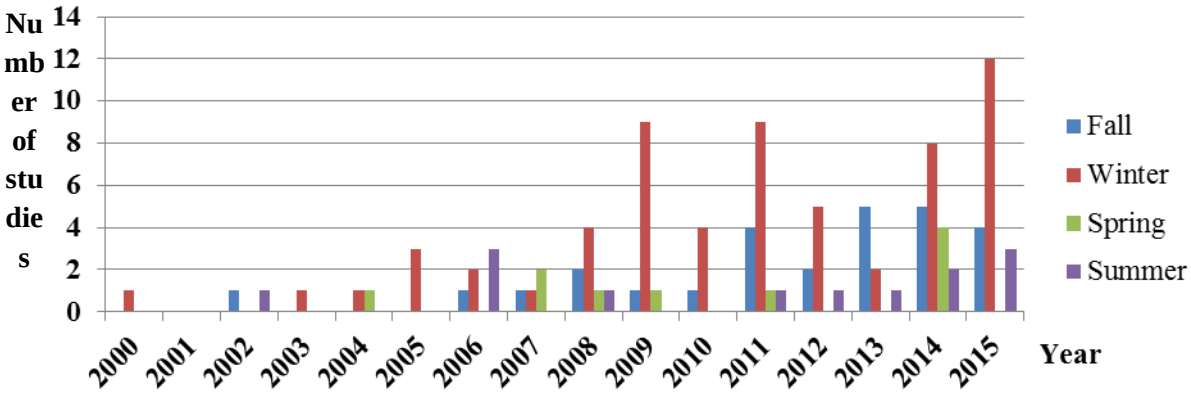


Figure 4. Flow diagram of NoV study selection in MENA countries, 2000-2015

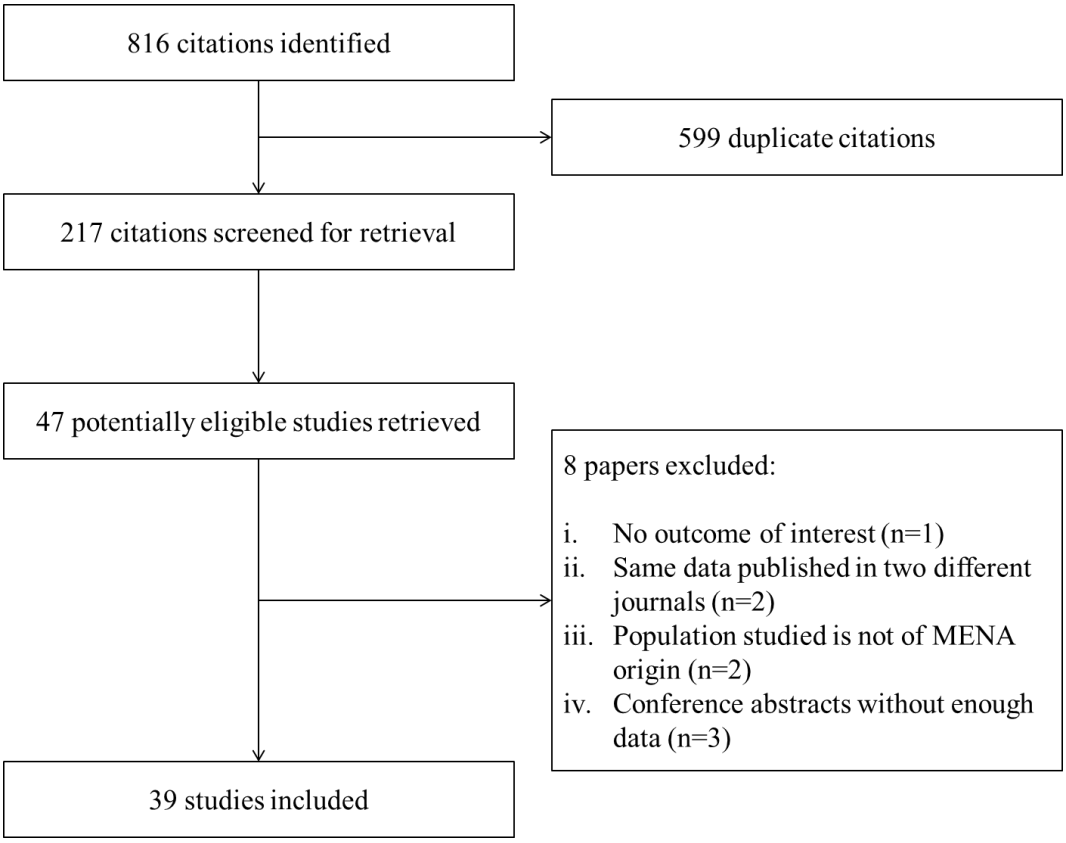
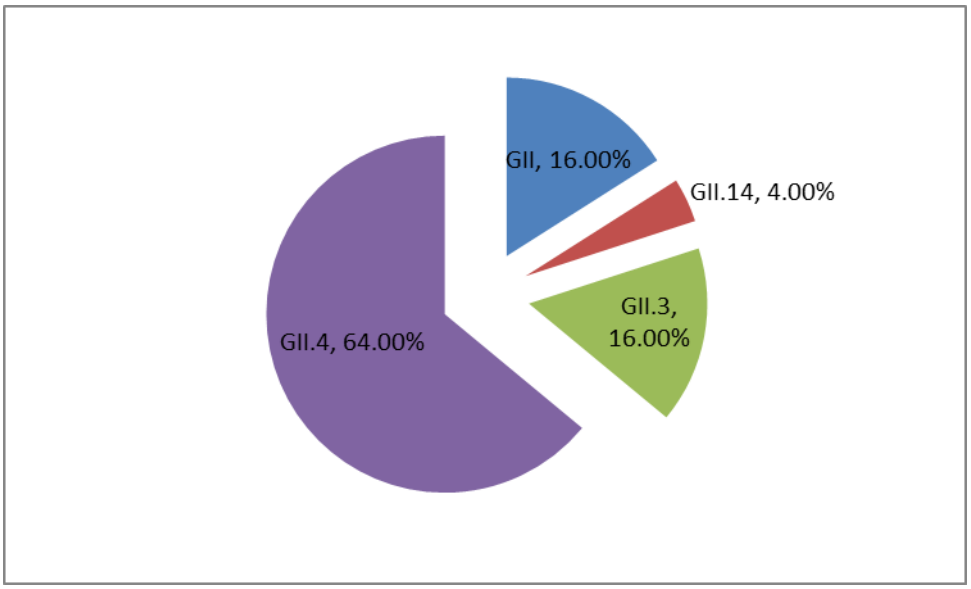
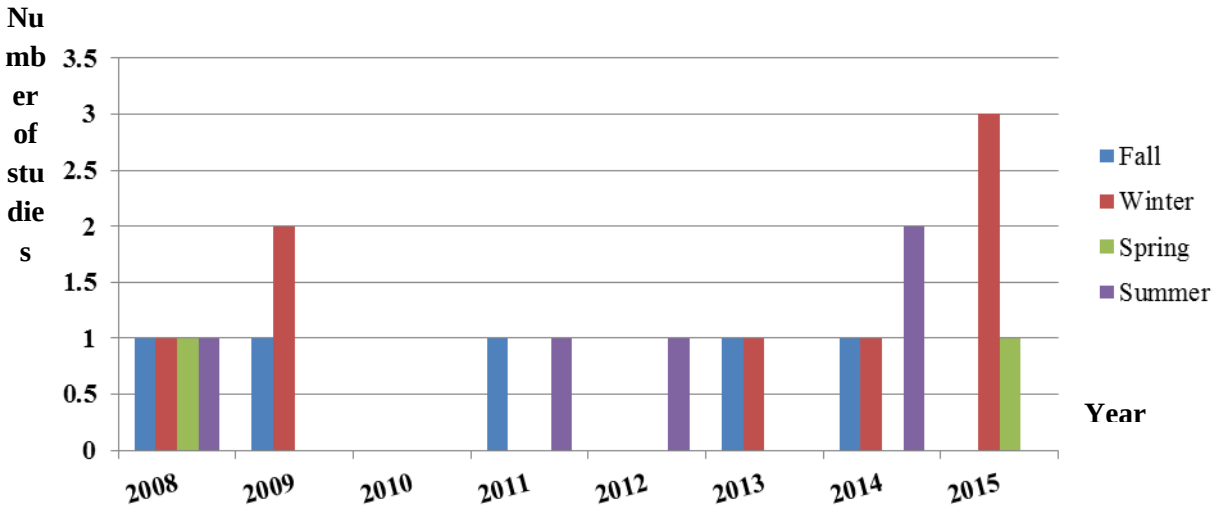


Figure 5. NoV genogroups and genotypes in MENA countries between 2000 and 2015



The percentages are distributed against the number of studies where each genogroup or genotype was the predominant.

