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Human infection with respiratory adenovirus in China: a systematic review and meta-analysis --Manuscript Draft--

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Abstract:	<p>Background</p> <p>Human adenovirus (HAdV) is a major pathogen that causes respiratory tract infections (ARTI) and frequently associated with outbreaks. The HAdV prevalence and the predominant types that were responsible for the ARTI outbreaks remained obscure in China.</p> <p>Methods</p> <p>A systematic review was performed to retrieve literature that reported outbreaks or etiological surveillance of HAdV in China from January 2009 to March 2021. The genetic characteristics and epidemiological characteristics of HAdVs were investigated.</p> <p>Results</p> <p>A total of 950 articles (91 about outbreaks and 859 about etiological surveillance) meeting the selection criteria were included. Predominant HAdV types from etiological surveillance studies differed from those in outbreak events. Among the 70 outbreaks for which the HAdVs were typed, nearly half (45·71%) were caused by HAdV-7 with an overall attack rate of 22·32% after meta-analysis. Military camp and school were predominant settings of outbreaks with HAdV-55 and HAdV-7 respectively identified as the leading type and with significantly different seasonal pattern and attack rate. Among 859 hospital-based surveillance studies, positive detection rates of HAdV-3 (32·73%) and HAdV-7 (27·48%) were significantly higher than other types. Clinical manifestations mainly depended on HAdV types and patient age with significant discrepancy among them, and infection with HAdV-55 tends to develop pneumonia with a poorer prognosis, especially for children <5 years old.</p> <p>Conclusions</p> <p>This study improves the understanding of epidemiological and clinical features of HAdV infections and outbreaks with different types, and helps to inform future surveillance and control efforts in different settings.</p>
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1 **Human infection with respiratory adenovirus in China: a systematic**
2 **review and meta-analysis**

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15

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17

18

19 **Abstract**

20 **Background** Human adenovirus (HAdV) is a major pathogen that causes respiratory
21 tract infections (ARTI) and frequently associated with outbreaks. The HAdV
22 prevalence and the predominant types that were responsible for the ARTI outbreaks
23 remained obscure in China.

24 **Methods** A systematic review was performed to retrieve literature that reported
25 outbreaks or etiological surveillance of HAdV in China from January 2009 to March
26 2021. The genetic characteristics and epidemiological characteristics of HAdVs were
27 investigated.

28 **Results** A total of 950 articles (91 about outbreaks and 859 about etiological
29 surveillance) meeting the selection criteria were included. Predominant HAdV types
30 from etiological surveillance studies differed from those in outbreak events. Among
31 the 70 outbreaks for which the HAdVs were typed, nearly half (45.71%) were caused
32 by HAdV-7 with an overall attack rate of 22.32% after meta-analysis. Military camp
33 and school were predominant settings of outbreaks with HAdV-55 and HAdV-7
34 respectively identified as the leading type and with significantly different seasonal
35 pattern and attack rate. Among 859 hospital-based surveillance studies, positive
36 detection rates of HAdV-3 (32.73%) and HAdV-7 (27.48%) were significantly higher
37 than other types. Clinical manifestations mainly depended on HAdV types and patient
38 age with significant discrepancy among them, and infection with HAdV-55 tends to
39 develop pneumonia with a poorer prognosis, especially for children <5 years old.

40 **Conclusions** This study improves the understanding of epidemiological and clinical
41 features of HAdV infections and outbreaks with different types, and helps to inform
42 future surveillance and control efforts in different settings.

43
44 **Keywords:** Human adenovirus; China; respiratory tract infections; Meta-analysis.

45

46 Introduction

47 Infection with HAdV causes a broad spectrum of clinical illnesses that varies
48 depending on the infecting types: pharyngoconjunctival fever, keratoconjunctivitis,
49 pneumonia, hemorrhagic cystitis, gastroenteritis, acute respiratory disease, severe
50 disseminated disease, cardiomyopathy, and encephalitis[1]. Even unexplained liver
51 injury or hepatitis were reported by two recent independent studies of UK children
52 with HAdV- 2 infection, suggesting that HAdV-2 may trigger liver damage through
53 the immune mechanisms of genetically predisposed children.[2, 3] There are at least
54 113 recognized HAdV types (<http://hadv.wg.gmu.edu/>), which are assigned to seven
55 subgroups (A–G) according to biophysical, biochemical, and genetic characteristics,
56 with marked differences in tissue tropism and clinical manifestations[4]. The types
57 most commonly found in respiratory samples belong to HAdV species C (HAdV-C1,
58 HAdV-C2, HAdV-C5, and HAdV-C6) and to HAdV species B, subspecies B1
59 (HAdV-B3 and HAdV-B7) and B2 (HAdV-B14), which are endemic and epidemic,
60 respectively, in pediatric populations[5].

61 In recent years, new serotypes or subspecies were increasingly recognized by
62 using of phylogenetic analysis, which arise from genome recombination between the
63 hexon gene, fiber, and penton genes. For any of the emerging new types or
64 recombinant strains, high potential of spreading widely and even epidemic outbreaks
65 might be resulted, due to the lack of herd immunity and specific vaccine intervention,
66 posing severe threats to public health[6-9]. Acute respiratory infection caused by
67 HAdV is the leading cause of morbidity in military forces worldwide. Since 1971,
68 U.S. military recruits have been vaccinated with oral HAdV-4 and HAdV-7 vaccines,
69 which has significantly decreased the epidemics of HAdV in the military[10][11].

70 In recent years, there has been an increase in studies from hospital-based
71 surveillance, reflecting a growing awareness of the importance of HAdV as
72 respiratory pathogens. In general, there is still a lack of data on the HAdV prevalence

73 and the predominant type ~~that were~~ responsible for the ARTI sporadic outbreaks or
74 epidemics in China.

75 Here we conduct a systematic review of all published research articles on
76 outbreak investigation and active surveillance of HAdV at the nation-wide level,
77 between January 2009 and March 2021 to evaluate the HAdV prevalence, types,
78 seasonality, as well as to characterize patients' demographic and clinical data. This
79 information might help to comprehensively understand the epidemic patterns of
80 HAdV in China and support the adoption of targeted prevention and control measures.
81

82 **Materials and Methods**

83 This review was conducted according to the Preferred Reporting Items for
84 Systematic Reviews and Meta-Analyses (PRISMA) statement, and has been
85 registered with the international prospective register of systematic reviews
86 (PROSPERO) (International Prospective Register of Ongoing Systematic Reviews)
87 (CRD42022303015)[12].

