



Published in final edited form as:

J Infect Public Health. 2025 July ; 18(7): 102800. doi:10.1016/j.jiph.2025.102800.

A systematic review and meta-analysis of the global prevalence of human enteric adenovirus infections

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Abstract

Human adenovirus (HAdV), especially HAdV species F (HAdV-F) is recognized as a cause of acute gastroenteritis (AGE) worldwide. To assess the global prevalence of HAdV in case-patients of all ages with AGE, we conducted a systematic literature search for studies published in English during 2015–2022. We generated pooled prevalence estimates using generalized linear mixed models. Using data from 147 included articles, the overall pooled prevalence among AGE case-patients of any species of HAdV (pan-HAdV) was 5.8 % and 6.0 % for HAdV-F. The prevalence of HAdV was significantly higher among case-patients < 5 years of age compared with case-patients ≥ 5 years of age (pan-HAdV: 6.6 % vs. 2.0 %, $p < 0.0001$; HAdV-F: 8.7 % vs. 2.3 %, $p = 0.04$). Prevalence was significantly higher in high mortality developing countries and lowest in developed countries (pan-HAdV: 9.4 % vs. 4.0 %, $p < 0.0001$; HAdV-F: 11.6 % vs. 3.2 %, $p = 0.0003$). Understanding the burden of HAdV-associated AGE may be useful for targeted interventions, including future vaccine development.

Keywords

Adenovirus; Gastroenteritis; Diarrhea; Meta-analysis; Literature review

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Declaration

MEW contributed to study design, performed data extraction, reviewed extracted data, analyzed data, and drafted the manuscript, tables, and figures. AKK produced figures, conducted the meta-analysis, and contributed to the manuscript. CPM and PC performed data extraction, reviewed extracted data, and contributed to the manuscript. OO and TR performed data extraction. JV, CDK, UDP, and SAM contributed to study design and contributed to the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Introduction

Acute gastroenteritis (AGE), characterized by diarrhea and vomiting, remains a significant cause of morbidity and mortality worldwide [1]. In 2016, diarrheal disease was the fifth leading cause of death in children aged < 5 years, with most of the burden seen in low-income countries [2]. Despite the introduction of rotavirus vaccines in many countries in the last two decades, rotavirus remains the primary cause of severe pediatric AGE [3]. However, as rotavirus infection rates have declined, other AGE viruses such as noroviruses, sapoviruses, astroviruses and species F adenoviruses (HAdV-F) have gained more recognition for their contribution to global AGE illnesses and deaths [2,3]. In one recent study, HAdV-F was estimated to be the fourth leading cause of diarrheal mortality among all ages and the third leading cause of diarrheal mortality in children < 5 years of age [2].

First discovered in 1953 [4], human adenoviruses (HAdVs) are currently classified into seven species (A-G) with over 100 different genotypes [5]. HAdV-F includes type 40 (HAdV-F40) and type 41 (HAdV-F41) viruses and is associated with AGE. Other HAdV species have also been detected in stool from patients with AGE, though their causal association with AGE is not yet confirmed [6,7]. Other diseases, including respiratory infections, conjunctivitis, myocarditis, and meningoencephalitis are associated with infection with other HAdV species [8]. HAdV-F is spread easily through the fecal-oral route and is responsible for both endemic transmission and outbreaks, particularly in childcare centers, hospitals, and other semi-closed settings [7,9]. There is currently no vaccine to prevent HAdV-associated AGE, nor is one currently in active development.

Traditionally, viral culture and antigen-based methods like enzyme immunoassay (EIA) were used to detect HAdVs in stool specimens. However, these techniques have since been replaced by more sensitive polymerase chain reaction (PCR) methods [10]. Thus, the method used to detect HAdV may also affect estimated prevalence. Current PCR assays either detect all species of HAdV (pan-HAdV) or specifically detect HAdV-F viruses [6,10]. Recent advances in detection of enteric pathogens using multi-pathogen panels, which include targets for HAdV-F, have allowed more accurate detection of HAdV-F in stool [11,12]. This change has increased the availability of data on burden of AGE attributed to HAdV-F, including data from large, multi-national studies. We conducted a systematic literature review and meta-analysis to estimate the global prevalence of pan-HAdV and HAdV-F in stool specimens of patients of all ages with AGE.