Figure 6. Number of studies reporting seasonal peaks of NoV infection, MENA countries 2000-2015



APPENDIX II

TABLES

Table 1. Rotavirus infection rates in countries of the MENA region between 2000 and 2015

Country	Number of Studies	Minimum Rate	Maximum Rate	Median
Bahrain	2	11.30%	44.77%	-
Egypt	17	8.10%	76.92%	25.24%
Iran	31	15.34%	67.65%	30.00%
Iraq	7	5.79%	43.28%	29.50%
Israel	9	16.05%	48.97%	32.36%
Jordan	7	26.64%	49.46%	35.20%
Kuwait	1	43.60%		-
Lebanon	3	27.93%	48.10%	30.61%
Libya	8	13.39%	58.29%	32.27%
Morocco	5	17.21%	43.95%	40.25%
Oman	2	49.34%	57.42%	-
Palestine	2	2.00%	28.00%	-
Qatar	1	10.42%		-
Saudi Arabia	19	4.51%	65.54%	19.00%
Sudan	4	11.69%	36.27%	19.00%
Tunisia	13	17.33%	28.28%	26.21%
Turkey	32	0.60%	78.21%	20.19%
UAE	3	24.74%	50.26%	25.03%
Yemen	3	26.90%	45.03%	35.30%
MENA	169	0.60%	78.21%	27.39 %

Table 2. Country distribution and molecular characteristics of rotavirus, MENA 2000-2015

Country	Population	Participants' Setting	Study Period (months)	Detection Method	n	Positive Rate	Seasonal Peaks	Predominant Serotype / Genotype	Article Number
Bahrain	Children < 5	Inpatients	12	EIA / RT-PCR / Reverse Hybridization	239	44.77%		G1 [P8]	(272)
	Children < 15	Inpatients	20	LA / RT-PCR	805	11.30%		Group A	(271)
Egypt	Children < 5	Inpatients	6	IC / ELISA / RT-PCR	65	76.92%			(132)
	Children < 5	Inpatients	12	RT-PCR / rRT-PCR	110	45.45%	Fall	Group A	(134)
	Children < 2	In and Outpatients	12	EIA / RT-PCR	197	39.09%	Winter	G3 [P8]	(131)
	Children < 5	Inpatients	24	ELISA	356	10.67%	Summer		(133)
	Children < 2	Outpatients	40	ELISA / RT-PCR	348	40.23%	Fall	G1 [P8]	(136)
	NM	Community	NM	ELISA / RT-PCR	47	19.15%			(135)
	Children < 15	Outpatients	12	RT-PCR	500	39.00%			(137)
	Children < 5	In and Outpatients	24	ELISA	430	19.53%			(138)
	Children < 3	Inpatients	54	ELISA	526	9.12%			(139)
	Children < 5	Inpatients	12	LA / EIA / ELISA / RT-PCR	450	35.11%	Fall and Winter	G1	(140)
	Children < 5	Outpatients	24	EIA	2112	8.10%	Summer		(141)
	Children < 5	Inpatients	24	EIA / Nested RT-PCR	1026	25.24%		G1 [P8]	(142)
	Children < 18	In and	12	ELISA / RT-PCR	230	57.39%	Winter	G2 [P4]	(144)

		Outpatients							
	Children < 5	Inpatients	12	EIA / EM	172	16.86%			(143)
	Children < 5	Inpatients	NM	ELISA	61	39.34%			(145)
	Children < 5	Inpatients	2	ELISA	253	17.00%			(147)
	Children < 6	In and Outpatients	24	EIA	1275	16.00%	Summer and Fall		(146)
Iran	Infants < 1	In and Outpatients	3	IC	82	41.46%			(148)
	Children < 9	Inpatients	24	IC / Nested RT-PCR	80	48.75%	Winter		(149)
	Children < 5	Inpatients	11	RT-PCR	100	30.00%		G1 and G9	(150)
	Children < 5	Inpatients	12	ELISA / Nested RT-PCR	184	28.26%	Fall	G8	(151)
	Children < 5	Inpatients	12	ELISA	2988	55.49%			(157)
	Children < 8	Inpatients	12	IC	50	48.00%			(152)
	Children < 12	Inpatients	18	EIA	827	41.96%	Fall		(154)
	Children < 5	Inpatients	12	ELISA	180	35.00%	Fall		(156)
	Children < 5	Inpatients	12	EIA / Nested RT-PCR	138	34.78%	Winter	G4	(160)
	Children < 7	Inpatients	24	EIA	375	24.27%	Winter		(153)
	Children < 18	Inpatients	12	PAGE / RT-PCR	105	20.00%	Fall	G1 [P8]	(155)
	Children < 5	Inpatients	12	EIA / Nested RT-PCR	163	46.01%	Winter	G4	(159)
	Children < 5	Inpatients	12	ELISA	180	32.78%	Fall		(158)
	Children < 5	Inpatients	24	ELISA / Nested Multiplex RT-PCR	141	28.37%	Summer	G2	(159)
	Children < 3	Inpatients	24	ELISA	511	55.58%	Fall and Winter		(163)
	Children < 5	Inpatients	12	EIA / Nested Multiplex RT-PCR	316	27.85%	Fall	G1	(162)

	Children < 5	Inpatients	48	PAGE / Semi-Nested Multiplex RT-PCR	700	18.71%		G1 [P8]	(161)
	All Ages	Inpatients	12	EIA	400	62.00%	Winter		(166)
	Children < 6	Inpatients	12	LA	156	28.85%	Winter		(164)
	Adults	Community	12	RT-PCR	670	22.39%			(165)
	Children < 5	Inpatients	12	EIA / RT-PCR	2198	59.05%	Winter	G4 [P8]	(167)
	Children < 5	Inpatients	5	ELISA / LA	102	67.65%			(169)
	Children < 5	Inpatients	36	EIA / PAGE	1250	32.32%	Fall and Winter		(168)
	Children < 14	Inpatients	NM	ELISA	208	61.06%	Spring		(170)
	Children < 2	Inpatients	6	LA	80	26.25%			(171)
	Children < 5	Inpatients	12	ELISA / RT-PCR	374	24.60%	Spring and Fall	G1 [P8]	(172)
	Children < 5	Inpatients	12	ELISA / PAGE / RT-PCR	372	25.27%	Winter	G1	(174)
	Children < 5	Inpatients	12	ELISA	276	24.64%	Winter		(173)
	Children < 2	In and Outpatients	5	PAGE	200	29.50%			(175)
	Children < 5	In and Outpatients	12	EIA / EM / PAGE / RT-PCR	618	23.62%	Winter	G1 [P8]	(177)
	Children < 5	In and Outpatients	9	ELISA	704	15.34%	Spring		(176)
Iraq	Children < 12	Outpatients and Community	9	IC	600	7.17%			(178)
	Children < 5	Inpatients	12	EIA / Multiplex RT-PCR	976	40.37%		G2 [P6]	(179)
	Children < 5	Inpatients	12	LA	259	5.79%			(180)

	Children < 2	In and Outpatients	6	LA	315	22.54%			(181)
	Children < 5	Inpatients	3	ELISA / RT-PCR	260	36.92%		G1 [P8]	(183)
	Children < 2	Inpatients	12	ELISA	200	29.50%	Summer		(182)
	Children < 5	Inpatients	5	ELISA	268	43.28%			(184)
Israel	Children < 5	Inpatients	48	IC	188	33.51%			(185)
	Children < 6	Inpatients	81	IC	3514	32.36%	Winter		(186)
	Children < 5	In and Outpatients	84	ELISA	7584	30.85%	Winter		(188)
	Children < 6	Outpatients	112	NM	18133	16.05%	Winter		(187)
	Children < 18	Inpatients	24	IC	533	37.90%			(189)
	Children < 3	Outpatients	4	IC	145	48.97%	Winter		(190)
	Children < 5	Inpatients	12	IC / RT-PCR	412	39.08%	Winter	G1 [P8]	(192)
	Children < 18	Inpatients	48	ELISA	35833	0.99%	Winter		(191)
	Children < 5	In and Outpatients	12	ELISA	987	30.70%			(193)
Jordan	Children < 18	Inpatients	12	NM	1378	35.20%			(194)
	Children < 5	Inpatients	24	ELISA / Multiplex Semi-Nested RT-PCR	368	49.46%		G1 [P8]	(196)
	Children < 4	Inpatients	12	IC / RT-PCR	698	35.53%	Winter	G1 [P8]	(195)
	Children < 5	Inpatients	12	ELISA	148	39.86%	Fall		(197)
	All Ages	Inpatients	48	ELISA	1028	27.14%	Summer		(198)
	All Ages	In and Outpatients	48	LA	1400	26.64%	Summer and Fall		(199)
	Children < 5	Inpatients	8	ELISA	265	32.45%			(200)
Kuwait	Children < 5	Inpatients	7	ELISA / RT-PCR	172	43.60%		G1 [P8]	(273)

Lebanon	Children < 15	Inpatients	60	LA	1395	30.61%			(274)
	Children < 5	Inpatients	18	EIA / RT-PCR	487	27.93%	Winter	G4 [P8]	(275)
	Children < 10	Inpatients	2	IC	79	48.10%			(276)
Libya	Children < 5	Inpatients	9	EIA	410	58.29%	Winter		(201)
	Children < 5	In and Outpatients	9	EIA	545	57.06%	Winter		(202)
	Children < 5	Inpatients	9	ELISA	200	33.00%	Winter		(204)
	Children < 5	In and Outpatients	12	EIA / Semi-Nested Multiplex RT-PCR	520	31.54%	Winter	G9 [P8]	(205)
	Children < 5	Outpatients	8	EIA	239	13.39%	Fall and Spring		(203)
	Children < 5	Inpatients	15	LA	1046	26.96%	Winter		(206)
	Children < 12	Inpatients	12	LA	169	26.63%	Winter		(207)
	Children < 5	Inpatients	2	RT-PCR	73	47.95%		G1 [P8]	(208)
Morocco	Children < 5	Inpatients	14	ELISA / RT-PCR	533	24.02%	Fall and Winter	G1 [P8]	(278)
	Children < 5	Inpatients	12	Multiplex RT-PCR	122	17.21%	Winter	G1 [P8]	(277)
	Children < 5	Inpatients	36	ELISA / RT-PCR	1388	41.71%	Fall	G1 [P8]	(279)
	Children < 5	Inpatients	47	EIA	1841	40.25%	Winter		(280)
	Children < 5	Inpatients	11	EIA / RT-PCR	314	43.95%	Fall and Winter	G1 [P8]	(281)
Oman	Children < 6	Inpatients	12	ELISA / PAGE / RT-PCR	310	57.42%		G1 [P8]	(282)
	Children < 5	Inpatients	24	EIA / RT-PCR	3470	49.34%	Winter and Spring	G2 [P4]	(283)