88 **Search strategy and selection criteria**

89 Literature search was performed from the major databases including the PubMed
90 database (<https://pubmed.ncbi.nlm.nih.gov/>), China National Knowledge
91 Infrastructure (CNKI) (<http://www.cnki.net/>), Chongqing VIP (CQVIP)
92 (<http://www.cqvip.com>) and Wanfang databases (<http://www.wanfangdata.com.cn/>),
93 with the keywords ('HAdV' OR 'adenovirus' [Title/Abstract]) AND ('respiratory'
94 [Title/Abstract] OR 'pneumonia' [Title/Abstract]), AND ('China' OR 'the mainland of
95 China' OR 'Chinese mainland' OR 'Taiwan' OR 'Hong Kong' OR 'Macau' OR 'Macao'
96 [Title/Abstract]) (Appendix 1 p 2). All the articles published between January 2009
97 and March 2021 were searched without language limitations.

98 We included studies of human infection with HAdV, across all settings (i.e.,
99 hospital, community, long-term care) and among all age groups (pediatric and adult
100 patients). We included etiological surveillance studies and outbreak investigation, but

101 excluded reviews, editorials, letters, case studies, randomized controlled trials and
102 experimental studies. Studies were eligible if they explicitly described the total
103 number of individuals tested and those that were positive for HAdV infections in
104 humans. The following articles were excluded: (1) drug, vaccine trials, mechanism
105 studies, animal experiments or reviews for HAdV; (2) etiological surveillance studies
106 with sampling size <100 for laboratory test or HAdV positive detection <10; (3)
107 describing cases imported from abroad after international travel; (4) lacking
108 information about methods of laboratory diagnosis, specimens tested; (5) evaluations
109 on laboratory methods for HAdV; (6) study period beyond the duration 2009–2020;
110 (Appendix 1 pp 3–4).

111 Titles and abstracts of the retrieved studies were screened using Endnote X9
112 independently by two reviewers (MCL and TTL) to identify studies potentially
113 eligible for inclusion, and then the full texts were retrieved and independently
114 assessed for eligibility. Discrepancies between reviewers were resolved by consensus
115 or a third reviewer (QX). Studies potentially describing overlapping data were noted
116 and the duplication were removed (e.g., same hospital and population during an
117 overlapping time period).

118 **Data extraction and variable definition**

119 One of the authors (MCL) extracted data from included studies using a
120 standardized data collection form. The following variables were collected: reference
121 id, author, publish year, study sites, start and end dates, name(s) of healthcare facility;
122 study design (surveillance study, outbreak investigation), outbreak setting
123 (school/daycare outbreaks, healthcare comprised of hospitals and long-term care
124 facilities, military camps, swimming pools), age group, patient population, mean or
125 median age, gender proportion, laboratory test methods (molecular, serological) and
126 type of HAdV, sample size, absolute number or rate of positive detection, presence of
127 clinical symptoms or syndromes of patients if reported (Appendix 1 pp 5–6). For

128 quality assurance, another two authors (QX, TW) randomly sampled 25% of recorded
129 data to confirm accuracy and completeness.

130 For definition of outbreak event, all those recognized and reported outbreaks
131 related to HAdV by health agencies were included. Otherwise, an outbreak event was
132 defined as a number of clustered HAdV cases with a higher incidence than the
133 average or expected incidence for a region where the cases occur. All the events had
134 to be laboratory confirmed, e.g., etiological pathogen determined to be HAdV by
135 molecular methods (PCR) or serological methods (ELISA, IFA), while those
136 outbreaks reporting suspected HAdV without laboratory ~~confirm~~ for HAdV were not
137 included in the analysis. For outbreak investigation, we extracted additional
138 information regarding the exact date of outbreak, attack rate, numbers of primary
139 cases, persons at risk, and number of secondary cases if available. For articles
140 reporting more than one outbreak, data were separately extracted for each outbreak.
141 For outbreaks reported in multiple publications, we included the one that reported
142 more detailed data.

143 Four age groups were defined for comparison, including children (<5 years old),
144 ~~adolescence~~ (5–17 years old), adult (18–59 years old), the elderly (≥ 60 years old).
145 When a study did not mention any age information, the all-age groups were specified.
146 Seven regions were defined according to the ecoclimatic characteristics, i.e.,
147 Northeast China, North China, Inner Mongolia-Xinjiang, Qinghai-Tibet, Southwest
148 China, Central China, and South China[13].

149 **Meta-analysis**

150 We performed meta-analysis to evaluate demographic characteristics of patients,
151 attack rate, or positive rate for HAdV. Briefly, the pooled proportion and 95% CI
152 were estimated using the inverse variance combined with fixed effects or random
153 effects models depending on the degree of the heterogeneity between studies.
154 Heterogeneity was quantified using the statistic Higgin's I^2 , when its value was
155 greater than 50%, random effects model was used, otherwise, fixed effects model was

156 applied[14]. We performed meta-analysis on 105 articles with a clinical
157 manifestations study size greater than 20 patients, to estimate the clinical
158 manifestations that were related to different HAdV types. For those clinical
159 manifestations which were mentioned in only one study, the proportion was
160 calculated without a 95% CI estimated (Appendix2). All maps were produced using
161 the ArcGIS 10.7 software. The Meta program package in R 4.1.2 software was used to
162 merge the rates and draw forest plots. All analyses were conducted with R 4.1.2
163 software.

164

165 **Results**

166 **Temporal and spatial features of publications and patients**

167 A total of 5056 studies published from January 2009 to March 2021 were
168 identified and after duplicate removal, 3874 studies underwent title and abstract
169 screening, among whom 1329 were assessed via full-text screening. We included 950
170 studies (881 in Chinese and 69 in English) in the final analysis, comprised of 859
171 surveillance studies involving 119 838 patients and 91 outbreak investigations
172 involving 15 940 patients (Fig 1, Appendix3).

173

174 **Fig 1. The flow diagram of the literature review.** Literature search was performed
175 from the major databases including the PubMed database
176 (<https://pubmed.ncbi.nlm.nih.gov/>), China National Knowledge Infrastructure (CNKI)
177 (<http://www.cnki.net/>), Chongqing VIP (CQVIP) (<http://www.cqvip.com>) and
178 Wanfang databases (<http://www.wanfangdata.com.cn/>), we included 950 studies (881
179 in Chinese and 69 in English) in the final analysis.

180

181 Of the 91 articles reporting 97 outbreak events, 68 (74.73%) were published
182 during 2014—2019, with the highest number of articles published in 2014 (14
183 articles), followed by 2017 (13 articles) (Fig 2A). Of the 859 surveillance studies, 594

184 (69.15%) were published during 2015–2020, with the largest number published in
185 2015 (135 articles), followed by 2016 (103) (Fig 2C).