Methods

Systematic literature search

Study methods were based on previously conducted systematic reviews and meta-analyses for norovirus and sapovirus [13,14]. We conducted a systematic literature search, last conducted February 2023, of the Medline, Embase, Cochrane Library, CINAHL (Ebsco-Host), and Scopus databases for relevant studies in humans published in English during 2015–2022 to capture more modern testing methods. Search terms for all databases were

“adenovirus” or “adenoviridae” or “ictadenovirus” plus “enteric”, “entero”, “gastro”, or “diarrhea” in any field (Table S1). Articles were selected using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. 1) [15]. Titles and abstracts were reviewed by one of a group of three independent reviewers. Articles had to contain data from studies conducted continuously for at least one year (12 months) that enrolled participants with AGE from a specified catchment area (geographical area or group of people) and tested stool from all participants for HAdV. Only full articles with primary data on HAdV prevalence were included; review articles and conference abstracts were excluded. Studies that tested for HAdV only among previously tested pathogen-negative specimens were also excluded to avoid artificially inflating prevalence of HAdV. We also excluded outbreak studies and those that only tested for HAdV among immunocompromised patients (e.g., transplant recipients, HIV-positive patients), as prevalence in these studies may be higher than the general population.

Data abstraction

Data were abstracted from each full text article using a standardized REDCap (Research Electronic Data Capture) database developed for the review [16]. Articles were reviewed for relevance and data were abstracted by one reviewer and then were reviewed in full by a second, independent reviewer. The two reviewers also used the Joanna Briggs Institute (JBI) critical appraisal checklist for studies reporting prevalence data to evaluate individual study quality [17]. Any incongruencies were resolved by consensus of both reviewers. For included articles, data elements abstracted were country, study period, diagnostic method used, case definition of AGE, method of testing (PCR, antigen, or other/unknown), number of case-patients tested, number of case-patients positive for HAdV (including HAdV-F, HAdV-F40, and HAdV-F41 if available), number of controls (i.e., patients without AGE) tested (if available), and number of HAdV-positive controls (i.e., patients without AGE with HAdV detected in their stool). We counted specimens with both HAdV and another pathogen detected (e.g., rotavirus) as HAdV-positives, so as not to introduce a bias against studies that did not test specimens for other pathogens.

We also abstracted data for age groups and setting (community, outpatient and emergency department [ED], or inpatient) and stratified data from studies that reported multiple settings, countries, or age groups into separate data points, so the total number of data points sometimes exceeded the total number of included studies. If multiple age groups or settings were included in a study and could not be stratified into separate data points, the data was included in the “Mixed or unknown” category. Where prevalence data was presented in graphical format only, the GetData Graph Digitizer software was used and/or the study authors were contacted to obtain raw numbers [18]. For age, we abstracted data into two categories where possible: < 5 years and ≥ 5 years of age. Age groups that included participants ≤ 60 months were included in the < 5 years of age group. We conducted a secondary analysis comparing age groups < 2 years and ≥ 5 years of age to explore the prevalence in very young children.

Countries in which studies were conducted were classified into three “development index” categories, based on the United Nations Development Programme Human Development

Index (HDI) for 2015 [19,20]. Countries were first classified as “developed” (HDI > 0.80) or “developing” (HDI < 0.80). Developing countries were then divided into “low-mortality developing” (LMD) “high-mortality developing” (HMD) based on child mortality rates for 2015 generated by the United Nations Interagency Group for Child Mortality Estimation [21].

Statistical analysis

Generalized linear mixed models were used to estimate pooled prevalence. Subgroup analyses were conducted to assess differences in prevalence by age, setting, development index, and method of detection; studies with unknown values any of these subgroups were excluded from that subgroup analysis. A p-value of < 0.05 was used to determine statistical significance. The I^2 statistic was calculated as a proxy for heterogeneity across studies, and prediction intervals were calculated for overall pooled estimates to estimate the range of prevalence that may be found in future studies. Overall publication bias was evaluated using Peters’ regression test as well as visual analysis of the Doi plot and calculation of the *LFK* index [22]. Analyses were conducted in R (version 4.3.1, R Core Team, 2023, Vienna, Austria) [23-25].

Results

A total of 3532 unique records were identified from the literature search with publication dates during 2015–2022 (Fig. 1). After title and abstract screening, 470 full-text articles were reviewed for inclusion in the study, and 147 were included in the final meta-analysis (Appendix). All included articles were judged to be of good quality, with a JBI score of at least seven out of the nine checklist items. The articles included data from 75 countries (Fig. 2, Table S2). China was represented in 28 (15 %) studies, followed by Turkey (n = 10, 5 %) and India (n = 9, 5 %); 48 countries were represented by a single study. Fifty-nine (39 %) studies were conducted in developed countries, followed by 54 (35 %) studies in LMD countries. All studies were conducted between 1998–2022 and had a median duration of 2 years (range 1 – 17 years). Seventy-five (51 %) studies included data only for children < 5 years of age, and 30 (20 %) studies included adults ≥ 18 years of age. Inpatients (i.e., hospitalized patients) were included in 70 (48 %) studies (Table 1). Most studies (n = 107, 73 %) used PCR-based testing methods, followed by 39 (27 %) that used antigen-based methods, and one (< 1 %) study that used clinical testing records but did not specify the exact method used. Forty-two (29 %) studies used testing methods that specifically detected HAdV-F in stool, and pooled prevalences were calculated for these studies in a sub-analysis where cell sizes allowed. Seventy-three (50 %) studies used testing methods that detected any species (A-G) of HAdV, and a further 32 (22 %) studies detected pan-HAdV but conducted further typing for HAdV-F or HAdV-F40/HAdV-F41 on a subset of HAdV-positive samples.

