Abstract: Human mastadenovirus (HAdV) is a non-enveloped icosahedral virus with double-stranded DNA genomes [1]. Since Wallace P. Rowe isolated and named the adenoviral serotype HAdV from human tonsils and adenoids in 1953, more than 120 distinct adenoviral serotypes have been discovered in humans, animals, birds, fish, and reptiles. Seven subgroups (A through G) have been assigned to them [2]. Adenoviral virions often show a crystalline arrangement in infected nuclei [4]. HAdV also contains 26 to 48 kb of linear double-stranded DNA genomes [5]. It creates transcripts of early-stage (E), interim-stage (I), and late-stage (L) regions based on the amount of time that has passed since infection [6]. HAdV is a seasonally transmitted virus that prevails from February to April [7–9]. It is a widespread virus that affects humans and is primarily spread by respiratory droplets and feces [10–12]. HAdV infections are often seen in military recruits, students, and nursery and kindergarten children, especially children under the age of four, elderly people, and people with compromised immunity [13–15].

The clinical manifestations of HAdV infections are very extensive, ranging from a symptom to life-threatening severe respiratory infections and tissue-invasive infections [16,17]. HAdV can cause many symptoms similar to the common cold, including
rhinorrhea, fever, cough, and sore throat [18,19]. Bronchitis, bronchiolitis, and pneumonia are examples of lower respiratory diseases that can be serious or even fatal [20]. HAdV infections can also be linked to other conditions such as conjunctivitis, gastroenteritis, cystitis, myocarditis, cardiomyopathy, and meningoencephalitis [21]. A variety of clinical illnesses, including respiratory tract infections, disorders of the respiratory system, keratocconjunctivitis, gastroenteritis, and urinary infections, may be caused by various adenoviral serotypes [22]. Immunocompromised patients are susceptible to invasive adenoviral infection [23]. In immunocompromised patients, HAdV may reactivate or cause new infections, resulting in multi-organ infections like enteritis, hemorrhagic cystitis, hepatitis, and pneumonia [24].

The systematic review and meta-analysis conducted by GU, Jie et al. showed that the mortality rate of AdV infection is 35.5%, while gastroenteritis HAdV infections, HAdV pneumonia, and disseminated disease tend to show a worse outcome, with rates ranging from 44.2% to 50%. However, in the context of immunocompetent patients is associated with a mortality of up to 32.9% [25]. Furthermore, the fatality rates for severe HAdV pneumonia or disseminated disease may exceed 50% in previous reports [25]. In addition, HAdV can cause infections at any age but most commonly in the pediatric population, especially in young children and infants [19]. Invasive HAdV infections do more harm to children [26]. Moreover, by the age of 10 years old, most children have had at least one episode of HAdV infections [19]. Additionally, HAdV testing has produced positive results in 77% of cases of severe acute hepatitis of unknown causes that have been detected in children in many countries [27].

Early diagnosis and supportive therapy are crucial for immunocompromised patients, especially for children [28]. Some large children’s hospitals even recommend HAdV testing as a screening item for children with respiratory tract infections [29,30]. HAdV testing can be performed by isolated cell culture, serological identification, and PCR [31]. However, due to a long time of HAdV cell culture, the limited value of antibody tests in immunosuppressed people, and the lack of quantifying and genotyping functions, the actual clinical application effects are undesirable [32]. By contrast, RT–PCR can be directly used to test nucleotide sequences specific to HAdV pathogens, with high specificity, sensitivity, and desirable genotyping advantages [33]. This also explains why RT–PCR is highly favored. The European Society for Blood and Marrow Transplantation (EBMT) recommends that quantitative PCR (qPCR) be adopted to diagnose and monitor the HAdV in the blood and feces samples of children and adults receiving transplantation so that interventions can be provided as early as possible [34].

Most countries in the Arab World have not yet introduced national HAdV vaccination programs. Although regional and local information on the prevalence and burden of HAdV and strain distribution is important for healthcare practitioners and officials to make appropriate policies and recommendations about HAdV vaccination, there is a remarked lack of comprehensive literature reviews on the prevalence of HAdV infections among children that have been published for the Arab World, particularly in the Middle East and North Africa. Therefore, the purpose of this review is to assess the current status of HAdV infections among children in the Arab World in the Middle East and North Africa. Understanding the current status of HAdV infection prevalence and its associated gastroenteritis, respiratory tract infections, and acute hemorrhagic conjunctivitis is critical to evaluating the performance of surveillance systems where available and to expanding the implementation of these systems.