186 **Fig 2. Number of recruited studies by publish year of HAdV in China, 2009–**
187 **2021.** (A) number of outbreaks articles group by publish year, (B) number of outbreak
188 types group by publish year, (C) number of surveillance articles group by publish
189 year, (D) number of surveillance types group by publish year. Other rarely seen types
190 including HAdV-21 (with 30 patients report), HAdV-57 (18), HAdV-31 (five),
191 HAdV-50 (two), HAdV-12 (one), HAdV-35 (one), and HAdV-104 (one).

192

193 A comparable number of outbreaks took place in Northern and Southern China
194 (Table 1). The geographic discrepancy of seasonal timing was shown for the
195 outbreaks, with most of the outbreak events occurring in the winter season in
196 Northern China (28/46), while showed a dual seasonal timing in Southern China,
197 observed at the turn of spring and summer and winter separately (44/51) (Fig 3A).
198 The overall attack rate was estimated to be 15.91% (95% CI: 13.85–17.98). A higher
199 attack rate was observed in Northern China than in Southern China (19.01%, 95% CI:
200 14.42–23.60 versus 13.53%, 95% CI: 11.28–15.77). When the outbreak settings
201 were compared, the highest attack rate was observed in military camps (23.55%, 95%
202 CI:18.02–29.07), followed by swimming pools (22.47%, 95% CI: 12.49–32.45),
203 hospitals (19.75% , 95% CI: 8.64–30.86) and schools (6.19%, 95% CI: 4.92–7.46)
204 (Fig 3B). In contrast with the outbreak events, surveillance study reported comparable
205 interregional positive rate (4.13%, 95% CI: 3.95–4.31 in Southern China, 4.15% ,
206 95% CI: 3.95–4.34 in Northern China), and the overall detection rate was estimated
207 to be 4.21% (95% CI: 4.07–4.34) (Fig 3C, Appendix1 pp 7–11)

208 **Table 1. Attack rate and positive detection rate by meta-analysis of HAdV by areas, season, age, settings and types.**

	Outbreak events			Surveillance		
	Number of outbreak investigation articles (No. of outbreaks)	Cases	Attack rate by meta- analysis % (95% CI)*	Number of surveillance investigation articles	Cases	Detection rate by meta-analysis % (95% CI)
Number	91 (97)	15940	15.91 (13.85, 17.98)	859	119838	4.21(4.07, 4.34)
Mortality	4 (4)	4	-	9	37	-
Areas**						
Northern	44 (46)	9182	19.01 (14.42, 23.60)	283	19955	4.15 (3.95, 4.34)
Southern	48 (51)	6758	13.53 (11.28, 15.77)	584	97162	4.13 (3.95, 4.31)
Season						
Spring	19 (20)	899	5.92 (4.47, 7.36)	39	2047	5.21 (4.35, 6.07)
Summer	16 (17)	440	16.76 (12.47, 21.04)	39	1780	4.64 (3.82, 5.47)
Autumn	16 (17)	394	5.71 (3.41, 8.01)	36	1278	3.62 (2.95, 4.29)
Winter	40 (43)	8453	22.65 (16.33, 28.96)	37	2042	3.54 (2.83, 4.24)
Age						
Child	6 (6)	121	12.78 (7.95, 17.62)	174	10671	4.04 (3.76, 4.31)
Adolescence	40 (43)	2042	6.52 (5.5, 7.55)	8	531	4.45 (2.55, 6.36)
Adult	44 (47)	13734	23.56 (18.31, 28.8)	28	1219	3.44 (2.76, 4.12)
The elderly	0 (0)	0		9	229	2.81 (1.84, 3.78)
All-age groups	1 (1)	43	25.29	644	107188	4.29 (4.12, 4.45)
Settings						
School	41 (43)	3386	6.19 (4.92, 7.46)	0	0	
Military camp	37 (40)	11849	23.55 (18.02, 29.07)	0	0	
Hospital	5 (5)	142	19.75 (8.64, 30.86)	859	119838	4.21(4.07, 4.34)
Swimming pool	9 (9)	563	22.47 (12.49, 32.45)	0	0	

Types†						
HAdV-1	0 (0)	0	-	40	466	6.70 (5.39, 8.01)
HAdV-2	0 (0)	0	-	44	772	8.90 (7.31, 10.50)
HAdV-3	9 (11)	711	5.55 (2.63, 8.48)	60	2869	32.73 (22.13, 43.34)
HAdV-4	7 (7)	150	8.75 (0.00, 21.30)	30	137	2.07 (1.41, 2.74)
HAdV-5	0 (0)	0	-	38	249	3.55 (2.78, 4.32)
HAdV-6	0 (0)	0	-	21	83	1.97 (1.23, 2.70)
HAdV-7	30 (32)	7048	22.32 (14.78, 29.86)	59	2518	27.48 (17.04, 37.91)
HAdV-11	0 (0)	0	-	4	186	16.14 (1.89, 30.40)
HAdV-14	3 (4)	92	8.83 (6.31, 11.35)	12	43	2.01 (0.92, 3.09)
HAdV-21	0 (0)	0	-	7	30	0.87 (0.17, 1.57)
HAdV-31	0 (0)	0	-	4	5	0.33 (0.00, 0.73)
HAdV-55	16 (16)	4043	27.18 (19.16, 35.20)	25	258	4.70 (3.40, 6.00)
HAdV-57	0 (0)	0	-	8	18	1.01 (0.51, 1.50)

209 * 53 outbreaks recording attack rate were included in the total; 2, 26, 24 and 1 outbreaks recording attack rate were included in the children age
210 group, adolescence age group, adult age group and all age groups, respectively; 13, 8, 6 and 25 outbreaks recording attack rate were included in
211 the spring, summer, autumn and winter group, respectively; 25 and 28 outbreaks recording attack rate were included in the north and south
212 group, respectively; 22, 2, 6 and 23 outbreaks recording attack rate were included in the military, hospital swimming pool and school group,
213 respectively; 4, 2, 17, 1 and 9 outbreaks recording attack rate were included in the HAdV-3, HAdV-4, HAdV-7, HAdV-14 and HAdV-55 group,
214 respectively.

215 ** Of the 848 articles mentioning locations, 19 mentioned both northern and southern China.

216 †HAdV type with case No> 5 were included, other rarely seen types including HAdV-50 (2), HAdV-12 (1), HAdV-35 (1), and HAdV-104 (1).