The overall estimated prevalence of pan-HAdV among AGE case-patients in all included studies was 5.8 % (95 % confidence interval [95 % CI] 4.9 – 6.8; Table 2). The I^2 value for between-study heterogeneity was 99.4 %, and the prediction interval ranged from 0.7 %–34.6 %. There was some evidence of publication bias in studies reporting prevalence

estimates among AGE case-patients (Peters' regression $p = 0.04$; LFK index = -1.16). Pan-HAdV prevalence was significantly different by age group, method of detection, and country development index. Children < 5 years of age had a significantly higher prevalence of pan-HAdV (6.6 % [95 % CI 5.5 – 7.8]) than case-patients ≥ 5 years of age (2.0 % [95 % CI 1.2 – 3.3]; $p < 0.0001$). Sixty-two studies included data specifically on children < 2 years of age; the estimated prevalence in this age group was 7.8 % (95 % CI 6.1 – 10.0) which was also significantly higher than case-patients ≥ 5 years of age ($p < 0.0001$). There were insufficient data on prevalence among children 2–4 years of age to allow calculation of a pooled prevalence in this age group. Studies using PCR-based methods of detection also had a significantly higher prevalence of pan-HAdV (6.4 % [95 % CI 5.2 – 7.9]) than those studies using antigen-based methods (4.5 % [95 % CI 3.5 – 5.6]; $p = 0.02$). Pan-HAdV prevalence did not differ significantly by setting of study but did differ significantly by development index. Prevalence was highest in countries classified as HMD at 9.4 % (95 % CI 7.3 – 12.0) and lowest in developed countries (4.0 % [95 % CI 2.9 – 5.4]; $p < 0.0001$).

Among the 42 studies that specifically tested for HAdV-F, estimated overall prevalence among AGE case-patients was 6.0 % (95 % CI 4.3 – 8.2) (Table 2). Prevalence of HAdV-F was 8.7 % (95 % CI 6.5 – 11.7) among children < 5 years of age and 12.1 % (95 % CI 8.6 – 17.0), under < 2 years of age; both significantly higher than the 2.3 % prevalence among individuals ≥ 5 years of age (95 % CI 0.5 – 10.4; $p = 0.04$ and $p = 0.01$, respectively). Prevalence was also significantly different ($p = 0.009$) by setting, with the highest prevalence noted in community-based studies (12.5 % [95 % CI 6.0 – 24.3]) and the lowest among outpatient/ED studies (3.9 % [95 % CI 2.4 – 6.5]). Studies conducted in HMD countries again had the highest pooled prevalence at 11.6 % (95 % CI 7.5 – 17.5), compared to 5.9 % (95 % CI 3.0 – 11.3) in LMD countries and 3.2 % (95 % CI 1.9 – 5.4) in developed countries ($p = 0.0003$). Prevalence of HAdV-F did not vary significantly by method of detection.

Eighteen (11 %) studies included data on non-AGE controls (Table S3). These studies were conducted during 2006 – 2019 and had a median duration of 2 years (range 1 – 4.6 years). Ten (56 %) studies contained data only on children < 5 years of age, and eight (47 %) studies were conducted in developed countries. Seven (39 %) studies used testing methods that specifically detected HAdV-F in stool. Seven (39 %) studies used testing methods that detected pan-HAdV, and four (22 %) additional studies detected pan-HAdV but conducted further typing for HAdV-F on a subset of pan-HAdV positive samples. Inpatients were enrolled in 8 (44 %) studies, and thirteen (72 %) studies used PCR methods.

Overall prevalence among non-AGE controls was 2.0 % (95 % CI 1.0 – 3.8) for pan-HAdV. Between-study variance was high, with an I^2 of 93.7 %, and a prediction interval of 0.1–22.2 %. There was evidence of publication bias among studies with data on controls (Peters' regression $p = 0.5$; LFK index = -5.12). Prevalence was 2.1 % for HAdV-F (95 % CI 0.9 – 4.9; Table 3). Pooled prevalence was not statistically different among controls by age, setting, or method of detection. Prevalence of pan-HAdV was statistically different by development index ($p = 0.01$). Studies conducted in developed countries had a pooled prevalence of 3.6 % (95 % CI 1.5 – 8.5), followed by 2.1 % (95 % CI 0.8 – 5.5) in HMD countries and 0.5 % (95 % CI 0.0 – 5.3) in LMD countries. There was an insufficient

number of studies with non-AGE control data to estimate pooled prevalences of HAdV-F by setting, method of detection, or development index.