Palestine	Children < 5	Community	6	EIA	150	2.00%			(285)
	Children < 5	Inpatients	4	IC	150	28.00%	Summer		(284)
Qatar	All Ages	In and Outpatients	6	Multiplex rRT-PCR	288	10.42%			(286)
Saudi Arabia	Children < 5	Inpatients	12	ELISA / RT-PCR	970	40.72%	Summer	G1 [P8]	(209)
	Children < 18	Inpatients	12	ELISA / RT-PCR	541	31.61%	Fall	G1 [P8]	(210)
	Children < 2	Inpatients	12	IC / RT-PCR	80	15.00%		G1 [P8]	(211)
	Children < 6	NM	12	EM	1049	18.02%			(213)
	Children < 5	Inpatients	12	LA / RT-PCR	200	16.50%	Summer	G1 [P8]	(212)
	All Ages	Inpatients	60	ELISA / RT-PCR	1575	4.51%		G4 [P8]	(214)
	Children < 6	Inpatients	13	ELISA / RT-PCR	428	39.95%	Summer	G1 [P8]	(215)
	Children < 14	Inpatients	12	EIA	301	33.55%	Fall		(216)
	Children < 5	Inpatients	6	LA / RT-PCR	100	16.00%			(217)
	Children < 5	Inpatients	34	ELISA	1007	65.54%			(218)
	Children < 5	In and Outpatients	12	IC / ELISA	156	23.72%			(219)
	Children < 5	Inpatients	6	ELISA	270	22.22%			(220)
	Children < 5	In and Outpatients	12	ELISA / PAGE / RT-PCR	984	19.00%	Winter	G1 [P8]	(222)
	All Ages	In and Outpatients	5	EIA / PAGE / Semi-Nested Multiplex RT-PCR/	454	11.89%		G1 [P8]	(223)
	Children < 6	In and Outpatients	12	ELISA / RT-PCR	1000	6.00%	Spring	G1 [P8]	(221)
	Children < 5	Inpatients	6	EIA	284	33.10%			(224)
	Children < 12	In and Outpatients	72	EIA	614	25.41%			(226)
	Children < 5	Inpatients	12	LA / ELISA	479	10.02%			(225)

	Children < 5	In and Outpatients	11	ELISA / PAGE	576	16.67%		G1	(227)
Sudan	Children < 5	Inpatients	12	IC	437	21.97%	Winter		(287)
	Children < 5	Inpatients	24	ELISA	10910	36.27%	Fall and Spring		(288)
	Children < 5	In and Outpatients	6	ELISA / PAGE	755	16.03%			(289)
	All Ages	Inpatients	30	IC / rRT-PCR	710	11.69%		Group A	(290)
Tunisia	Children < 6	Inpatients	4	ELISA / RT-PCR	114	28.07%	Winter	G9 [P8]	(229)
	Children < 5	Inpatients	24	ELISA / RT-PCR	279	23.30%	Winter	G3 [P8]	(228)
	Children < 6	Outpatients and Community	12	ELISA / Multiplex RT-PCR	178	26.97%	Fall and Winter	G2 [P4]	(230)
	Children < 5	Inpatients	17	ELISA / Multiplex RT-PCR	550	27.27%	Winter	G3 [P8]	(231)
	Children < 13	In and Outpatients	36	ELISA / RT-PCR	435	28.28%	Winter	G1 [P8]	(233)
	Children < 12	In and Outpatients	53	ELISA / Multiplex Semi-Nested RT-PCR	788	27.92%	Winter	G3 [P8]	(232)
	Children < 5	In and Outpatients	45	LA / ELISA / Semi-Nested Multiplex RT-PCR	309	26.21%	Winter	G1 [P8]	(234)
	Children < 5	Inpatients	228	ELISA	533	27.39%	Winter		(236)
	Children < 5	NM	156	ELISA / Multiplex Semi-Nested RT-PCR	2428	20.96%		G1 [P8]	(235)
	Children < 12	In and	30	EIA / RT-PCR	632	22.47%	Winter	G3 [P8]	(237)

		Outpatients							
	Children < 5	In and Outpatients	120	LA / ELISA / RT-PCR	982	22.40%		G1 [P8]	(238)
	Children < 5	In and Outpatients	24	EIA / RT-PCR	638	20.85%	Winter		(239)
	Children < 5	Inpatients	52	LA / ELISA / PAGE / RT-PCR	375	17.33%	Winter	G1 [P8]	(240)
Turkey	Children < 18	Inpatients	9	rRT-PCR	84	54.76%			(241)
	Children < 17	In and Outpatients	12	Multiplex RT-PCR	240	18.33%	Summer		(244)
	Children < 5	Inpatients	84	IC	4702	16.95%	Winter		(243)
	Children < 5	Inpatients	7	ELISA / RT-PCR / PAGE	181	13.26%		G9 [P8]	(245)
	Children < 5	In and Outpatients	12	IC / Semi-Nested Multiplex RT-PCR	1297	5.63%	Winter	G9 [P8]	(242)
	Children < 5	Inpatients	24	LA / IC / EIA / RT-PCR	2102	78.21%	Winter and Spring	G9 [P8]	(130)
	Children < 16	Inpatients	12	IC	3607	16.55%	Fall and Spring		(247)
	Children < 16	Inpatients	60	IC	3106	13.59%	Winter		(248)
	Children < 16	Inpatients	12	IC	588	12.76%	Winter and Spring		(246)
	Children < 18	Inpatients	12	ELISA / PCR-Reverse Line Blot Hybridization	495	48.08%		G1 [P8]	(252)
	Children < 5	Inpatients	48	EIA / LA	1079	26.14%			(249)
	Children < 6	NM	11	EIA / RT-PCR	150	23.33%		G2 [P4]	(251)

	All Ages	Inpatients	24	EIA	1112	18.08%			(250)
	Children < 5	Outpatients	12	IC / Multiplex RT-PCR	494	27.73%	Winter	G9 [P8]	(253)
	Children < 5	Inpatients	12	IC	1543	25.02%	Winter		(255)
	Children < 15	Inpatients	12	IC	497	20.93%	Fall and Winter		(254)
	All Ages	Inpatients	2	IC	300	0.60%			(129)
	Children < 6	NM	11	Multiplex RT-PCR	144	19.44%			(257)
	All Ages	Inpatients	42	IC	2962	16.31%			(256)
	Children < 6	In and Outpatients	8	EIA / RT-PCR	675	8.00%		G2 [P4]	(258)
	Children < 5	Inpatients	12	ELISA / RT-PCR	338	52.96%	Winter	G1 [P8]	(261)
	Children < 18	Inpatients	12	IC	961	30.07%			(260)
	Children < 5	In and Outpatients	40	ELISA / PAGE / RT-PCR	470	28.51%	Winter	G1 [P8]	(262)
	All Ages	Inpatients	12	IC	672	18.75%			(263)
	Children < 18	Outpatients	52	NM	1950	17.54%			(259)
	Children < 5	In and Outpatients	16	EIA / RT-PCR	322	39.75%	Fall and Winter	G1 [P8]	(264)
	Children < 5	Inpatients	3	IC	100	25.00%			(265)
	All Ages	Inpatients	12	IC	66	4.55%			(266)
	Children < 17	Inpatients	33	IC	1099	36.76%	Winter		(267)
	Children < 7	Inpatients	21	EIA / LA / PAGE / RT-PCR	508	23.43%		G4 [P8]	(268)
	Children < 3	Outpatients	6	LA / ELISA / PAGE	135	15.56%			(269)
	Children < 5	Inpatients	12	ELISA / RT-PCR	920	39.78%	Winter	G1	(270)
UAE	Children < 5	Inpatients	12	EIA / RT-PCR	758	50.26%	Winter	G1 [P8]	(291)
	Children < 5	Inpatients	12	NM	970	24.74%	Winter		(292)

	All Ages	Inpatients	12	IC	911	25.03%			(293)
Yemen	Children < 5	In and Outpatients	84	EIA	5495	35.30%	Fall		(294)
	Children < 5	Inpatients	16	ELISA / PAGE / RT-PCR	795	45.03%	Summer	G2 [P4]	(295)
	Children < 5	In and Outpatients	17	ELISA / RT-PCR	290	26.90%		G1 [P8]	(296)

Table 3. Norovirus infection rates in countries of the MENA region between 2000 and 2015

