Contents lists available at ScienceDirect



International Journal of Infectious Diseases



journal homepage: www.elsevier.com/locate/ijid

Epidemiology of respiratory viruses among children during the SARS-CoV-2 pandemic: A systematic review and meta-analysis^{†‡}

Leonie K. Dallmeyer¹, Marit L. Schüz¹, Paraskevi C. Fragkou^{2,4}, Jimmy Omony³, Hanna Krumbein¹, Dimitra Dimopoulou^{4,5}, Konstantina Dimopoulou⁶, Chrysanthi Skevaki^{1,4,*}

¹ Institute of Laboratory Medicine, Universities of Giessen and Marburg Lung Centre (UGMLC), Philipps University of Marburg, German Centre for LUNG Research (DZL), Marburg, Germany

² First Department of Critical Care Medicine & Pulmonary Services, Evangelismos General Hospital, National and Kapodistrian University of Athens, Athens, Greece

³ Institute for Asthma and Allergy Prevention (IAP), Helmholtz Zentrum Munich, German Research Centre for Environmental Health (GmbH), Munich, Germany

⁴ European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Respiratory Viruses (ESGREV)

⁵ Second Department of Pediatrics, "Aghia Sophia" Children's Hospital, Athens, Greece

⁶ Department of Gastroenterology, Hippokration General Hospital, Athens, Greece

ARTICLE INFO

Article history: Received 14 August 2023 Revised 3 October 2023 Accepted 30 October 2023

Keywords: Epidemiology Children Respiratory viruses Prevalence Pandemic

ABSTRACT

Objective: This meta-analysis aimed to assess the prevalence of respiratory viruses among children under the special conditions of the COVID-19 pandemic.

Methods: Five databases were systematically searched to assess the pooled prevalence of various respiratory viruses in different age groups, regions, seasons, and in patients with and without confirmed SARS-CoV-2 coinfection. Moreover, we looked at the virus distribution in the first and second half of the pandemic and countries with distinct economic status. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed, and the systematic review was registered on PROSPERO (CRD42022379297).

Results: Enterovirus/rhinovirus and human respiratory syncytial virus (HRSV) were the most prevalent pathogens among children. The prevalence of HRSV increased in the second half of the pandemic. The prevailing viruses vary according to the SARS-CoV-2-coinfection status, season, region, and country's economic status.

Conclusion: This meta-analysis shows the epidemiology of respiratory viruses other than SARS-CoV-2 in children aged 0 to 12 years during the COVID-19 pandemic. Because major events, such as a pandemic, can alter epidemiology patterns, it is important to know them to improve health education measures, develop vaccines and medicines for vulnerable groups, as a guide for prevention strategies, and help with clinical decisions.

© 2023 The Authors. Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

Introduction

On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a pandemic [1]. To prevent further spread of the virus many countries introduced public health measures such as closure of educational institutions, mandatory quarantine, stayat-home restrictions, and personal protective equipment like face masks [2]. Due to similar transmission routes, it seems plausible to assume that these measures also influenced the spread and distribution of other viruses.

Respiratory viral infections represent a leading cause of pediatric morbidity and mortality around the globe [3,4]. However, unusual for respiratory infections, children were less severely affected by SARS-CoV-2 than adults [5]. Therefore, this systematic review and meta-analysis assessed the distribution of respiratory viruses in the context of the COVID-19 pandemic to examine how

 $^{^{\}dagger}$ L. K. Dallmeyer and M. L. Schüz contributed equally to this work and shared first authorship.

[‡] P. C. Fragkou and J. Omony shared second authorship.

^{*} Corresponding author.

E-mail address: chrysanthi.skevaki@uk-gm.de (C. Skevaki).

https://doi.org/10.1016/j.ijid.2023.10.023

^{1201-9712/© 2023} The Authors. Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

International Journal of Infectious Diseases 138 (2024) 10-18

SARS-CoV-2 may have changed the spectrum of respiratory viruses among children. In particular, we looked at the prevalence in different geographic regions, in age groups, and during the seasons of the year.

Our results can help to understand current infection patterns, especially under the specific conditions of the pandemic. In addition, our findings may be useful as a basis for clinical decisionmaking and a guide for prevention strategies for children in future outbreaks.

Methods

For this systematic review and meta-analysis, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (2020) [6] and developed a protocol, published under the registration number CRD42022379297 on PROSPERO.

Search strategy and selection criteria

The databases PubMed, The Cochrane Library, Embase, Scopus, and Web of Science were systematically searched for studies published between 1 November 2019 and 1 March 2023 in English, German, or Spanish language by two independent researchers (LD, MS) on 1 March 2023. The search terms consisted of four concepts including different combinations of terms related to: "epidemiology", "respiratory viruses", "children" and "pandemic".