A total of 94 (64 %) studies reported test results for at least one pathogen other than pan-HAdV. Among pan-HAdV positive AGE case-patients, the median proportion of an additional co-detected pathogen was 27 % (range 0 – 100 %). Seven (5 %) studies reported test results for at least one pathogen other than pan-HAdV among non-AGE controls. Among non-AGE controls, the median proportion of pan-HAdV positives with a co-detected pathogen was 49 % (range 22 % – 100 %).

HAdV-F40 and HAdV-F41 genotyping results were available for 2618 pan-HAdV positive specimens across 30 (20 %) studies. A total of 317 (12 %) specimens were typed as HAdV-F40, 1487 (57 %) as HAdV-F41, and 814 (31 %) as another HAdV genotype. The proportion of HAdV-F40 and HAdV-F41 varied widely by study; HAdV-F40 was reported for 0 % – 61 % of genotyped HAdVs in each study, and HAdV-F41 was reported for 10 % – 100 % of genotyped HAdVs in each study. No studies reported genotyping data for non-AGE controls. There was insufficient number of studies with genotyping results to estimate the pooled prevalence for HAdV-F40 and HAdV-F41.

Discussion

HAdV, particularly HAdV-F, is recognized as an important cause of diarrheal morbidity and mortality worldwide, especially among young children [1-3]. In recent decades, many studies have been published that report the detection of HAdV-F or pan-HAdV in stool specimens from AGE case-patients in a variety of countries, settings, and age groups, including one meta-analysis focused on pediatric patients [26]. However, to our knowledge, this is the first systematic review and meta-analyses to assess the global prevalence of HAdV-F and pan-HAdV in AGE case-patients of all ages. Using data from 147 studies, we estimated that among AGE case-patients, the prevalence of pan-HAdV was 5.8 %, and the prevalence of HAdV-F was 6.0 %.

Our meta-analysis adds to another very recent meta-analysis of pan-HAdV by Khales, et al [26]. That study presented a higher prevalence in children < 5 years of age (11 %) than our study (6.6 %). However, their analysis included only PCR-based testing methods, which generally have a higher sensitivity than antigen-based testing methods [10]. Their analysis also included studies with a duration of less than one year, which may have led to preferential inclusion of studies conducted during the AGE season and inflated the pooled prevalence. Our study adds to that work by including adult AGE patients, though we were unable to calculate a separate pooled prevalences for that age group. Furthermore, our study provides stratified pooled prevalences for HAdV-F, which has not been presented previously.

Among AGE case-patients in this review, pooled prevalence of pan-HAdV and HAdV-F was highest in young children, particularly those aged < 2 years. This parallels findings from other studies showing children aged < 2 years to be at highest risk of HAdV-as-associated AGE [9,26,27], with lower incidence among the elderly [2]. Our analysis found a lower prevalence of HAdV among case-patients older than 5 years of age compared to children

< 5 years of age. This may suggest that HAdV infections in early childhood provide some protection against subsequent infection and/or severe illness. AGE in adults is generally less well-studied than in children; only 30 studies in this systematic review included adults aged ≥ 18 years. Never-theless, diarrhea, including that caused by HAdV-F, remains a leading cause of morbidity and mortality in adults aged ≥ 65 years and should be a focus of study along with AGE in younger age groups [2,28]. Additionally, understanding the patterns of HAdV-F mortality and morbidity throughout the age spectrum may provide insight on heterotypic and homotypic immunity, which may be useful in vaccine development.

Consistent with other studies, our review found that studies utilizing PCR-based methods had a higher pooled prevalence of both pan-HAdV and HAdV-F than antigen-based methods [27,29]. Molecular-based diagnostics are generally more sensitive than antigen-based methods and viral culture, and their adoption has also led to increased recognition of HAdV as a common cause of AGE [3,10]. However, highly sensitive molecular methods may also increase the detection of asymptomatic or persistent shedding that is not clinically relevant, so viral load quantification should also be considered with PCR-based detection [10,29]. The development of multi-pathogen panels that include HAdV-F has further increased testing for HAdV-F in samples from AGE case-patients. This also increases the odds of detecting multiple pathogens in a single sample, which may make interpretation and attribution of disease more difficult. In this review, studies that reported test results for both pan-HAdV or HAdV-F along with additional pathogens found co-detected pathogens in a median of 27 % of HAdV-positive case-patients and 49 % of HAdV-positive controls. Additional analysis is needed to determine whether these co-detections contributed to or were the primary cause of illness in case-patients, or whether they represent detection of rotavirus vaccine shedding or detection of colonizing pathogens like *Clostridioides difficile* in very young children [30,31].