Country	Number of Studies	Minimum Rate	Maximum Rate	Median
Djibouti	1	25.33%		-
Egypt	4	13.48%	26.00%	20.89%
Iran	6	4.14%	32.92%	11.21%
Iraq	1	30.00%		-
Israel	2	9.95%	17.280%	-
Jordan	1	11.41%		-
Kuwait	1	8.23%		-
Lebanon	1	6.32%		-
Libya	2	15.48%	17.50%	-
Morocco	2	0.82%	16.12%	-
Qatar	1	28.47%		-
Saudi Arabia	3	0.38%	4.58%	3.56%
Tunisia	5	8.99%	36.84%	16.24%
Turkey	8	9.81%	27.70%	16.09%
Yemen	1	10.35%		-
MENA	39	0.38%	36.84%	15.13%

Table 4. Country distribution and molecular characteristics of norovirus, MENA 2000-2015

Country	Population	Participants' Setting	Study Period (months)	Detection Method	n	Positive Rate	Seasonal Peaks	Predominant Genogroup/Genotype	Article Number
Djibouti	Adults	Inpatients	18	RT-PCR	75	25.34%		GII.14	(299)
Egypt	Children < 3	Inpatients	24	RT-PCR	86	25.58%		GII	(305)
	Children < 15	Outpatients	12	RT-PCR	500	16.20%			(137)
	Children < 5	Outpatients	36	EIA	2112	26.00%	Summer		(306)
	Children < 18	In and Outpatients	12	RT-PCR	230	13.48%	Winter	GII.4	(144)
Iran	Infants < 1	In and Outpatients	3	IC	82	32.92%			(148)
	Children < 7	Inpatients	24	EIA	375	12.53%	Fall		(308)
	Children < 5	Inpatients	NM	RT-PCR	2170	4.14%			(307)
	All Ages	Inpatients	12	RT-PCR	293	9.89%		GII.4	(309)
	Children < 5	Inpatients	24	Nested RT-PCR	143	6.29%		GII	(310)
	Children < 17	Inpatients	24	Nested RT-PCR	47	21.30%		GII.4	(311)
Iraq	Children < 5	Inpatients	2	RT-PCR	260	30.00%		GII.4	(300)
Israel	Children < 5	In and Outpatients	84	rRT-PCR	673	9.95%		GII.4	(301)
	Children < 5	Inpatients	38	rRT-PCR	515	17.28%		GII.4	(302)

Jordan	Children < 5	Inpatients	24	rRT-PCR	368	11.41%		GII.3	(196)
Kuwait	Children < 5	Inpatients	9	ELISA / RT-PCR	170	5.23%		GII.4	(303)
Lebanon	Children < 10	Inpatients	2	EIA / RT-PCR	79	6.32%		GII	(276)
Libya	Children < 5	In and Outpatients	12	rRT-PCR	520	17.50%	Summer	GII.4	(205)
	Children < 5	Outpatients	8	EIA	239	15.48%	Fall		(203)
Morocco	Children < 5	Inpatients	12	Multiplex RT-PCR	122	0.82%	Winter		(277)
	Children < 5	Inpatients	12	rRT-PCR	335	16.12%	Summer	GII.4	(304)
Qatar	All Ages	In and Outpatients	6	Multiplex rRT-PCR	288	28.47%			(286)
Saudi	Children < 6	NM	12	EM	1049	0.38%			(213)
Arabia	Children < 6	In and Outpatients	12	ELISA	253	3.56%	Fall and Spring		(221)
	Children < 5	Inpatients	6	EIA	284	4.58%			(224)
Tunisia	Children < 6	Inpatients	18	rRT-PCR	114	36.84%	Winter	GII.3	(298)
	Children < 6	Outpatients and Community	12	Multiplex RT-PCR	178	8.99%	Fall and Winter	GII.3	(230)
	Children < 13	In and Outpatients	36	RT-PCR	407	9.34%	Winter	GII.3	(312)
	Children < 12	In and	52	RT-PCR	788	16.24%	Fall and	GII.4	(313)

		Outpatients					Winter		
	Children < 12	In and Outpatients	30	RT-PCR	632	17.40%	Winter and Summer	GII.4	(237)
Turkey	Children < 17	In and Outpatients	12	Multiplex RT-PCR	240	23.34%			(244)
	Children < 16	In and Outpatients	24	IC	1027	10.90%	Spring and Winter		(317)
	Children < 5	In and Outpatients	16	RT-PCR	150	10.00%		GII	(318)
	Children < 16	Inpatients	12	IC	520	9.81%	Summer		(316)
	Children < 6	NM	11	ELISA / RT-PCR	150	22.80%		GII.4	(251)
	Children < 14	Inpatients	16	ELISA / RT-PCR / rRT-PCR	238	15.13%		GII.4	(315)
	Children < 6	NM	11	Multiplex RT-PCR / EM	144	27.70%		GII.4	(257)
	Children < 10	Inpatients	8	RT-PCR	88	17.05%		GII.4	(314)
Yemen	Children < 5	In and Outpatients	17	RT-PCR	290	10.35%		GII.4	(296)

APPENDIX III

MESHTERMS AND KEYWORDS

Database: Ovid Medline

1.	Algeria/ or Algeria*.mp.	3,244
2.	Bahrain/ or Bahrain*.mp.	661
3.	Cyprus/ or (Cyprus or Cypriot*).mp.	1,471
4.	Djibouti/ or (Djibouti* or Somaliland*).mp.	389
5.	Egypt/ or (Egypt* or United Arab Republic*).mp.	16,796
6.	Iran/ or Iran*.mp.	20,248
7.	Iraq/ or Iraq*.mp	7,314
8.	Israel/ or Israel*.mp.	32,592
9.	Jordan/ or Jordan*.mp.	4,593
10.	Kuwait/ or Kuwait*.mp.	3,180
11.	Lebanon/ or (Lebanon or Lebanese).mp.	4,112
12.	Libya/ or Libya*.mp.	1,293
13.	Mauritania/ or Mauritan*.mp.	626
14.	Morocco/ or (Morocco* or Moroccan* or ifni*).mp.	6,037
15.	Oman/ or (Oman* or Muscat*).mp.	1,686
16.	(Palestin* or Gaza* or (West* adj2 Bank)).mp.	2,528
17.	Qatar/ or (Qatar* or Katar or Quatar*).mp.	832
18.	Saudi Arabia/ or (Saud* or KSA).mp.	16,186
19.	Somalia/ or Somal*.mp.	2,728
20.	Sudan/ or Sudan*.mp.	7,739
21.	Syria/ or Syria*.mp.	10,038
22.	Tunisia/ or Tunis*.mp.	8,208

23. Turkey/ or (Turkey or Turkish).mp.	39,538
24. United Arab Emirates/ or (Emirat* or UAE or Abu Dahbi or Trucial state*).mp.	3,335
25. Yemen/ or (Yemen* or Aden or Sanaa).mp.	1,709
26. exp Africa, Northern/ or (North* adj2 Africa*).mp.	31,149
27. exp Middle East/ or (Middle adj2 East*).mp.	101,363
28. exp Mediterranean Region/ or Mediterranean*.mp.	29,602
29. (Arab* or MENA or EMRO or (Near adj2 East*)).mp.	98,845
30. or/1-29	297,720
31. Norovirus/ or (Norovirus* or Noroviral or (Noro adj virus)).mp.	3,481
32. Norwalk virus/ or Norwalk*.mp.	1,331
33. Small Round Structured Virus*.mp.	193
34. or/31-33	4,557
35. Rotavirus/ or (Rotavirus* or Rotaviral or (Rota adj virus)).mp.	12,234
36. Rotavirus Infections/ or Rotavirus Infection*.mp.	6,897
37. ((Neonatal adj2 Calf) or (Calf adj2 Diarrhea)).mp.	542
38. or/35-37	12,636
39. 30 and 34	100
40. 30 and 38	389
41. limit 39 to yr="2000 - 2016"	87
42. limit 40 to yr="2000 - 2016"	249

Database: Pubmed

1.	Algeria OR Algeria*[tw]	5,074
2.	Bahrain OR Bahrain*[tw]	1,462
3.	((Cyprus) OR Cyprus[tw]) OR Cypriot*[tw]	3,913
4.	((Djibouti) OR Djibouti*[tw]) OR Somaliland*[tw]	455
5.	((Egypt) OR Egypt*[tw]) OR United Arab Republic*[tw]	52,493
6.	Iran OR Iran*[tw]	89,822
7.	Iraq OR Iraq*[tw]	9,832
8.	Israel OR Israel*[tw]	178,762
9.	Jordan OR Jordan*[tw]	25,506
10.	Kuwait OR Kuwait*[tw]	7,598
11.	((Lebanon) OR Lebanon[tw]) OR Lebanese[tw]	17,373
12.	Libya OR Libya*[tw]	2,061
13.	Mauritania OR Mauritan*[tw]	704
14.	(((Morocco) OR Morocco*[tw]) OR Moroccan*[tw]) OR ifni*[tw]	10,265
15.	((Oman) OR Oman*[tw]) OR Muscat*[tw]	5,915
16.	((Palestin*[tw]) OR Gaza*[tw]) OR West Bank[tw]	2,583
17.	(((Qatar) OR Qatar*[tw]) OR Katar[tw]) OR Quatar*[tw]	4,100
18.	((Saudi Arabia) OR Saud*[tw]) OR KSA[tw]	40,837
19.	Somalia OR Somal*[tw]	3,020
20.	Sudan OR Sudan*[tw]	9,631
21.	Syria OR Syria*[tw]	11,172
22.	Tunisia OR Tunis*[tw]	15,237
23.	((Turkey) OR Turkey[tw]) OR Turkish[tw]	179,005
24.	((((United Arab Emirates) OR Emirat*[tw]) OR UAE[tw]) OR Abu Dahbi[tw]) OR Trucial state*[tw]	7,418
25.	(((Yemen) OR Yemen*[tw]) OR Aden[tw]) OR Sanaa[tw]	2,289