2. Materials and Methods

Electronic literature searches of Web of Science, Scopus, PubMed, EMBASE, and Google Scholar databases for publications in English were systematically conducted without time limit up to July 2022 for studies on HAdV in children in the Arab World in the Middle East and North Africa. A combination of search methods was employed to increase
the search scale, namely: (1) search MESH (Human mastadenovirus) using the following terms: “Adenovirus”, “Children”, and “Infection”, and (2) free-text search.

The following were the inclusion requirements: Studies have described the prevalence of HAdV infections in children in the Arab World in the Middle East and North Africa. On the other hand, the following exclusion criteria were considered: (1) reviews; (2) non-English language; (2) case reports; (3) studies not focused on HAdV infections in children; (4) studies that were not performed in the Middle East and North Africa; (4) studies lacking pertinent data; and (4) studies without full text.

The screening procedures were managed, and duplicates were eliminated using EndNote V.X8 software. After removing duplicates, the authors individually the titles, abstracts, and full texts to determine whether the studies were eligible.

The study region, study country, study design, targeted children, sample size, sample location, disease, and HAdV prevalence rate were extracted and recorded using a standardized data collection form that was developed in accordance with the sequence of variables required from the primary source.

3. Results

Our literature search identified 21 articles on HAdV infections in children in the Arab World in the Middle East and North Africa between 2001 and 2021. In total, 5807 articles were found during the search across five databases: Web of Science (n = 964), Scopus (n = 1126), PubMed (n = 1006), EMBASE (n = 1064), Google Scholar (n = 1647). The duplicates were then removed, leaving 1478 studies. We eliminated 763 studies by title screening and then used abstract screening to eliminate 339 irrelevant studies out of 557. Following this, we read the full texts of the remaining 158 publications and omitted 137 pieces of research since they did not meet our inclusion criteria (Figure 1).

Figure 1. The PRISMA flowchart for the process of selecting and identifying studies.
Studies reporting on HAdV infections in children were conducted in 17 out of the 22 countries of the Arab World in the Middle East and North Africa region. We could not find relevant studies published in the following five countries: the Comoros Islands, Djibouti, Mauritania, Somalia, and Syria. Eleven studies were conducted in Middle East countries, namely: Iraq ($n = 2$) [35, 36], Jordan ($n = 2$) [37, 38], Kuwait ($n = 2$) [39, 40], Yemen ($n = 2$) [41, 42], Bahrain ($n = 1$) [43], Lebanon ($n = 1$) [44], and the United Arab Emirates ($n = 1$) [45]. Whereas 10 studies were from North African countries, namely: Egypt ($n = 3$) [46–48], Morocco ($n = 2$) [49, 50], Sudan ($n = 2$) [51, 52], Algeria ($n = 1$) [53], Libya ($n = 1$) [54], Tunisia ($n = 1$) [55].

A wide range of HAdV infections in children has been reported in the Arab World in the Middle East and North African countries. The average prevalence rate of HAdV infections in children was 12.7%, with average prevalence rates of 12.82% and 12.58% in the Middle East and North African countries, respectively. The highest prevalence rate of HAdV infections in children (28.3%) was reported in the descriptive cross-sectional observational study conducted in Egypt by Elmahdy Elmahdy et al. 2019, which targeted children suffering from gastroenteritis [47]. On the other hand, the lowest prevalence rate of HAdV infections in children (1.5%) was reported in the descriptive cross-sectional observational study conducted in Sudan by Wafa Elhag et al. 2013, which targeted children under 14 years old with acute diarrhea [51].

Most of the included studies reporting on HAdV infections in children were clinical observational studies. Eleven studies were descriptive cross-sectional observational studies in design; four studies were descriptive prospective cross-sectional studies in design; four studies were descriptive retrospective studies in design; one study was a descriptive case-control observational study, and one study was a case study in design [43].

In all the included studies, HAdV infections in children were reported in hospitalized children. These studies presented children with signs and symptoms associated with gastroenteritis ($n = 8$), acute respiratory infection ($n = 8$), acute diarrhea ($n = 4$), and acute hemorrhagic conjunctivitis ($n = 1$).