The pooled prevalence of both pan-HAdV and HAdV-F was highest in community settings, followed by inpatient and then outpatient and emergency healthcare settings. AGE caused by HAdV-F is typically mild and self-limiting, and sick individuals or their caregivers may choose to self-treat at home rather than seek formal medical care [32,33]. However, only four studies included in this review were conducted in a community setting. Moreover, all four of these studies were conducted among children aged < 5 years (data not shown), which may have artificially inflated the pooled prevalence in this setting.

Our review also found significant differences in the pooled prevalence of both pan-HAdV and HAdV-F by country development index, with the highest prevalence among HMD countries and the lowest prevalence among developed countries. There may be multiple reasons for these differences. First, effective home-based symptom management, e.g., oral rehydration solutions and anti-diarrheal medications, may be more widely available in developed countries. Sick individuals and their caregivers may be more likely to self-treat the illness at home, whereas sick individuals and their caregivers in developing countries may lack ready access to these treatments and thus may be more likely to seek formal medical care for treatment [34]. Secondly, HAdV-F is easily spread through the fecal-oral route, so access to clean water and sanitation are critical to reducing spread of HAdV-F-

associated AGE. Poor access to clean water and sanitation may lead to increased prevalence of HAdV-F in developing countries [35].

In our review, the estimated prevalence of pan-HAdV and HAdV-F among non-AGE controls was 2.0 % and 2.1 %, respectively. Asymptomatic shedding of other viral AGE pathogens like norovirus and sapovirus have also been noted in the literature [13,14,36]. These detections in non-AGE controls may represent shedding from a recent infection, shedding before symptoms begin, or shedding from a true asymptomatic infection [9,36]. Significant publication bias was detected among studies that included data on non-AGE controls, with along with the wide prediction interval, suggest that future studies may find higher or lower or prevalence among non-AGE controls. However, only 18 studies included in our analysis included data on non-AGE controls. Inclusion of non-AGE controls in burden studies is an increasingly useful tool to determine illness attribution, especially as molecular diagnostic testing becomes more sensitive, and additional studies including controls may lessen the risk and impact of publication bias as seen in the current analysis [37].

Only 30 studies included in our review provided genotyping results for at least some of the pan-HAdV positive specimens, and no studies that enrolled non-AGE controls reported genotyping results. Overall, HAdV-F was the predominant (69 %) species with geno-types-40 and 41 detected in 12 % and 57 % of the AGE case-patients, respectively. Other HAdV species (A-E and G) were detected in 31 % of the samples. While some studies view this as evidence that non-group F HAdV also contribute to the global AGE burden [6], others are more cautious in their interpretation, noting that quantitative testing methods and comparison to controls indicate incidental shedding of non-group F HAdV likely related to non-AGE infections [7,10]. Of the studies included in this review that tested for pan-HAdV without further genotyping, the proportion of HAdV-F is unknown, and therefore the prevalence of pan-HAdV among AGE case-patients should be interpreted with caution. In future studies, quantitative methods evaluating viral load and genotyping of HAdV-positive specimens from both AGE case-patients and non-AGE controls are needed to fully elucidate the role of non-group F HAdV in global AGE.

Only two studies included in our review began after the onset of the COVID-19 pandemic in 2020 (Appendix). The prevalence of pan-HAdV reported in those studies were 5.0 % and 14.7 %, both lower and higher than the prevalence estimated in our review. Recent papers examining changes in prevalence and incidence of AGE viruses since the COVID-19 pandemic have found overall stark decreases in AGE, including AGE caused by HAdV-F [38]. Although we had insufficient data to examine changes in prevalence of HAdV before and after the COVID-19 pandemic, it will be important for future systematic reviews to consider potential differences.

The findings of this study include some limitations. Between-study variance was high, as indicated by a high I^2 and wide prediction intervals. More specifically, future studies of pan-HAdV prevalence in populations similar to those included in this meta-analysis may find a prevalence anywhere from 0.7 %–34.6 %. This may be expected due to the wide range of study locations, sample sizes, and population characteristics observed in the included studies. While we have included some assessment of these differences by virtue of our

subgroup analyses, other factors not specifically assessed here may also affect prevalence. The *LFK* index (-1.16) indicated there may be some slight publication bias, though this was not significant by Peters' regression ($p = 0.04$), and each included study was judged to be of good quality.