26. ((exp Africa, Northern) OR North Africa*[tw]) OR Northern Africa*[tw]	7,233
27. (exp Middle East) OR Middle East*[tw]	13,283
28. (exp Mediterranean Region) OR Mediterranean*[tw]	30,418
29. (((Arab*[tw]) OR MENA[tw]) OR EMRO[tw]) OR Near East*[tw]	107,532
30. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29)	776,686
31. ((Norovirus) OR Norovirus*[tw]) OR Noroviral[tw]	4,506
32. Norwalk Virus OR Norwalk*[tw]	1,368
33. Small Round Structured Virus*[tw]	187
34. (#31 OR #32 OR #33)	5,016
35. ((Rotavirus) OR Rotavirus*[tw]) OR Rotoviral[tw]	13,001
36. Rotavirus Infections OR Rotavirus Infection*[tw]	8,348
37. (Neonatal Calf[tw]) OR Calf Diarrhea*[tw]	535
38. (#35 OR #36 OR #37)	13,398
39. (#30 AND #34)	126
40. #30 AND #38	555
41. (#30 AND #34) Filters: Publication date from 2000/01/01 to 2016/12/31	110
42. (#30 AND #38) Filters: Publication date from 2000/01/01 to 2016/12/31	385

Database: Embase

1.	algeria'/exp OR ‘algeria*’:ab,ti	4,966
2.	bahrain'/exp OR ‘bahrain*’:ab,ti	1,417
3.	cyprus'/exp OR ‘cyprus’:ab,ti OR ‘cypriot*’:ab,ti	2,225
4.	djibouti'/exp OR ‘djibouti*’:ab,ti OR ‘somaliland*’:ab,ti	485
5.	egypt'/exp OR ‘egypt*’:ab,ti OR ‘united arab republic*’:ab,ti	24,321
6.	iran'/exp OR ‘iran*’:ab,ti	44,118
7.	iraq'/exp OR ‘iraq*’:ab,ti	9,249
8.	israel'/exp OR ‘israel*’:ab,ti	37,527
9.	jordan'/exp OR ‘jordan*’:ab,ti	6,987
10.	kuwait'/exp OR ‘kuwait*’:ab,ti	4,782
11.	lebanon'/exp OR ‘lebanon’:ab,ti OR ‘lebanese’:ab,ti	5,416
12.	libya'/exp OR ‘libya*’:ab,ti	1,886
13.	mauritania'/exp OR ‘mauritan*’:ab,ti	767
14.	morocco'/exp OR ‘morocco*’:ab,ti OR ‘moroccan*’:ab,ti OR ‘ifni*’:ab,ti	8,556
15.	oman'/exp OR ‘oman*’:ab,ti OR ‘muscat*’:ab,ti	2,751
16.	'palestine'/exp OR ‘palestin*’:ab,ti OR ‘gaza*’:ab,ti OR ‘West* NEAR/2 Bank’:ab,ti	3,194
17.	qatar'/exp OR ‘qatar*’:ab,ti OR ‘katar’:ab,ti OR ‘quatar*’:ab,ti	1,954
18.	saudi arabia'/exp OR ‘saud*’:ab,ti OR ‘ksa’:ab,ti	25,426
19.	somalia'/exp OR ‘somal*’:ab,ti	3,490
20.	sudan'/exp OR ‘sudan*’:ab,ti	9,585
21.	syria'/exp OR ‘syria*’:ab,ti	11,637
22.	tunisia'/exp OR ‘tunis*’:ab,ti	11,306
23.	turkey'/exp OR ‘turkey’:ab,ti OR ‘turkish’:ab,ti	49,968
24.	united arab emirates'/exp OR ‘emirat*’:ab,ti OR ‘uae’:ab,ti	

OR ‘abu dahbi’:ab,ti OR ‘trucial state*’:ab,ti	5,384
25. yemen'/exp OR ‘yemen*’:ab,ti OR ‘aden’:ab,ti OR ‘sanaa’:ab,ti	2,260
26. 'north africa'/exp OR ‘north* NEAR/2 africa*’:ab,ti	32,986
27. middle east'/exp OR ‘middle NEAR/2 east*’:ab,ti	129,113
28. ‘mediterranean*’:ab,ti	29,838
29. 'arab*':ab,ti OR 'mena':ab,ti OR 'emro':ab,ti OR 'near near/2 east*':ab,ti	99,466
30. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	376,530
31. norovirus'/exp OR 'norovirus infection'/exp OR ‘norovirus*’:ab,ti OR ‘noroviral’:ab,ti OR ‘noro NEAR/1 virus’:ab,ti	5,636
32. ‘norwalk*’:ab,ti	1,322
33. ‘small round structured virus*’:ab,ti	205
34. #31 OR #32 OR #33	6,196
35. rotavirus'/exp OR ‘rotavirus*’:ab,ti OR ‘rotaviral’:ab,ti OR ‘rota NEAR/1 virus’:ab,ti	15,366
36. ‘Rotavirus Infection*’:ab,ti	2,766
37. 'neonatal calf diarrhea':AB,TI	109
38. #35 OR #36 OR #37	15,425
39. #30 AND #34	129
40. #30 AND #38	482
41. #39 AND [2000-2016]/py	120
42. #40 AND [2000-2016]/py	347

Database: Cocharne

1.	MeSH descriptor: [Algeria] "Algeria*":ti,ab,kw	25
2.	MeSH descriptor: [Bahrain] "Bahrain*":ti,ab,kw	23
3.	MeSH descriptor: [Cyprus] "Cyprus":ti,ab,kw or "Cypriot*":ti,ab,kw	39
4.	MeSH descriptor: [Djibouti] "Djibouti*":ti,ab,kw or "Somaliland*":ti,ab,k	1
5.	MeSH descriptor: [Egypt] "Egypt*":ti,ab,kw or "United Arab Republic*":ti,ab,kw	813
6.	MeSH descriptor: [Iran] "iran*":ti,ab,kw	2,207
7.	MeSH descriptor: [Iraq] "iraq*":ti,ab,kw	191
8.	MeSH descriptor: [Israel] "israel*":ti,ab,kw	1,121
9.	MeSH descriptor: [Jordan] "jordan*":ti,ab,kw	215
10.	MeSH descriptor: [Kuwait] "kuwait*":ti,ab,kw	77
11.	MeSH descriptor: [Lebanon] "lebanon":ti,ab,kw OR "lebanese":ti,ab,k	94
12.	MeSH descriptor: [Libya] "libya*":ti,ab,kw	18
13.	MeSH descriptor: [Mauritania] "mauritan*":ti,ab,kw	6
14.	MeSH descriptor: [Morocco] "morocco*":ti,ab,kw OR "moroccan*":ti,ab,kw OR "ifni*":ti,ab,kw	66
15.	MeSH descriptor: [Oman] "oman*":ti,ab,kw OR "muscat*":ti,ab,kw	38
16.	"palestin*":ti,ab,kw OR "gaza*":ti,ab,kw OR "West* Bank":ti,ab,kw	42
17.	MeSH descriptor: [Qatar] "qatar*":ti,ab,kw OR "katar":ti,ab,kw OR "quatar*":ti,ab,kw	12
18.	MeSH descriptor: [Saudi Arabia] "saud*":ti,ab,kw OR "ksa":ti,ab,kw	577
19.	MeSH descriptor: [Somalia] "somal*":ti,ab,kw	19
20.	MeSH descriptor: [Sudan] "sudan*":ti,ab,kw	159
21.	MeSH descriptor: [Syria] "syria*":ti,ab,kw	40

22. MeSH descriptor: [Tunisia] “tunis*”:ti,ab,kw	102
23. MeSH descriptor: [Turkey] “turkey”:ti,ab,kw OR “turkish”:ti,ab,kw	2,142
24. MeSH descriptor: [UAE] “emirat*”:ti,ab,kw OR “uae”:ti,ab,kwOR “abu dahbi”:ti,ab,kw OR “trucial state*”:ti,ab,kw	335
25. MeSH descriptor: [Yemen] “yemen*”:ti,ab,kw OR “aden”:ti,ab,kw OR “sanaa”:ti,ab,kw	37
26. MeSH descriptor: [North Africa] "north* africa*":ti,ab,kw	352
27. MeSH descriptor: [Middle East] "middle east*":ti,ab,kw	2,236
28. MeSH descriptor: [Mediterranean Region] “mediterranean*”:ti,ab,kw	759
29. "arab*":ti,ab,kw OR "mena":ti,ab,kw OR "emro":ti,ab,kw OR "near east*":ti,ab,kw	1,432
30. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	10,018
31. MeSH descriptor: [Norovirus] “norovirus*”:ti,ab,kw OR “noroviral”:ti,ab,kw OR “noro NEAR/1 virus”:ti,ab,kw	43
32. MeSH descriptor: [Norwalk virus] “norwalk*”:ti,ab,kw	35
“small round structured virus*”:ti,ab,kw	0
33. #31 OR #32 OR #33	67
34. MeSH descriptor: [Rotavirus] “rotavirus*”:ti,ab,kw OR “rotaviral”:ti,ab,kw OR “rota NEAR/1 virus”:ti,ab,kw	658
35. MeSH descriptor: [Rotavirus Infections]	
36. “Rotavirus Infection*”:ti,ab,kw	423