Fig 3. Attack rate of outbreak and detection rate of surveillance for HAdV in China. (A) attack rate by region, (B) attack rate by settings, (C) detection rate by regions, (D) attack rate by age groups.

(A, B, D) The bars indicate the number of outbreaks, and the intervals indicate the attack rate and 95% CI which is obtained by meta-analysis. (C) The bars indicate the number of surveillance cases, and the intervals indicate the detection rate and 95% CI which is obtained by meta-analysis.

Demographic characteristics of patients

The highest number of outbreak events were observed in the adult group (47), followed by adolescents (43) and children (6). The highest attack rate was in adults (23.56%, 95% CI: 18.31–28.80), followed by children (12.78%, 95% CI: 7.95–17.62) and adolescents (6.52%, 95% CI: 5.50–7.55). An age pattern of HAdV infection was shown from the surveillance data, with higher positive rate observed in children (4.04%, 95% CI: 3.76–4.31) and adolescents (4.45%, 95% CI: 2.55–6.36) than those of the two older groups (Table 1). Seasonal pattern differed among age groups. For children and adolescent, over half of the outbreaks occurred in autumn and spring (29 of 49 outbreaks), while for adult groups, most outbreaks occurred in winter (38/47) (Fig 3D, Appendix 1 pp 12).

Among 97 outbreaks that reported settings, the highest number was reported in schools (44.33%, 43/97), followed by military camps (41.24%, 40/97), swimming pools (9.28%, 9/97), and hospitals (5.15%, 5/97). The seasonality was largely dependent on the outbreak settings, with most of the military camps outbreaks occurring in winter (85.00%, 34/40), and swimming pool outbreaks occurring in summer (88.89%, 8/9), while school outbreaks occurring in spring and autumn during school terms as expected (69.77%, 30/43). A total of 41 deaths with confirmed HAdV infection were reported from 13 articles, with an overall case fatality rate of 0.03% (Table 1).

Temporal and geographic pattern of HAdV types in China

Sequence information was available for 70 outbreak events involving 12 044 cases and 67 surveillance studies involving 7639 cases. The most common type responsible for outbreak events was HAdV-7, accounting for 45.71% (32/70) of the totally typed outbreaks, followed by HAdV-55 (16/70), HAdV-3 (11/70), HAdV-4 (7/70), and HAdV-14 (4/70) (Fig 2B). The case numbers involved in outbreaks caused by HAdV-7, HAdV-55 and HAdV-3 were 7048, 4043 and 711, respectively, based on which the attack rate of HAdV-55 was estimated to be 27.18% (95% CI: 19.16–35.20), which was significantly higher than that of HAdV-7 (22.32%, 95% CI: 14.78–29.86) and HAdV-3 (5.55%, 95% CI: 2.63–8.48) (Table1). A difference of the predominant HAdV type in outbreak events was shown between Northern China and Southern China. Among all the outbreaks reporting HAdV types and study sites, HAdV-55 (12 events involving 3841 cases) and HAdV-7 (17 events involving 2614 cases) were predominant in Northern China, while HAdV-7 (15 events involving 4434 cases), HAdV-3 (seven events involving 640 cases), and HAdV-55 (four events involving 202 cases) were predominant in Southern China (Fig 4A). According to the ecological regions of China, we found that HAdV-55 was dominated pathogen for outbreak events in four regions including Inner Mongolia-Xinjiang, North China, Qinghai-Tibet, and South China, while HAdV-7 was dominated in the others including Northeast China and Central China, expecting for one region without reporting outbreaks (Southwest China) (Appendix 1 p15).

Fig 4. Comparison of types by region, age, and setting. (A) comparison of the types of outbreaks in different regions, (B) comparison of the types of surveillance in different regions, (C) comparison of the types of outbreaks in different age groups, (D) comparison of the types of outbreaks in different settings.

(A, C, D) Solid circles indicate the number of outbreaks, and hollow circles indicate the number of cases. (B) Solid circles indicate the number of surveillances, and hollow circles indicate the number of cases.

The predominant HAdV types from etiological surveillance studies differed from those in outbreak events. The most common type was HAdV-3 (2869 cases), followed by HAdV-7 (2518), HAdV-2 (772), HAdV-1 (466), HAdV-55 (258), and HAdV-5 (249) (Fig 2D). The positive rate of HAdV-3 was determined as 32.73% (95% CI: 22.13–43.34), which was significantly higher than that of HAdV-7 (27.48%), HAdV-11 (16.14%), HAdV-2 (8.90%), HAdV-1 (6.70%), HAdV-55 (4.70%), and HAdV-5 (3.55%). Both HAdV-3 and HAdV-7 were the common types identified in northern and southern China (Fig 4B, Table1).

Among 70 outbreaks providing information on age and HAdV type, HAdV-7 (25) and HAdV-55 (15) were responsible for all the 40 outbreaks reported in the adult group; HAdV-7 (3) and HAdV-4 (3) were determined in the six outbreaks reported from children, while a higher diversity of types were observed in the 24 outbreaks reported in the adolescent group, including HAdV-3 (11), HAdV-4 (4), HAdV-7 (4), HAdV-14 (4), HAdV-55 (1) (Fig 4C). Among the 70 outbreaks with reported settings and types, HAdV-7 (21) and HAdV-55 (12) were responsible for all the 33 outbreaks in military camps, which involved 5111 and 3674 cases respectively. HAdV-55 (3 outbreaks) and HAdV-7 (2) were responsible for the five outbreaks in hospitals, with 113 and 29 cases involved respectively. HAdV-3 (2 outbreaks), HAdV-4 (1), and HAdV-7 (2) were determined to be responsible for the five swimming pool outbreaks, with 199, 147, and nine cases involved respectively. Five HAdV types were responsible for the 28 outbreaks in schools, main including HAdV-3 (9), HAdV-7 (7), HAdV-4 (6), HAdV-14 (4), and HAdV-55 (2), with 1761 cases with HAdV-7 and 512 cases with HAdV-3 infection taking the large part of the case (Fig 4D).

Clinical manifestations

Altogether 105 articles with HAdV cases greater than 20 were included for the investigation of clinical manifestations. Among children with HAdV infection, cough was the most prevalent, identified in 76.47% cases, followed by pneumonia (66.56%), expectoration (56.28%), respiratory failure (11.05%), breathing difficulties (34.69%), running nose (29.58%), vomiting (25.00%), and diarrhea (16.87%). Among adolescent group, tonsillar enlargement (70.89%), pneumonia (21.69%) and vomiting (15.43%) were frequently seen. Among adult group, less diverse clinical presentations were seen, including expectoration (31.19%), running nose (8.05%) and vomiting (4.60%) (Fig 5A, Appendix1 pp 13).