Additionally, age groups were defined inconsistently across studies. We were unable to fully compare the prevalence of either pan-HAdV and HAdV-F among very young children aged < 2 years to those aged 2–4 years and aged ≥ 5 years. Very few studies included data for older age groups (e.g., age > 65 years), so we were unable to calculate a pooled estimate for this group. Secondly, although this review includes data from 75 countries, 48 of those countries were only represented by a single study. Many more countries are not represented in our dataset, particularly on the African continent. Furthermore, classifying countries broadly as developed, LMD, and HMD does not capture the within-country variation of socioeconomic status and access to potable water and sanitation that can affect risk of AGE.

In summary, this systematic review, to our knowledge, is the first to assess the global prevalence of both HAdV-F and pan-HAdV in AGE case-patients of all ages and illustrates that HAdV are frequently detected in patients with AGE with the highest prevalence in young children and in case-patients from developing countries. Of these, only HAdV-F are confirmed causes of AGE while the role of non-group F HAdV is unknown. With the increasing availability of molecular multi-enteric pathogen platforms, future studies of AGE burden and pathogen prevalence should continue to include HAdV-F as an important cause of AGE. In turn, we will be able to better understand their role in AGE and inform targeted interventions including future vaccine development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding

The authors have no competing interests to declare.

A formal protocol for this systematic review was not registered prior to commencement. Primary data points collected for this study have been made available in the Appendix.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Abbreviations

AGE	acute gastroenteritis
CI	confidence interval
ED	emergency department
EIA	enzyme immunoassay
HAdV	human adenovirus

HAdV-F	human adenovirus species F
HAdV-F40	human adenovirus species F, type 40
HAdV-F41	human adenovirus species F, type 41
HDI	Human Development Index
HMD	high-mortality developing
JBÍ	Joanna Briggs Institute
LMD	low-mortality developing
PCR	polymerase chain reaction
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
REDCap	Research Electronic Data Capture

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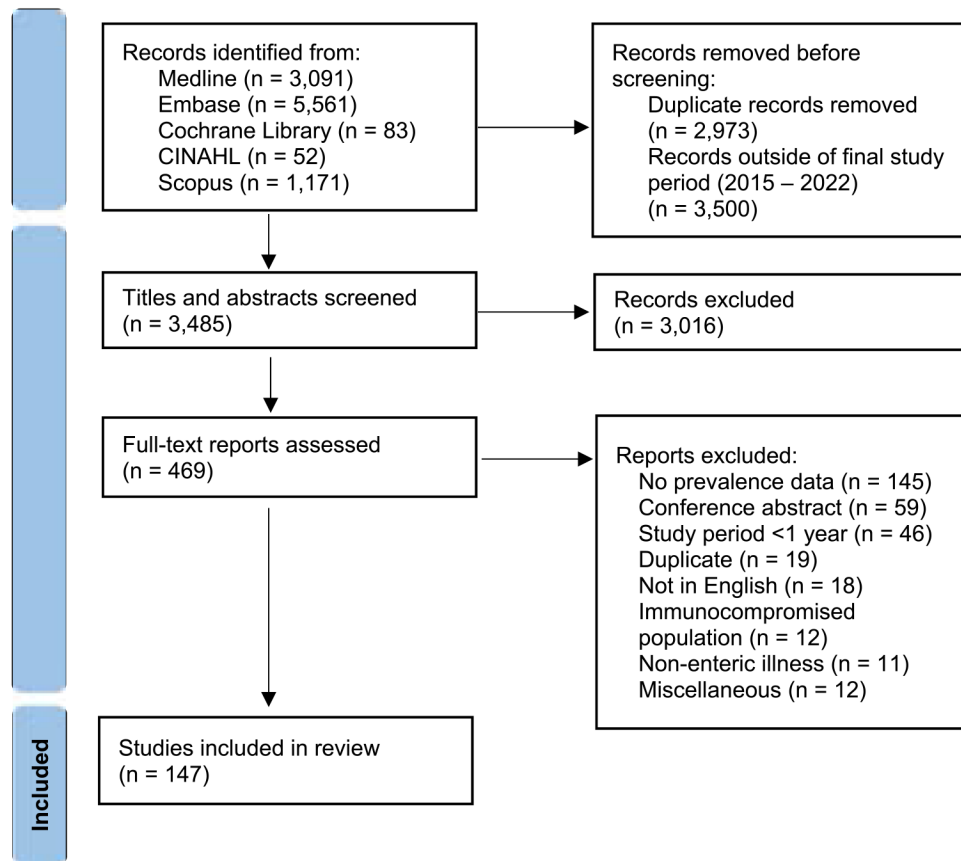


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for study selection process for human adenovirus (HAdV) meta-analysis.