37. "neonatal calf diarrhea":ti,ab,kw	0
38. #35 OR #36 OR #37	685
39. #30 AND #34	0
40. #30 AND #38	11
41. #30 AND #34 Publication Year from 2000 to 2016	0
42. #30 AND #38 Publication Year from 2000 to 2016	11

Database: Scopus

1. INDEXTERMS (algeria) OR TITLE-ABS-KEY (algeria*)	16,164
2. INDEXTERMS (bahrain) OR TITLE-ABS-KEY (bahrain*)	3,301
3. INDEXTERMS (cyprus) OR TITLE-ABS-KEY (cyprus) OR TITLE-ABS-KEY (cypriot*)	9,040
4. INDEXTERMS (djibouti) OR TITLE-ABS-KEY (djibouti*) OR TITLE-ABS-KEY (somaliland*)	1,112
5. INDEXTERMS (egypt) OR TITLE-ABS-KEY (egypt*) OR TITLE-ABS-KEY ("united arab republic*")	57,391
6. INDEXTERMS (iran) OR TITLE-ABS-KEY (iran*)	92,719
7. INDEXTERMS (iraq) OR TITLE-ABS-KEY (iraq*)	25,972
8. INDEXTERMS (israel) OR TITLE-ABS-KEY (israel*)	80,325
9. INDEXTERMS (jordan) OR TITLE-ABS-KEY (jordan*)	26,895
10. INDEXTERMS (kuwait) OR TITLE-ABS-KEY (kuwait*)	11,293
11. INDEXTERMS (lebanon) OR TITLE-ABS-KEY (lebanon) OR TITLE-ABS-KEY (lebanese)	10,800
12. INDEXTERMS (libya) OR TITLE-ABS-KEY (libya*)	7,021
13. INDEXTERMS (mauritania) OR TITLE-ABS-KEY (mauritan*)	2,647
14. INDEXTERMS (morocco) OR TITLE-ABS-KEY (morocco*) OR TITLE-ABS-KEY (moroccan*) OR TITLE-ABS-KEY (ifni*)	22,565
15. INDEXTERMS (oman) OR TITLE-ABS-KEY (oman*) OR TITLE-ABS-KEY (muscat*)	10,761
16. TITLE-ABS-KEY (palestin*) OR TITLE-ABS-KEY (gaza*) OR TITLE-ABS-KEY (“west* w/2 bank”)	14,415
17. INDEXTERMS (qatar) OR TITLE-ABS-KEY (qatar*) OR TITLE-ABS-KEY (katar) OR TITLE-ABS-KEY (quatar*)	6,076
18. INDEXTERMS (saudi arabia) OR TITLE-ABS-KEY (saud*)	

OR TITLE-ABS-KEY (ksa)	50,821
19. INDEXTERMS (somalia) OR TITLE-ABS-KEY (somal*)	7,445
20. INDEXTERMS (sudan) OR TITLE-ABS-KEY (sudan*)	20,152
21. INDEXTERMS (syria) OR TITLE-ABS-KEY (syria*)	23,212
22. INDEXTERMS (tunisia) OR TITLE-ABS-KEY (tunis*)	21,863
23. INDEXTERMS (turkey) OR TITLE-ABS-KEY (turkey) OR TITLE-ABS-KEY (turkish)	136,043
24. INDEXTERMS (united arab emirates) OR TITLE-ABS-KEY (emirat*) OR TITLE-ABS-KEY (uae) OR TITLE-ABS-KEY ("abu dahbi") OR TITLE-ABS-KEY ("trucial state*")	11,865
25. INDEXTERMS (yemen) OR TITLE-ABS-KEY (yemen*) OR TITLE-ABS-KEY (aden) OR TITLE-ABS-KEY (sanaa)	6,334
26. INDEXTERMS (north africa) OR TITLE-ABS-KEY (“north* w/2 africa*”)	10,757
27. INDEXTERMS (middle east) OR TITLE-ABS-KEY (“middle w/2 east*”)	24,654
28. INDEXTERMS (mediterranean region) OR TITLE-ABS-KEY (mediterranean*)	116,712
29. TITLE-ABS-KEY (“Arab*”) OR TITLE-ABS-KEY (“MENA”) OR TITLE-ABS-KEY (“EMRO”) OR TITLE-ABS-KEY (“Near w/2 East*”)	221,998
30. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	87,655
31. INDEXTERMS (norovirus) OR TITLE-ABS-KEY (norovirus*)	

OR TITLE-ABS-KEY (noroviral)	
OR TITLE-ABS-KEY ("noro w/1 virus")	5,065
32. INDEXTERMS (norwalk virus)	
OR TITLE-ABS-KEY (norwalk*)	1,922
33. TITLE-ABS-KEY (“small round structured virus*”)	241
34. #31 OR #32 OR #33	6,503
35. INDEXTERMS (rotavirus) OR TITLE-ABS-KEY (rotavirus*)	
OR TITLE-ABS-KEY (rotoviral)	
OR TITLE-ABS-KEY (“rota w/1 virus”)	17,071
36. INDEXTERMS (rotavirus infections)	
OR TITLE-ABS-KEY ("rotavirus infection*")	10,831
37. TITLE-ABS-KEY ("neonatal calf diarrhea")	142
38. #35 OR #36 OR #37	17,149
39. #30 AND #34	19
40. #30 AND #38	82
41. #39 AND (LIMIT-TO (PUBYEAR ,	14
42. #40 AND (LIMIT-TO (PUBYEAR ,	49

Database: Web of Science

1. TOPIC: (Algeria*)	21,395
2. TOPIC: (Bahrain*)	2,224
3. TOPIC: (Cyprus OR Cypriot*)	12,496
4. TOPIC: (Djibouti* OR Somaliland*)	1,126
5. TOPIC: (Egypt* OR ”United Arab Republic*”)	77,542
6. TOPIC: (Iran*)	120,425
7. TOPIC: (Iraq*)	30,532
8. TOPIC: (Israel*)	115,702
9. TOPIC: (Jordan*)	36,708
10. TOPIC: (Kuwait*)	12,640
11. TOPIC: (Lebanon OR Lebanese)	15,164
12. TOPIC: (Libya*)	7,710
13. TOPIC: (Mauritan*)	2,791
14. TOPIC: (Morocco* OR Moroccan* OR ifni*)	31,492
15. TOPIC: (Oman* OR Muscat*)	14,302
16. TOPIC: (Palestin* OR Gaza OR “West* NEAR/2 Bank")	19,334
17. TOPIC: (Qatar* OR Katar OR Quatar*)	3,134
18. TOPIC: ("Saudi Arabia" OR Saud* OR KSA)	85,987
19. TOPIC: (Somal*)	10,252
20. TOPIC: (Sudan*)	28,940
21. TOPIC: (Syria*)	36,480
22. TOPIC: (Tunis*)	32,762
23. TOPIC: (Turkey OR Turkish)	194,479
24. TOPIC: ("United Arab Emirates” OR Emirat* OR UAE OR ”Abu Dahbi” OR ”Trucial state*”)	13,091
25. TOPIC: (Yemen* OR Aden OR Sanaa)	8,615

26. TOPIC: ("North Africa*")	18,464
27. TOPIC: ("Middle East" OR "Middle Near/2 East")	40,626
28. TOPIC: (mediterranean*)	177,694
29. TOPIC: (Arab* OR MENA OR EMRO OR “Near NEAR/2 East*")	406,595
30. #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR#12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1	1,374,085
31. TOPIC: (Norovirus* OR Noroviral OR “Noro NEAR/1 virus”)	10,384
32. TOPIC: (Norwalk*)	3,223
33. TOPIC: ("Small Round Structured Virus*")	225
34. #33 OR #32 OR #31	12,804
35. TOPIC: (Rotavirus* OR Rotaviral OR “Rota NEAR/1 virus”)	29,920
36. TOPIC: ("rotavirus infection*")	10,777
37. TOPIC: ("neonatal calf diarrhea")	257
38. #37 OR #36 OR #35	30,133
39. #34 AND #30	167
40. #38 AND #30	673
41. #34 AND #30 Refined by: PUBLICATION YEARS	151
42. #38 AND #30 Refined by: PUBLICATION YEARS	484

Database: Global Health Library

1. (TW:(Algeria*))	3,019
2. (TW:(Bahrain*))	1,252
3. (tw:(Cyprus)) OR (tw:(Cypriot*))	1,489
4. (tw:(Djibouti*)) OR (tw:(Somaliland*))	393
5. (tw:(Egypt*)) OR (tw:(”United Arab Republic*”))	29,894
6. (TW:(Iran*))	34,393
7. (TW:(Iraq*))	8,940
8. (TW:(Israel*))	33,639
9. (TW:(Jordan*))	6,095
10. (TW:(Kuwait*))	4,485
11. (tw:(Lebanon)) OR (tw:(Lebanese))	4,290
12. (TW:(Libya*))	1,832
13. (TW:(Mauritan*))	652
14. (tw:(Morocco*)) OR (tw:(Moroccan*)) OR (tw:(ifni*))	8,791
15. (tw:(Oman*)) OR (tw:(Muscat*))	2,997
16. (tw:(Palestin*)) OR (tw:(Gaza)) OR (tw:("West Bank"))	11,181
17. (tw:(Qatar*)) OR (tw:(Katar)) OR (tw:(Quatar*))	1,304
18. (tw:("Saudi Arabia")) OR (tw:(Saud*)) OR (tw:(KSA))	2,013,624
19. (TW:(Somal*))	3,042
20. (TW:(Sudan*))	10,210
21. (TW:(Syria*))	24,052
22. (TW:(Tunis*))	9,149
23. (tw:(Turkey)) OR (tw:(Turkish))	40,934
24. (tw:("United Arab Emirates")) OR (tw:(Emirat*)) OR (tw:(UAE)) OR (tw:("Abu Dahbi")) OR (tw:("Trucial state*"))	3,978
25. (tw:(Yemen*)) OR (tw:(Aden)) OR (tw:(Sanaa))	2,310