A total of 14 studies were carried out among children less than five years of age. The prevalence of HAdV infections among children less than 5 years old was reported in the included studies as follows: Iraq, 14/320 (4.5%) [36]; Iraq, 3/100 (3%) [35]; Jordan, 54/350 (15.4%) [37]; Kuwait, 27/743 (3.6%) [40]; Yemen, 36/326 (11%) [51]. The remaining studies reported HAdV infections among older children.

There was a noticeable difference in sample sizes between studies and between studies conducted in the same country.

The highest prevalence of HAdV infections among children was in stool samples associated with gastroenteritis for children under 12 years [44] and below ten years [39], at 25.3% and 23.2%, respectively. Whereas the lowest prevalence of HAdV infections among children, 1.5% and 1.6%, was in stool samples associated with acute diarrhea for children below five years in Sudan [51, 52] (Table 1).
Table 1. Reported HAdV infections among children in the Arab World, particularly in the Middle East and North Africa, up to July 2022.

| Region | Country | Study | Study Design | Targeted Children | Sample Size | Sample Location | Disease | Prevalence Rate |
|--------|---------|-------|--------------|--------------------|-------------|-----------------|---------|-----------------|
| Middle East | Iraq | Ali Harb et al., 2019 | A descriptive cross-sectional observational study | Children below five years with acute diarrhea | 320 children | Stool specimens | Gastroenteritis | 4.5% |
| | Iraq | Dilshad Jaff et al., 2016 | A descriptive cross-sectional observational study | Children below five years of age with gastroenteritis | 100 children | Stool specimens | Gastroenteritis | 3.0% |
| | Jordan | Nasser Kaplan et al., 2008 | A descriptive prospective cross-sectional study | Children below five years with an acute respiratory infection | 326 children | Nasopharyngeal aspirates | Acute respiratory infection | 18.0% |
| | Jordan | Mamdoh Meqdam et al., 2001 | A descriptive cross-sectional observational study | Children below thirteen years old with respiratory tract infections | 350 children | Nasopharyngeal aspirates | Acute respiratory infection | 15.4% |
| | Kuwait | Hawraa Mohammad et al., 2020 | A 4-year descriptive retrospective study | Children below ten years with gastroenteritis | 84 children | Stool samples | Gastroenteritis | 23.2% |
| | Kuwait | Wassim Chehadeh et al., 2018 | A 4-year descriptive retrospective study | Children below four years with severe respiratory disease | 743 children | Nasopharyngeal aspirate and Nasopharyngeal swab | Severe respiratory infections | 3.6% |
| | Yemen | Khaled Al-Moyed et al., 2015 | A descriptive cross-sectional observational study | Children below five years with gastroenteritis | 326 children | Stool samples | Gastroenteritis | 11% |
| | Yemen | Mohammad Al Amad et al., 2019 | A descriptive retrospective study | Children below fifteen years of age with severe acute respiratory infections | 1413 children | Nasopharyngeal and oropharyngeal swabs | Acute respiratory infection | 7.0% |
| | Bahrain | Aysha Agab et al., 2016 | A case study | A seven-year-old male and a five-year-old female | Two Bahraini siblings | Conjunctival swabs | Acute hemorrhagic conjunctivitis | NM |
| | Lebanon | Rasha Zaraket et al., 2020 | A 12-months descriptive retrospective study | Children below twelve years with acute gastroenteritis | 308 children | Stool samples | Gastroenteritis | 25.3% |
| | United Arab Emirates | Ahmed Al-suwaidi et al., 2021 | A descriptive case-control observational study | Children below five years with diarrhea | 203 children as a case | Stool samples | Acute diarrhea | 17.2% |
Table 1. Cont.