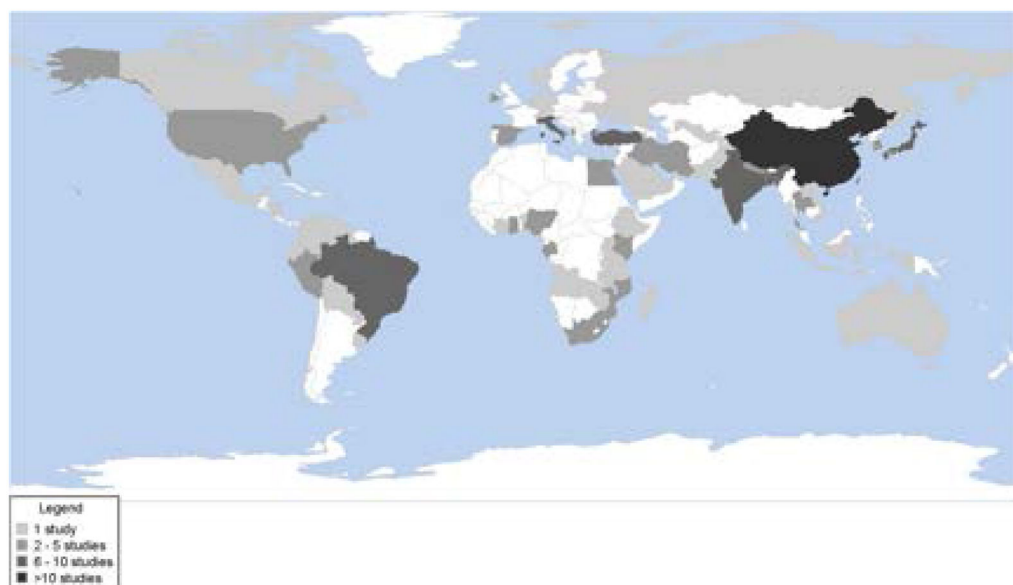


Fig. 2.
Map of countries where studies published during 2015 – 2022 included in human adenovirus (HAdV) meta-analysis were conducted.

Table 1
Characteristics of studies published during 2015 – 2022 and included in human adenovirus (HAdV) meta-analysis.

	All included studies (N = 147)			Studies that tested only for HAdV-F (N = 42)		
	Number of studies	Median number tested (range)	Median number positive (range)	Number of studies	Median number tested (range)	Median number positive (range)
Age Group of Cases ^a						
0–24 months ^b	62	444 (23 – 22,714)	30 (1 – 1045)	25	455 (72 – 3422)	41 (8 – 673)
0–59 months ^c	106	679 (23 – 42,658)	41 (0 – 5667)	38	872 (36 – 29, 502)	75 (2 – 5667)
≥ 60 months	26	495 (44 – 37,426)	14 (0 – 555)	8	1059 (116 – 22,593)	22 (4 – 298)
Mixed or unknown	53	586 (6 – 64,263)	35 (0 – 2773)	11	2545 (105 – 64,263)	35 (5 – 2773)
Setting						
Inpatient	70	524 (23 – 80,054)	35 (0 – 5667)	21	684 (57 – 29,502)	51 (5 – 5667)
Outpatient or ED	35	804 (75 – 64,263)	46 (0 – 2773)	10	1797 (105 – 64,263)	46 (7 – 2773)
Community	4	659 (455 – 6748)	21 (8 – 1715)	3	729 (455 – 6748)	23 (8 – 1715)
Mixed or unknown	38	945 (83 – 31,570)	57 (4 – 1473)	8	7479 (175 – 23,829)	99 (9 – 523)
Method of Detection						
PCR methods	107	677 (57 – 80,054)	47 (0 – 5667)	36	1647 (57 – 29,502)	73 (5 – 5667)
Antigen detection	39	618 (23 – 64,263)	35 (1 – 2773)	6	997 (119 – 64,263)	44 (8 – 2773)
Unknown	1	160 (no range)	2 (no range)	0	.	.
Development Index ^d						
Developed	59	730 (83 – 31,570)	44 (0 – 1473)	21	1089 (150 – 23,829)	53 (5 – 523)
Low mortality developing (LMD)	54	694 (23 – 80,054)	39 (0 – 2773)	11	1606 (57 – 64,263)	75 (7 – 2773)
High mortality developing (HMD)	39	564 (38 – 5516)	35 (1 – 1369)	16	707 (116 – 5516)	55 (9 – 1369)
Mixed or unknown	2	14,994 (485 – 29,502)	2903 (139 – 5667)	1	29,502 (no range)	5667 (no range)

^aMultiple age categories or settings were represented in certain studies.