26. (TW:(North Africa*))	12,076
27. (TW:(Middle East*))	19,762
28. (TW:(mediterranean*))	32,590
29. (tw:(Arab*)) OR (tw:(MENA)) OR (tw:(EMRO)) OR (tw:("Near East*"))	136,000
30. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	2,348,725
31. (tw:(Norovirus*)) OR (tw:(Noroviral))	3,941
32. (tw:(Norwalk*))	3,829
33. (tw:("Small Round Structured Virus*"))	47
34. #31 OR #32 OR #33	5,004
35. (tw:(Rotavirus*)) OR (tw:(Rotaviral))	14,145
36. (tw:("Rotavirus Infection"))	1,802
37. (tw:("neonatal calf diarrhea"))	8,071
38. #37 OR #36 OR #35	14,193
39. #34 AND #30	469
40. #38 AND #30	1,366
41. #39 AND (year_cluster:	332
42. #40 AND (year_cluster:	1,062

Database: Index Medicus for the Eastern Mediterranean Region (IMEMR) and African Index Medicus (AIM)

((TW:(Algeria*)) OR (TW:(Bahrain*)) OR (tw:(Cyprus)) OR (tw:(Cypriot*)) OR (tw:(Djibouti*)) OR (tw:(Somaliland*)) OR (tw:(Egypt*)) OR (tw:(”United Arab Republic*”)) OR (TW:(Iran*)) OR (TW:(Iraq*)) OR (TW:(Israel*)) OR (TW:(Jordan*)) OR (TW:(Kuwait*)) OR (tw:(Lebanon)) OR (tw:(Lebanese)) OR (TW:(Libya*)) OR (TW:(Mauritan*)) OR (tw:(Morocco*)) OR (tw:(Moroccan*)) OR (tw:(ifni*)) OR (tw:(Oman*)) OR (tw:(Muscat*)) OR (tw:(Palestin*)) OR (tw:(Gaza)) OR (tw:("West Bank")) OR (tw:(Qatar*)) OR (tw:(Katar)) OR (tw:(Quatar*)) OR (tw:("Saudi Arabia")) OR (tw:(Saud*)) OR (tw:(KSA)) OR (TW:(Somal*)) OR (TW:(Sudan*)) OR (TW:(Syria*)) OR (TW:(Tunis*)) OR (tw:(Turkey)) OR (tw:(Turkish)) OR (tw:("United Arab Emirates")) OR (tw:(Emirat*)) OR (tw:(UAE)) OR (tw:("Abu Dahbi")) OR (tw:("Trucial state*")) OR (tw:(Yemen*)) OR (tw:(Aden)) OR (tw:(Sanaa)) OR (TW:(North Africa*)) OR (TW:(Middle East*)) OR (TW:(mediterranean*)) OR (tw:(Arab*)) OR (tw:(MENA)) OR (tw:(EMRO)) OR (tw:("Near East*"))) AND ((tw:(Norovirus*)) OR (tw:(Noroviral)) OR (tw:(Norwalk*)))

((TW:(Algeria*)) OR (TW:(Bahrain*)) OR (tw:(Cyprus)) OR (tw:(Cypriot*)) OR (tw:(Djibouti*)) OR (tw:(Somaliland*)) OR (tw:(Egypt*)) OR (tw:(”United Arab Republic*”)) OR (TW:(Iran*)) OR (TW:(Iraq*)) OR (TW:(Israel*)) OR (TW:(Jordan*)) OR (TW:(Kuwait*)) OR (tw:(Lebanon)) OR (tw:(Lebanese)) OR (TW:(Libya*)) OR (TW:(Mauritan*)) OR (tw:(Morocco*)) OR (tw:(Moroccan*)) OR (tw:(ifni*)) OR (tw:(Oman*)) OR (tw:(Muscat*)) OR (tw:(Palestin*)) OR (tw:(Gaza)) OR (tw:("West Bank")) OR (tw:(Qatar*)) OR (tw:(Katar)) OR (tw:(Quatar*)) OR (tw:("Saudi Arabia")) OR (tw:(Saud*)) OR (tw:(KSA)) OR (TW:(Somal*)) OR (TW:(Sudan*)) OR (TW:(Syria*)) OR (TW:(Tunis*)) OR (tw:(Turkey)) OR

(tw:(Turkish)) OR (tw:("United Arab Emirates")) OR (tw:(Emirat*)) OR (tw:(UAE)) OR (tw:("Abu Dahbi")) OR (tw:("Trucial state*")) OR (tw:(Yemen*)) OR (tw:(Aden)) OR (tw:(Sanaa)) OR (TW:(North Africa*)) OR (TW:(Middle East*)) OR (TW:(mediterranean*)) OR (tw:(Arab*)) OR (tw:(MENA)) OR (tw:(EMRO)) OR (tw:("Near East*"))) AND ((tw:(Rotavirus*)) OR (tw:(Rotaviral)) OR (tw:("Rotavirus Infection")) OR (tw:("neonatal calf diarrhea")))

Database: ProQuest

1. Algeria*	420
2. Bahrain*	223
3. Cyprus OR Cypriot*	493
4. Djibouti* OR Somaliland*	127
5. Egypt* OR "United Arab Republic*"	2,527
6. Iran*	1,915
7. Iraq*	1,751
8. Israel*	3,798
9. Jordan*	4,003
10. Kuwait*	510
11. Lebanon OR Lebanese	906
12. Libya*	423
13. Mauritan*	156
14. Morocco* OR Moroccan* OR ifni*	748
15. Oman* OR Muscat*	547
16. Palestin* OR Gaza OR "West Bank"	1,059
17. Qatar* OR Katar OR Quatar*	270
18. "Saudi Arabia" OR Saud* OR KSA	1,155
19. Somal*	503
20. Sudan*	715
21. Syria*	864
22. Tunis*	522
23. Turkey OR Turkish	2,926
24. "United Arab Emirates" OR Emirat* OR UAE OR "Abu Dahbi" OR "Trucial state*"	436
25. Yemen* OR Aden OR Sanaa	470

26. "North Africa*"	707
27. "Middle East*"	2,504
28. mediterranean*	1,527
29. Arab* OR MENA OR EMRO OR "Near East*"	4,435
30. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	14,308
31. Norovirus* OR Noroviral	35
32. Norwalk*	312
33. "Small Round Structured Virus*"	3
34. #31 OR #32 OR #33	335
35. Rotavirus* OR Rotaviral	60
36. "Rotavirus Infection*"	8
37. "neonatal calf diarrhea"	0
38. #37 OR #36 OR #35	60
39. #34 AND #30	0
40. #38 AND #30	0
41. PDN(>=2000) and PDN(<=2016)	0
42. PDN(>=2000) and PDN(<=2016)	0

Database: Open Grey

1. Algeria*	589
2. Bahrain*	166
3. Cyprus OR Cypriot*	426
4. Djibouti* OR Somaliland*	72
5. Egypt* OR "United Arab Republic*"	1,359
6. Iran*	920
7. Iraq*	473
8. Israel*	1,380
9. Jordan*	1,250
10. Kuwait*	421
11. Lebanon OR Lebanese	411
12. Libya*	403
13. Mauritan*	125
14. Morocco* OR Moroccan* OR ifni*	651
15. Oman* OR Muscat*	406
16. Palestin* OR Gaza OR "West Bank"	486
17. Qatar* OR Katar OR Quatar*	133
18. "Saudi Arabia" OR Saud* OR KSA	1,074
19. Somal*	152
20. Sudan*	521
21. Syria*	392
22. Tunis*	968
23. Turkey OR Turkish	1,342
24. "United Arab Emirates" OR Emirat* OR UAE OR "Abu Dahbi" OR "Trucial state*"	326
25. Yemen* OR Aden OR Sanaa	257

26. "North Africa*"	169
27. "Middle East*"	576
28. mediterranean*	1,421
29. Arab* OR MENA OR EMRO OR "Near East*"	5,124
30. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	17,947
31. Norovirus* OR Noroviral	35
32. Norwalk*	10
33. "Small Round Structured Virus*"	0
34. #31 OR #32 OR #33	41
35. Rotavirus* OR Rotaviral	131
36. "Rotavirus Infection*"	13
37. "neonatal calf diarrhea"	0
38. #37 OR #36 OR #35	131
39. #34 AND #30	2
40. #38 AND #30	2
41. Limit to 2000-2016	2
42. Limit to 2000-2016	2