Fig 5. Clinical manifestations of HAdV infection by age groups and types.

(A,B)The bars indicate the number of articles, and the intervals indicate the detection rate and 95% CI which is obtained by meta-analysis.

Comparison among HAdV types revealed HAdV-3 infection was related to higher frequency of cough (79.91%), running nose (20.59%) and vomiting (20.59%), compared with HAdV-55 and HAdV-7. HAdV-55 was related to higher frequency of tonsillar enlargement (96.91%), pneumonia (27.91%), while lower presence of cough (56.61%), expectoration (45.10%), running nose (6.90%), and vomiting (3.37%), diarrhea (1.50%), compared with HAdV-3 and HAdV-7. HAdV-7 was related to higher presence of expectoration (60.59%), breathing difficulties (26.80%), compared with HAdV-3 and HAdV-55 (Fig 5B, Appendix1 pp 14).

Discussion

The current study provided a most comprehensive and up to date estimation on the attack rate/positive rate of HAdV as well as the dominant genogroups, that differed across age, setting and seasons. Attack rates were significantly higher in

outbreaks related to military camps and in the winter season. HAdV55, HAdV7 and HAdV3 were the major causative agents for the outbreak setting, however, outbreaks in military camps were more likely to be associated with HAdV7 and HAdV55, while outbreaks in other setting were associated with more HAdV genotypes, particularly for the school outbreaks. This was also in line with the higher diversity of types in the adolescent group, who constituted the major part of school outbreaks. These genotyping results contrasted with the surveillance study where HAdV-3 and HAdV-7 were most frequently determined when an all-age group was studied. The current surveillance finding was highly consistent with the prior epidemiological investigation performed in China, where HAdV-3 and HAdV-B7 were most frequently detected among acute respiratory distress syndrome patients[15-18].

We found that school-related outbreaks were associated with the lowest attack rate, suggesting either a less confined space that limited the transmission or the lower transmission capacity relate to different HAdV types. We also revealed a different situation from that shown in other countries, for example, in the American troops, HAdV-4, HAdV-B7 and HAdV-B14 act as the predominant strains sequentially isolated from the outbreaks[7, 19-21]. HAdV vaccination program against these two-outbreak related genotypes in this high-risk population is urgently needed. Our meta-analysis showed that overall attack rate of adenovirus infection in outbreaks was estimated by 15.91% (95% CI: 13.85–17.98), which is comparable with the outbreak among college students in Pennsylvania, USA, of which a 15% (44/288) attack rate was reported based on the test of nasopharyngeal swabs for HAdV[22].

Our study for the first time revealed ~~an obvious~~ seasonal pattern for the outbreak events. The school outbreaks occurred mostly at the beginning of new school years, while the military outbreaks occurred at the recruit training seasons. A Korean study from 2013 to 2018 showed that HAdV was the most frequently detected respiratory virus in military recruits (6646/14630, 45.4%)[23]. HAdV has been implicated in

over half of the febrile respiratory illness cases reported at recruit training center clinics.

A total of 17 respiratory adenovirus infection types have been reported in China, mainly HAdV-3, HAdV-7 and HAdV-55. Outbreaks were dominated by HAdV-7 and HAdV-55, while other types included type HAdV-3, HAdV-4 and HAdV-14. The main types of outbreaks in different settings differ, with school outbreaks having more types, including HAdV-7, HAdV-55, HAdV-3, HAdV-4 and HAdV-14, with HAdV-3 and HAdV-7 predominating; swimming pool outbreaks having mainly HAdV-3, HAdV-7 and HAdV-4, mainly in summer; hospital outbreaks and military outbreaks having mainly HAdV-7 and HAdV-55. The types of outbreaks vary by age group, with children predominantly HAdV-7, HAdV-4, adults predominantly HAdV-7, HAdV-55, and adolescents with more types of outbreaks, including HAdV-7, HAdV-55, HAdV-3, HAdV-4, and HAdV-14. There are more types detected in adenovirus surveillance, including HAdV-3, HAdV-7, HAdV-2, HAdV-1, HAdV-55, HAdV-5, etc. The most common types are HAdV-3 and HAdV-7 and there is an increasing trend year-on-year, which may be related to the increasing number of infections and rising levels of surveillance. Differences in the main types in outbreak investigations and surveillance reports suggest that HAdV-55 is more infectious and more likely to lead to outbreaks, whereas HAdV-3 is less infectious than HAdV-55 and HAdV-7 and is easily detected during hospital surveillance. This may be because HAdV-55 is more symptomatic, more contagious and more likely to be reported. A study has shown that HAdV-7 replicates more robustly than HAdV-3, and promotes an exacerbated cytokine response, causing a more severe airway inflammation[24].

Overall, adenovirus circulates throughout the year, with slightly higher numbers reported during the summer and winter. Previous studies have shown that HAdV detection rates are positively correlated with the monthly mean temperature and sunshine duration, and negatively correlated with wind speed.[25] In our study, the main prevalent adenovirus types in China were HAdV-3, HAdV-7 and HAdV-55,

with other more frequent types such as HAdV-2, HAdV-4, HAdV-1 and HAdV-5. The main outbreak sites were schools and the military, with higher detection rates in the south than in the north. The prevalent typing varies between countries and regions, and a surveillance report in the United States from 2003–2016 showed that the common typing in the United States was HAdV-3, HAdV-2, HAdV-1, and HAdV-4[26]. An epidemiologic study based on HAdV molecular typing was conducted in the Korean military from January 2013 to April 2014, and HAdV-55 (42·0%) was the most frequently identified strain, followed by HAdV-4 (13·0%), HAdV-5 (1·4%), and HAdV-6 (1·4%)[27]. HAdV-55 is a relatively recently identified pathogen, which evolved from recombination between adenovirus 11 and 14[28, 29]. It was initially described as serotype 11a and was later re-labeled as HAdV-55 because of its recombinant genome[29]. HAdV-55 is mainly found in China and Korea[26].

The clinical presentation varies by age group and by type. Most adenovirus respiratory infections are light to moderate and self-limited; however, sometimes they may cause life-threatening conditions, comorbidities, and serious sequelae. The rate of pneumonia is higher in the children than in other age groups and, in addition, the children is more likely to have breathing difficulties. Attention should be paid to the occurrence of adenovirus pneumonia in children. The main symptoms are fever and tonsil enlargement in adolescents while the main symptoms are cough and tonsil enlargement in adults. Adolescents and adults have a stronger immune system and the symptoms are mainly mild. Compared to other types, HAdV-55 is more likely to cause pneumonia and has a high prevalence in the military camps, so attention should be paid to the prevention and control of adenovirus in the military camps.