^bStudies with children 0–24 months old are a subset of studies with children 0–59 months old.

^cIncludes study age groups with participants ≤ 60 months.

^dMultiple countries were represented in certain studies. Two studies presented data from multiple countries with different development indices and were excluded from this sub-analysis.

Table 2
Prevalence and 95 % confidence interval (95 % CI) of human adenovirus (HAdV) among AGE cases, overall and stratified by setting, method of detection, and development index.

	All included studies (N = 147)		Studies that tested only for HAdV-F (N = 42)	
	Prevalence of HAdV [95 % confidence interval]	p-value	Prevalence of HAdV-F [95 % confidence interval]	p-value
Overall	5.8 [4.9 – 6.8]		6.0 [4.3 – 8.2]	
Age Group of Cases ^a				
0–24 months ^b	7.8 [6.1 – 10.0]	< 0.0001	12.1 [8.6 – 17.0]	0.01
≥ 60 months	2.0 [1.2 – 3.3]		2.3 [0.5 – 10.4]	
Age Group of Cases ^a				
0–59 months ^c	6.6 [5.5 – 7.8]	< 0.0001	8.7 [6.5 – 11.7]	0.04
≥ 60 months	2.0 [1.2 – 3.3]		2.3 [0.5 – 10.4]	
Setting				
Community	11.1 [5.5 – 21.4]	0.08	12.5 [6.0 – 24.3]	0.009
Outpatient or ED	5.0 [3.6 – 7.2]		3.9 [2.4 – 6.5]	
Inpatient	6.8 [5.5 – 8.3]		7.2 [4.7 – 10.8]	
Method of Detection				
PCR methods	6.4 [5.2 – 7.9]	0.02	6.2 [4.3 – 8.8]	0.3
Antigen detection	4.5 [3.5 – 5.6]		4.6 [2.6 – 7.9]	
Development Index ^d				
Developed	4.0 [2.9 – 5.4]	< 0.0001	3.2 [1.9 – 5.4]	0.0003
Low mortality developing (LMD)	5.8 [4.5 – 7.4]		5.9 [3.0 – 11.3]	
High mortality developing (HMD)	9.4 [7.3 – 12.0]		11.6 [7.5 – 17.5]	

^aMultiple age categories or settings were represented in certain studies.
^bStudies with children 0–24 months old are a subset of studies with children 0–59 months old. Prevalence among children 25–59 months of age were not included in this comparison due to insufficient data.
^cIncludes study age groups with participants ≤ 60 months.
^dMultiple countries were represented in certain studies. Two studies presented data from multiple countries with different development indices and were excluded from this sub-analysis.

Table 3
Prevalence and 95 % confidence interval (95 % CI) of human adenovirus (HAdV) among non-AGE controls, overall and stratified by setting, method of detection, and development index.

	All included studies (N = 18)		Studies that tested only for HAdV-F (N = 7)	
	Prevalence of HAdV [95 % confidence interval]	p-value	Prevalence of HAdV-F [95 % confidence interval]	p-value
Overall	2.0 [1.0 – 3.8]	.	2.1 [0.9 – 4.9]	.
Age Group of Controls ^a		0.2		0.8
0–24 months ^b	3.7 [1.1 – 12.0]		3.0 [0.6 – 14.0]	
≥ 60 months	1.9 [1.1 – 3.1]		2.6 [0.7 – 9.0]	
Age Group of Controls ^a		0.4		0.9
0–59 months ^c	2.6 [1.1 – 6.0]		2.5 [0.7 – 8.3]	
≥ 60 months	1.9 [1.1 – 3.1]		2.6 [0.7 – 9.0]	
Setting		0.8		
Inpatient	2.5 [1.1 – 5.7]		.	.
Outpatient/ED	2.0 [0.3 – 11.6]		.	.
Method of Detection		0.4		
PCR methods	2.3 [1.0 – 5.0]		.	.
Antigen detection	1.4 [0.4 – 5.3]		.	.
Development Index ^d		0.01		
Developed	3.6 [1.5 – 8.5]		.	.
Low mortality developing (LMD)	0.5 [0.0 – 5.3]		.	.
High mortality developing (HMD)	2.1 [0.8 – 5.5]		.	.

^aMultiple age categories or settings were represented in certain studies.
^bStudies with children 0–24 months old are a subset of studies with children 0–59 months old. Prevalence among children 25–59 months of age were not included in this comparison due to insufficient data.
^cIncludes study age groups with participants ≤ 60 months.
^dMultiple countries were represented in certain studies. Two studies presented data from multiple countries with different development indices and were excluded from this sub-analysis.