| Region     | Country     | Study                                      | Targeted Children                                      | Sample Size | Sample Location       | Disease                  | Prevalence Rate |
|------------|-------------|--------------------------------------------|---------------------------------------------------------|-------------|-----------------------|--------------------------|-----------------|
| North Africa | Egypt       | Abdou Kamal Allayeh et al., 2018           | Children below five years with gastroenteritis          | 119 children | Fecal diarrhea samples | Gastroenteritis          | 6.7%           |
| North Africa | Egypt       | Maysaa El Sayed Zaki et al., 2017          | Children below five years with acute diarrhea           | 100 children | Stool sample          | Acute diarrhea           | 20.0%          |
| North Africa | Egypt       | Elmahdy Elmahdy et al., 2019               | Children below five years with gastroenteritis          | 60 children  | Stool samples         | Gastroenteritis          | 28.3%          |
| North Africa | Morocco     | Imane Jroundi et al., 2014                 | Children below five years with respiratory symptomatology | 700 children | Nasopharyngeal aspirates | Acute respiratory infection | 17.0%          |
| North Africa | Morocco     | Marcil Sarrah et al., 2018                 | Children below fourteen years with severe acute viral respiratory infections | 103 children | Nasopharyngeal aspirates | Acute respiratory infection | 16.5%          |
|             | Sudan       | Wafa Elhag et al., 2013                    | Children below fourteen years old with acute diarrhea   | 511 children | Stool samples         | Acute diarrhea           | 1.5%           |
|             | Sudan       | Mosab Adam et al., 2018                    | Children below five years with acute diarrhea           | 437 children | Stool samples         | Acute diarrhea           | 1.6%           |
|             | Algeria     | Fawzi Derrar et al., 2019                  | Children below two years with respiratory tract infections | 117 children | Nasal or nasopharyngeal aspiration | Acute respiratory infection | 7.5%           |
|             | Libya       | Amal Rahouma et al., 2011                  | Children below five years with acute diarrhea           | 239 children | Stool specimens       | Gastroenteritis          | 7.1%           |
|             | Tunisia     | Ines Brini et al., 2020                    | Children below five years with acute respiratory infections | 583 children | Nasopharyngeal aspirate | Acute respiratory infection | 19.6%          |

NM: denote to not mentioned.
4. Discussion

HAdV infections are one of the most significant etiological agents of serious gastroenteritis, respiratory infections, conjunctivitis, cystitis myocarditis, hemorrhagic cystitis, hepatitis, cardiomyopathy, meningoencephalitis, urinary tract infection, and chronic systemic infections, especially in infants and young children under the age of five [27,39,44,49,53]. This review was conducted to represent the current status of HAdV infections in children in the Arab World in the Middle East and North Africa. Our literature search identified 21 articles on HAdV infections in children in the Arab World in the Middle East and North Africa between 2001 and 2021. Studies reporting on HAdV infections in children were conducted in 17 out of the 22 countries of the Arab World in the Middle East and North Africa region. We could not find relevant studies published in the following five countries: the Comoros Islands, Djibouti, Mauritania, Somalia, and Syria. The main results of this review revealed that the average prevalence rate of HAdV infections in children was 12.7%, with average prevalence rates of 12.82% and 12.58% in the Middle East and North African countries, respectively. The highest prevalence rate of HAdV infections in children (28.3%) was reported in the descriptive cross-sectional observational study conducted in Egypt by Elmahdy Elmahdy et al., 2019, which targeted children suffering from gastroenteritis [47]. On the other hand, the lowest prevalence rate of HAdV infections in children (1.5%) was reported in the descriptive cross-sectional observational study conducted in Sudan by Wafa Elhag et al., 2013, which targeted children under 14 years old with acute diarrhea [51]. In comparison with other countries such as Australia, Brazil, Indonesia, Korea, Iran, the UK, Turkey, Hungary, and Sweden, the prevalence rates of HAdV infections ranged from 1% to 96.3% of patients [53,56–64].

Additionally, in this review, a total of 14 studies were carried out among children less than five years of age. The prevalence of HAdV infections among children less than 5 years old was reported in the included studies as follows: Iraq, 14/320 (4.5%) [36]; Iraq, 3/100 (3%) [35]; Jordan, 54/350 (15.4%) [37]; Kuwait, 27/743 (3.6%) [40]; Yemen, 36/326 (11%) [41], United Arab Emirates, 35/203 (17.2%) [45], Egypt, 8/119 (6.7%) [48], Egypt, 20/100 (20%) [46], Egypt, 17/60 (28.3%) [47], Morocco, 119/700 (17%) [49], Sudan, 7/437 (1.6%) [52], Algeria, 9/117 (7.5%) [53], Libya, 17/239 (7.1%) [54], and Tunisia, 3/583 (19.6%) [55]. The remaining studies reported HAdV infections among older children. Differences in prevalence rates in the current review as compared to other studies may be attributed to several reasons, such as the diagnostic technique used for detection, the difference in age of the studied population, and/or the geographical region of the study area. According to the centers for disease control and prevention (CDC), in the United States, the HAdV vaccine is only available for United States military personnel, and there is currently no HAdV vaccine available to the public [65]. Additionally, most countries in the Arab World have not yet introduced national AdV vaccination programs. Therefore, the regional and local information on the prevalence and burden of HAdV and strain distribution is important for healthcare practitioners and officials to make appropriate policies and recommendations about HAdV vaccination.