APPENDIX IV

RISK OF BIAS ASSESSMENT TOOL

Yes (LOW RISK) No (HIGH RISK)	**Djibouti 299**	**Egypt 137**	**Egypt 144**	**Egypt 305**	**Egypt 306**
External validity					
1. Was the study's target population a close representation of the national population in relation to relevant variables?	no	no	no	no	no
2. Was the sampling frame a true or close representation of the target population?	yes	yes	yes	yes	yes
3. Was some form of random selection used to select the sample, OR was a census undertaken?	yes	yes	yes	yes	yes
4. Was the likelihood of nonresponse bias minimal?	yes	yes	yes	yes	yes
Internal validity					
5. Were data collected directly from the subjects (as opposed to a proxy)?	yes	yes	yes	yes	yes
6. Was an acceptable case definition used in the study?	yes	yes	yes	yes	yes
7. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	yes	yes	yes	yes	no
8. Was the same mode of data collection used for all subjects?	no	yes	yes	yes	yes
9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	yes	yes	yes	yes	yes
10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	yes	yes	no	yes	no
Summary item on the overall risk of study bias (Yes)	8	9	8	9	7

Yes (LOW RISK) No (HIGH RISK)	Iran 148	Iran 307	Iran 308	Iran 309	Iran 310	Iran 311
External validity						
1. Was the study's target population a close representation of the national population in relation to relevant variables?	yes	yes	yes	no	no	no
2. Was the sampling frame a true or close representation of the target population?	yes	yes	yes	yes	yes	yes
3. Was some form of random selection used to select the sample, OR was a census undertaken?	yes	yes	yes	yes	yes	yes
4. Was the likelihood of nonresponse bias minimal?	yes	yes	yes	yes	yes	yes
Internal validity						
5. Were data collected directly from the subjects (as opposed to a proxy)?	yes	yes	yes	yes	yes	yes
6. Was an acceptable case definition used in the study?	yes	yes	yes	yes	yes	yes
7. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	no	yes	no	yes	yes	yes
8. Was the same mode of data collection used for all subjects?	yes	yes	yes	yes	yes	yes
9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	no	no	yes	yes	yes	yes
10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	yes	yes	yes	no	yes	no
Summary item on the overall risk of study bias (Yes)	8	9	9	8	9	8

Yes (LOW RISK) No (HIGH RISK)	**Iraq 300**	**Israel 301**	**Israel 302**	**Jordan 196**	**Kuwait 303**	**Lebanon 276**
External validity						
1. Was the study's target population a close representation of the national population in relation to relevant variables?	no	yes	yes	no	no	yes
2. Was the sampling frame a true or close representation of the target population?	yes	yes	yes	yes	yes	yes
3. Was some form of random selection used to select the sample, OR was a census undertaken?	yes	yes	yes	yes	yes	yes
4. Was the likelihood of nonresponse bias minimal?	yes	yes	yes	yes	yes	yes
Internal validity						
5. Were data collected directly from the subjects (as opposed to a proxy)?	yes	yes	yes	yes	yes	yes
6. Was an acceptable case definition used in the study?	yes	yes	yes	yes	yes	yes
7. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	yes	yes	yes	yes	yes	yes
8. Was the same mode of data collection used for all subjects?	yes	yes	yes	yes	yes	yes
9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	no	yes	yes	yes	yes	no
10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	yes	yes	yes	yes	yes	yes
Summary item on the overall risk of study bias (Yes)	8	10	10	9	9	9

Yes (LOW RISK) No (HIGH RISK)	Libya 203	Libya 205	Morocco 277	Morocco 304	Qatar 286
External validity					
1. Was the study's target population a close representation of the national population in relation to relevant variables?	no	no	no	yes	no
2. Was the sampling frame a true or close representation of the target population?	yes	yes	yes	yes	yes
3. Was some form of random selection used to select the sample, OR was a census undertaken?	yes	yes	yes	yes	yes
4. Was the likelihood of nonresponse bias minimal?	yes	yes	yes	yes	yes
Internal validity					
5. Were data collected directly from the subjects (as opposed to a proxy)?	yes	yes	yes	yes	yes
6. Was an acceptable case definition used in the study?	yes	yes	yes	yes	yes
7. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	no	yes	yes	yes	yes
8. Was the same mode of data collection used for all subjects?	yes	yes	yes	yes	yes
9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	no	yes	yes	yes	no
10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	yes	yes	yes	yes	yes
Summary item on the overall risk of study bias (Yes)	7	9	9	10	8

Yes (LOW RISK) No (HIGH RISK)	Saudi 213	Saudi 221	Saudi 224	Tunisia 230	Tunisia 237	Tunisia 298
External validity						
1. Was the study's target population a close representation of the national population in relation to relevant variables?	no	yes	no	no	no	no
2. Was the sampling frame a true or close representation of the target population?	no	yes	yes	yes	yes	yes
3. Was some form of random selection used to select the sample, OR was a census undertaken?	yes	yes	yes	yes	yes	yes
4. Was the likelihood of nonresponse bias minimal?	yes	yes	yes	yes	yes	yes
Internal validity						
5. Were data collected directly from the subjects (as opposed to a proxy)?	yes	yes	yes	yes	yes	yes
6. Was an acceptable case definition used in the study?	yes	yes	yes	yes	yes	yes
7. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	no	no	no	yes	yes	yes
8. Was the same mode of data collection used for all subjects?	yes	yes	yes	yes	yes	yes
9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	yes	yes	no	yes	yes	yes
10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	no	yes	yes	yes	no	no
Summary item on the overall risk of study bias (Yes)	6	9	7	9	8	8

Yes (LOW RISK) No (HIGH RISK)	Tunisia 312	Tunisia 313	Turkey 244	Turkey 251	Turkey 257	Turkey 314
External validity						
1. Was the study's target population a close representation of the national population in relation to relevant variables?	no	no	no	no	no	yes
2. Was the sampling frame a true or close representation of the target population?	yes	yes	yes	yes	yes	yes
3. Was some form of random selection used to select the sample, OR was a census undertaken?	yes	yes	yes	yes	yes	yes
4. Was the likelihood of nonresponse bias minimal?	yes	yes	yes	yes	yes	yes
Internal validity						
5. Were data collected directly from the subjects (as opposed to a proxy)?	yes	yes	yes	yes	yes	yes
6. Was an acceptable case definition used in the study?	yes	yes	yes	yes	yes	yes
7. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	yes	yes	yes	yes	yes	yes
8. Was the same mode of data collection used for all subjects?	yes	yes	yes	yes	yes	yes
9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	yes	yes	yes	no	no	no
10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	yes	yes	no	yes	yes	yes
Summary item on the overall risk of study bias (Yes)	9	9	8	8	8	9

Yes (LOW RISK) No (HIGH RISK)	**Turkey 315**	**Turkey 316**	**Turkey 317**	**Turkey 318**	**Yemen 296**
External validity					
1. Was the study's target population a close representation of the national population in relation to relevant variables?	no	no	no	no	no
2. Was the sampling frame a true or close representation of the target population?	yes	yes	yes	yes	yes
3. Was some form of random selection used to select the sample, OR was a census undertaken?	yes	yes	yes	yes	yes
4. Was the likelihood of nonresponse bias minimal?	yes	yes	yes	yes	yes
Internal validity					
5. Were data collected directly from the subjects (as opposed to a proxy)?	yes	yes	yes	yes	yes
6. Was an acceptable case definition used in the study?	yes	yes	yes	yes	yes
7. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	yes	no	no	yes	yes
8. Was the same mode of data collection used for all subjects?	yes	yes	yes	yes	yes
9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	yes	yes	yes	yes	yes
10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	yes	yes	yes	yes	no
Summary item on the overall risk of study bias (Yes)	9	8	8	9	8

APPENDIX V

ABBREVIATIONS

AGE	Acute Gastroenteritis
AIM	African Index Medicus
CDC	Centers for Disease Control and Prevention
DALYs	Disability-Adjusted Life Years
dsRNA	Double-Stranded RNA
EIA	Enzyme Immunoassay
ELISA	Enzyme Linked Immunosorbent Assays
EM	Electronic Microscopy
EU	European Union
FBVE	Food-Borne Viruses in Europe Network
FDA	Food and Drug Administration
FERG	Foodborne Disease Burden Epidemiology Reference Group
GA	Gold Immuno-assay
GBD	Global Burden of Disease
GHL	Global Health Library
GSK	GlaxoSmithKline
HBGA	Human Histo-Blood Group Antigen

HNORS	Hospital Norovirus Outbreak Reporting System
IC	Immunochromatography
IF	Immunofluorescence
IMEMR	Index Medicus for the Eastern Mediterranean Region
LA	Latex Agglutination
MENA	Middle East and North Africa
MeSH	Medical Subject Heading
NCIP	National Childhood Immunizations Program
NORS	National Outbreak Reporting System
NoV	Norovirus
NREVSS	National Respiratory and Enteric Virus Surveillance System
NVSN	New Vaccine Surveillance Network
PAGE	Polyacrylamide Gel Electrophoresis
PRISMA-P	Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PROSPERO	Prospective Register of Systematic Reviews
RCT	Randomized Clinical Trial
RNA	Ribonucleic Acid
RT-PCR	Reverse Transcription Polymerase Chain Reaction
rRT-PCR	Real Time Reverse Transcription Polymerase Chain Reaction
RV	Rotavirus

RVP	Rotavirus Vaccine Program
SPSS	Statistical Package for the Social Sciences
ssRNA	Single-Stranded RNA
UAE	United Arab Emirates
UK	United Kingdom
US	United States
USA	United State of America
USD	United States Dollar
VP	Viral Protein
WHO	World Health Organization

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