There were two main limitations to this study. First, inherent to systematic reviews, our study was influenced by publication bias. Most outbreaks are reported by passive surveillance which may not be as comprehensive as in active surveillance, and also subject to reporting biases. Secondly, as our data came from different studies, and did not have the same variables. This may have increased the likelihood of

misclassification bias also limited the number of variables that can be used for analysis.

Despite of these limitations, we have disclosed the incidence of HAdV and the major genotypes that differed over time, by location, and by characteristics such as patient age. Comparing and contrasting the features across diverse settings can help to attain an enhanced epidemiological and clinical understanding of human infections with different HAdV types, and thus enhancing the accuracy of HAdV surveillance systems.

Author Contributors

The author contributions are as follows. LQF and WL conceived, designed, and supervised the study. MCL, QX, TTL, TW, BGJ and CLL searched, screened, and assessed the publications. MCL and TTL created data extraction forms and extracted and analyzed the data. QX, TW, BGJ, CLL and XAZ helped with checking data and constructed the figures. QX, TW, BGJ and CLL provided statistical and clinical expertise in data analysis. MCL and QX wrote the drafts of the manuscript. MCL and QX interpreted the findings. LQF and WL commented on and revised drafts of the manuscript. All authors read the manuscript, provided feedback, and approved the final version.

Data Availability Statement

Data will be made available upon request made to the corresponding author.

Declaration of interests

We declare no competing interests.

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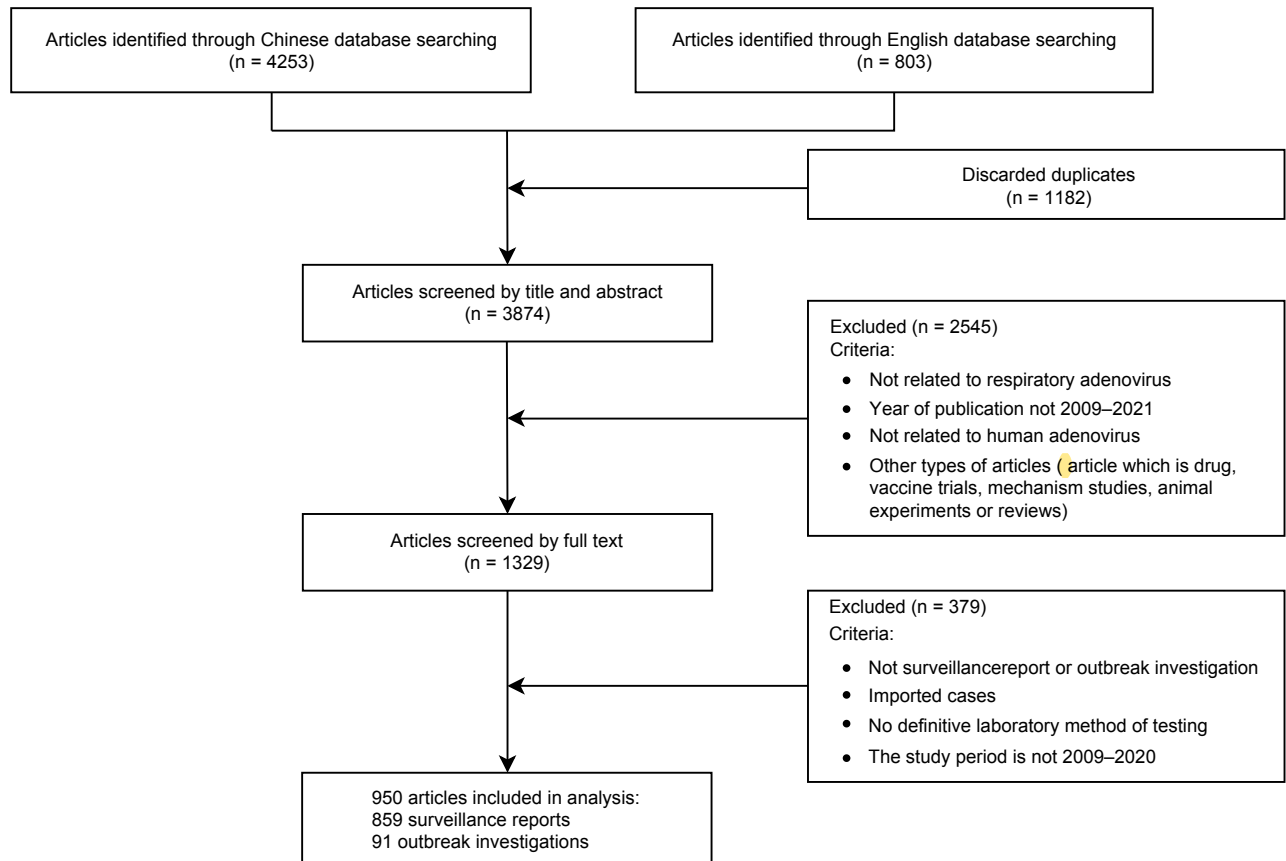
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Figure 1