Moreover, our results showed that in all the included studies, HAdV infections in children were reported in hospitalized children. These studies presented children with signs and symptoms associated with gastroenteritis \((n = 8)\), acute respiratory infection \((n = 8)\), acute diarrhea \((n = 4)\), and acute hemorrhagic conjunctivitis \((n = 1)\). Several serotypes of HAdV, but mainly enteric types 40 and 41, have been strongly associated with gastroenteritis in childhood [57]. In addition, HAdV is responsible for three to five percent of all respiratory infections and diarrhea in the USA and a higher percentage in underdeveloped nations [65,66]. These viruses are mostly distributed through the fecal-oral route, and antibodies to them have been found in 50% or more of children under the age of five throughout Asia, Africa, Europe, and South America, with comparable seropositive proportions in the different populations [67,68].

Diarrheal illnesses remain a major public health concern and represent the third leading cause of death globally. In recent years, viral diarrhea has gradually increased in
infants and children in both developing and developed countries [69]. Similar to diarrhea brought on by other viruses, HAdV-associated diarrhea may have slightly longer-lasting symptoms. The stools are watery, occasionally red, non-leucocyte-containing, and water-containing [70,71]. Although they are present all year round and everywhere in the world, they are most common in temperate areas in the spring or early summer and once more in the middle of winter [70–72]. Additionally, acute hemorrhagic conjunctivitis is a derivative of the highly contagious conjunctivitis virus, otherwise known as pink eye. There are three main viruses that have been studied and confirmed as the agents responsible for acute hemorrhagic conjunctivitis, including enterovirus 70, coxsackievirus A24 variant (CA24v), and HAdV [73].

Finally, this review demonstrated that the highest prevalence of HAdV infections among children was in stool samples associated with gastroenteritis for children under 12 years [44] and below ten years [39], at 25.3% and 23.2%, respectively. Whereas the lowest prevalence of HAdV infections among children, 1.5% and 1.6%, was in stool samples associated with acute diarrhea for children below five years in Sudan [51,52]. It appears that HAdV infection is a significant hygiene problem in these nations. Finding the precise prevalence rate of this virus is crucial since it will aid in future programming for the right control and selection of specialized treatment approaches for the illness during unique seasons and the HAdV outbreak. Furthermore, to limit the spread of infection, it is important to maintain infectious control practices and educate the infected individual to avoid sharing towels, glasses, or any other item in contact with the eyes. Additionally, these individuals should stay at home and avoid going to work or school when symptomatic in order to prevent spreading the infection.

The main strength of the current review is being the first review that shows the current status of HAdV infections among children in the Arab World in the Middle East and North Africa. However, our study has a number of limitations. The research population, times, locations, data collection techniques, and clinical disease care could all contribute to differences in estimates between and within countries. Because there were few studies conducted in each of these nations, the findings indicating the prevalence of HAdV infections may not be generalizable to several Arab nations. Some studies were carried out at large hospitals in urban areas, so the results might not be applicable to rural or other settings.

Additionally, the surveillance techniques used in the numerous published publications differ from country to country, and variances in the estimations may result from variations in HAdV detection techniques. Nevertheless, the overall results typically support earlier literature; thus, any systematic error is improbable. Finally, our study did not study the seasonality of HAdV prevalence.

5. Conclusions

In conclusion, the average prevalence rate of HAdV infections in children was 12.7%, with average prevalence rates of 12.82% and 12.58% in the Middle East and North African countries, respectively. Finding the precise prevalence rate of this virus is crucial because it will guide future planning for effective disease control and the selection of particular treatment options during epidemics and special seasons.

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