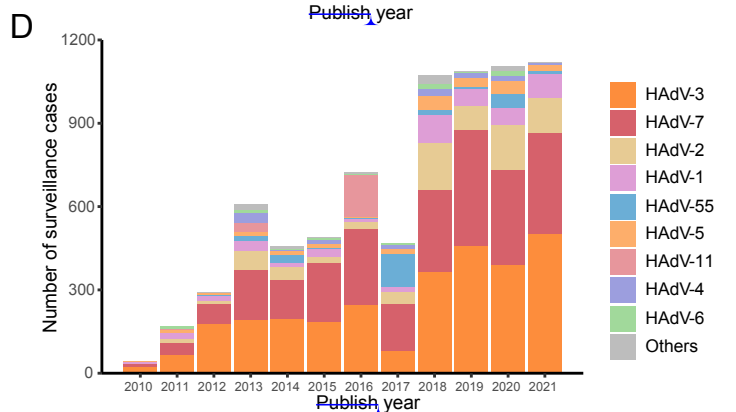
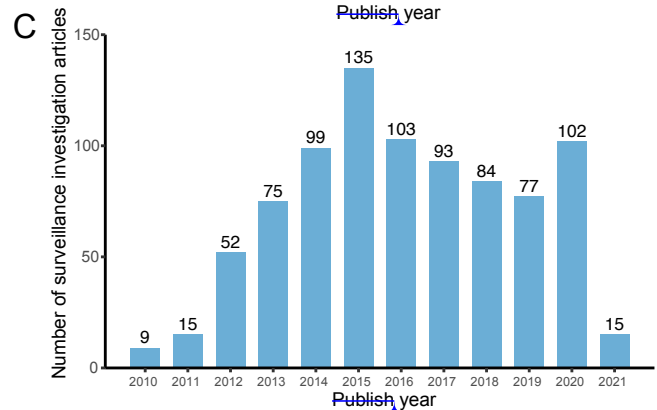
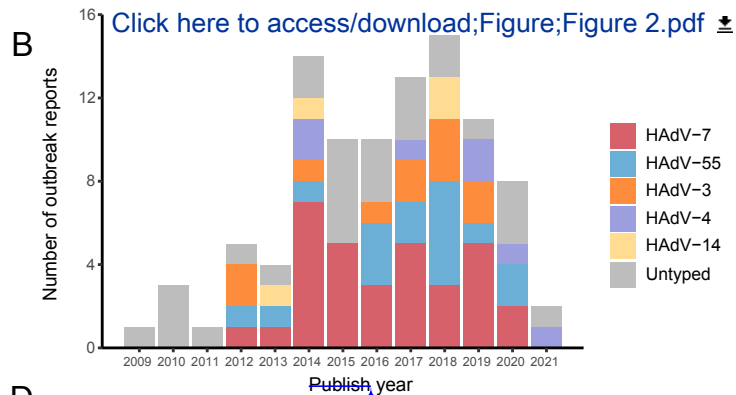
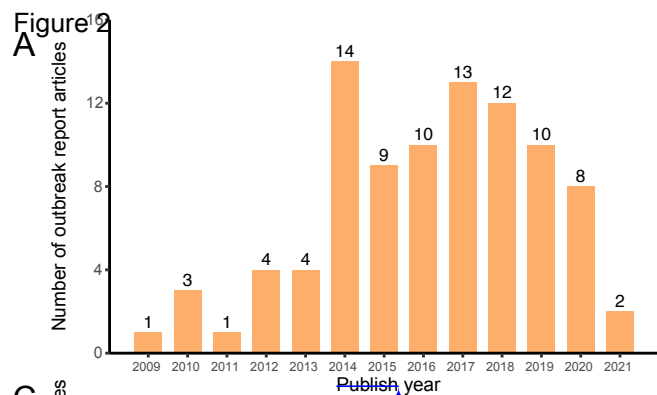


Figure 3

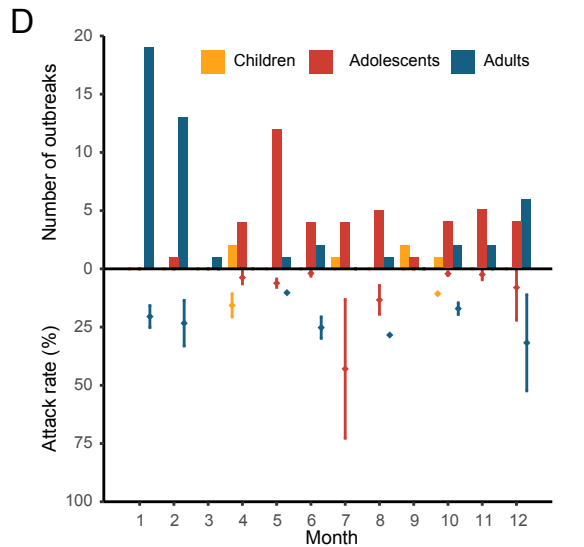
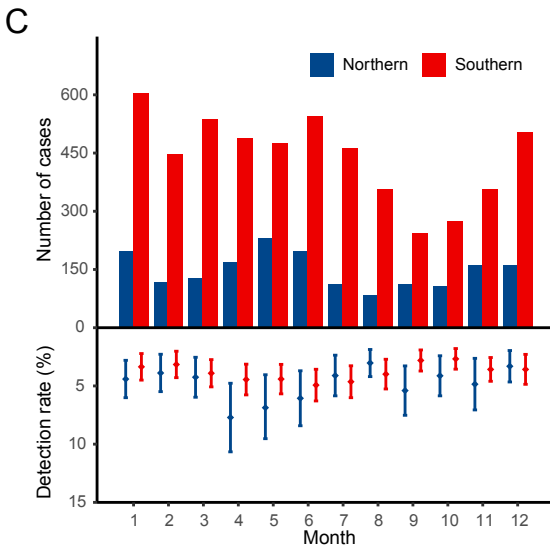
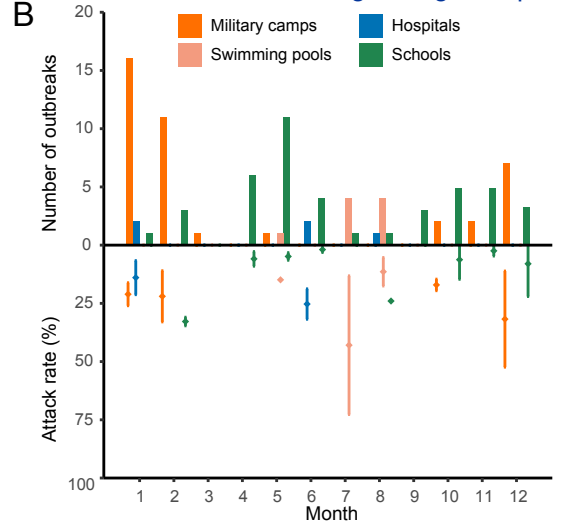
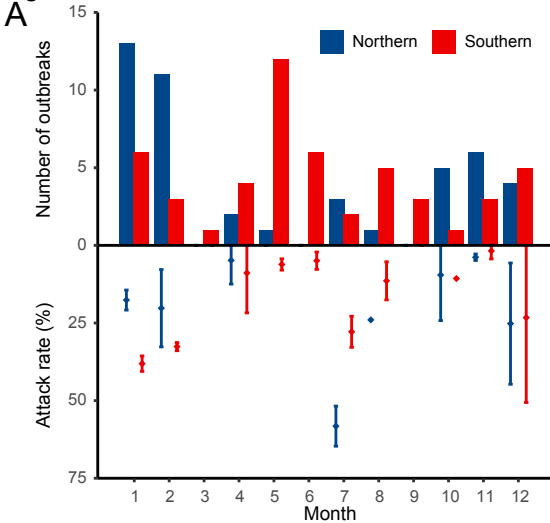
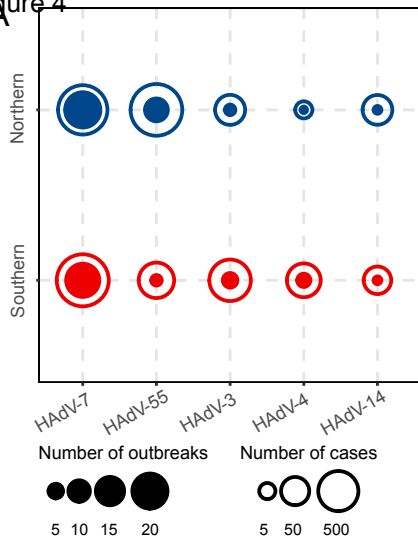


Figure 4



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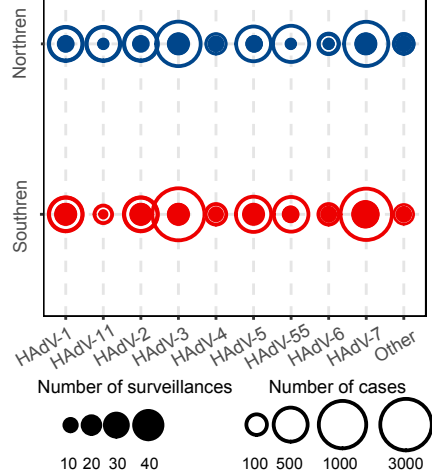


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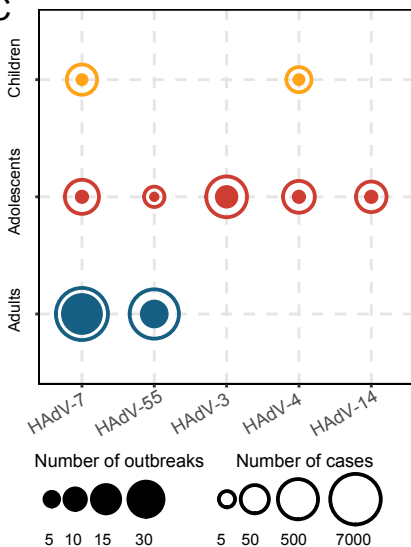


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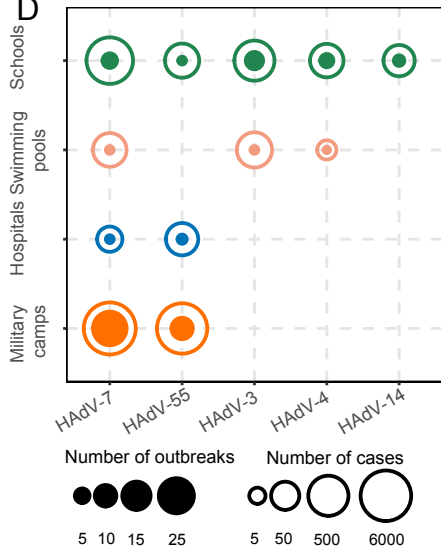
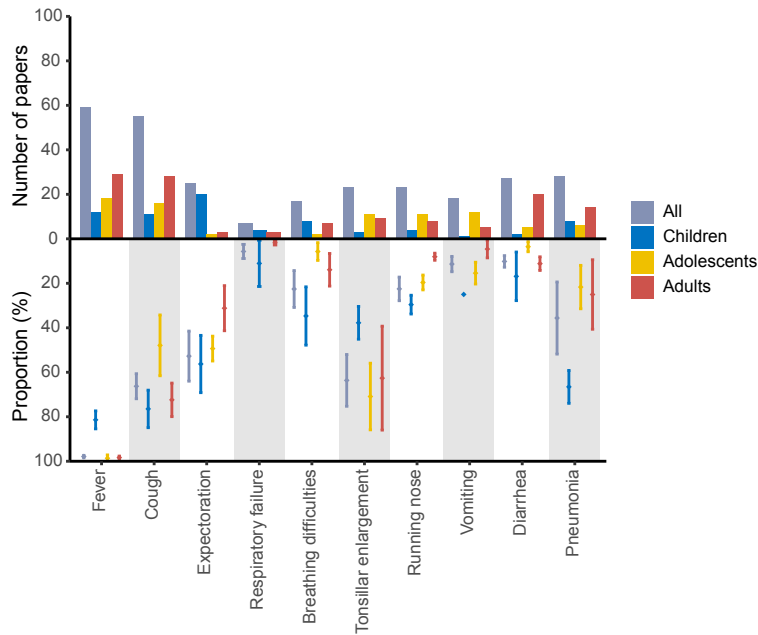
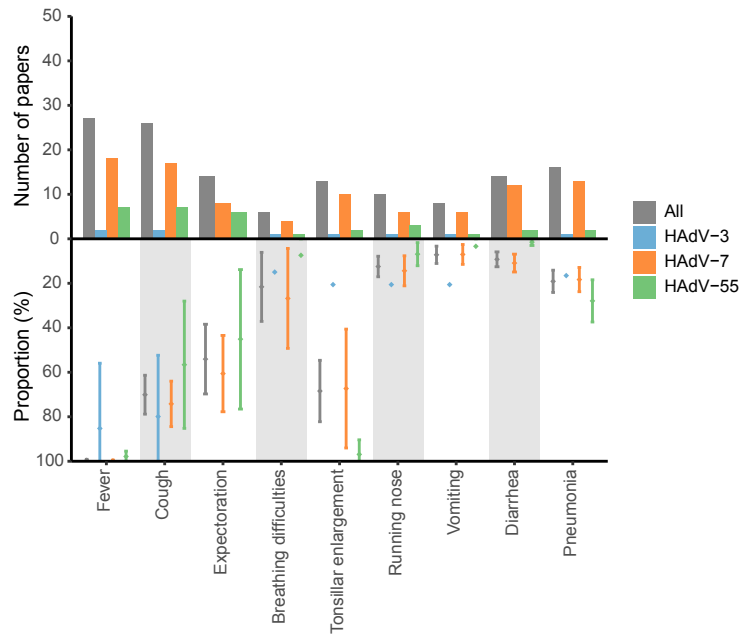


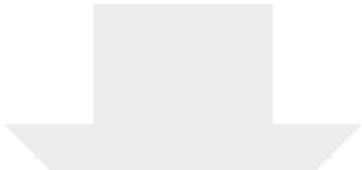
Figure 5




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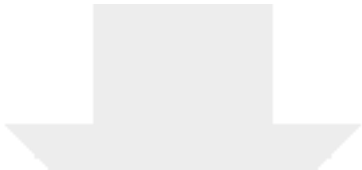


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