Additional search included inspecting reference lists of previously published studies and systematic reviews and a manual Google search with terms like: "influenza", "HRSV", "children", "COVID-19 pandemic", "surveillance", "nonpharmaceutical interventions", "prevalence" and was carried out on 3 March 2023. A detailed search strategy description is available in Supplementary Tables S1 and S2.

All studies identified by database and manual searches were listed by author, year, title, journal, and DOI and duplicates were removed through manual screening. Four independent reviewers (LD, MS, HK, DD) screened the titles and abstracts for the eligibility process. The full text of the studies that passed the first screening process were screened by five reviewers (LD, MS, HK, DD, KD). Discrepancies were identified and addressed based on consensus decision by the reviewers. The studies had to meet the following inclusion criteria: a test was performed for at least one respiratory virus except SARS-CoV-2, extractable data for children (12 years old or less), at least part of the data was collected after November 2019 and the studies report primary data with a minimum number of 50 participants. A more detailed description of the PICOS can be found in Supplementary Table S3.

Data extraction

Before data extraction, the included studies were screened for possible data overlap by sorting them using study location and author. For a suspected overlap, a reviewer (LD) contacted the authors for more detailed information. In cases where a data overlap was confirmed by the author or could not be excluded, one of the studies in question was excluded from the analysis. The detailed decision-making process is shown in Supplementary Table S4.

Two reviewers (LD, MS) performed data extraction from all included studies using a predefined form to extract the following data: title, author, publication date, journal, study type, location, study sites, number of participants, time period, season, testing method, symptoms, comorbidities, gender distribution of participants, age of participants, number of tests and test results, SARS-CoV-2-coinfection status. Authors were contacted if important information or data were missing.

Nomenclature and definitions

Terms and abbreviations for virus species are defined according to the International Committee on Taxonomy of Viruses [7]. The seasonal division was determined by the meteorological periods (Northern Hemisphere: winter includes December to February, spring March to May, summer June to August, autumn September to November, Southern Hemisphere: winter includes June to August, spring September to November, summer December to February, autumn March to May). The hemispheres are classified according to the World Population Review organization [8]. The geographic regions are based on the WHO definition [9].

First and second half of the SARS-CoV-2 pandemic were defined according to our search period in November 2019 to June 2021 (first half) and July 2021 to March 2023 (second half). The classification of the countries economic status follows the definition of the World Bank Atlas method, calculating gross national income (low-income economies are defined as those with a gross national income of \$1085 per capita or less in 2021, lower-middleincome economies with a gross national income between \$1086 and \$4255, upper middle-income economies between \$4256 and \$13,205 and high-income economies with \$13,205 or more) [10].

Risk of bias assessment

Risk of bias assessment was performed by two reviewers (LD, MS) independently using the Newcastle-Ottawa Quality Assessment Scale (NOS) for cross-sectional studies [11] and for cohort studies [12]. According to their score, the studies were ranked in low (<5 points), moderate (5-7 points), and high (>7 points) quality studies. The points can be achieved in the categories of selection, comparability, and outcome.

For the quality of evidence assessment, the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) method was used by two independent authors (LD, MS) to rate the domains' risk of bias, imprecision, inconsistency, indirectness, and publication bias for the main outcome [13].

Outcomes

The main outcome was the pooled prevalence of various respiratory viruses during the SARS-CoV-2 pandemic. We analyzed the epidemiology of the viruses in different age groups, geographical regions, seasons and in patients with and without a SARS-CoV-2-coinfection. We also assessed the virus distribution in the first and second half of the pandemic and in countries with low, lowermiddle, upper-middle, and high-income.

Statistical analysis

Statistical analysis was performed with the R Core Team (version 4.1.3) software [14] and "meta" and "metafor" packages were used [15]. Heterogeneity between studies was evaluated using l² statistic. In all models, meta-analysis was performed using the random-effects regression approach. We used "metaprop" to estimate the pooled effects of the prevalence. For each virus, we separately performed meta-analysis using different age groups of participants, SARS-CoV-2-coinfection status, regional and season of the year, and time distribution. We pooled studies using the inverse method and the logit-transformation approach was used to estimate the pooled prevalence with the Clopper-Pearson 95% confidence intervals (Cls). In the forest plots, we summarized results from the pooled effect estimates of the prevalence and precision measures. Funnel plots were used to inspect the distribution of studies, and quantitative assessment of publication bias was performed using Eggers' regression test [16]. Statistical significance was set at P < 0.05.

Results

Database search and screening

The database search yielded 14,906 studies, of which 6673 were identified as duplicates. The additional search, including manual internet search on Google and literature search using references of previously published, resulted in nine additional studies. Based on the title and abstract screening of the remaining 8233 studies, 564 studies were selected for full-text reading. Relating to predefined exclusion criteria, 486 studies were excluded. Most frequent reasons for exclusion were the age of the study population, the study period, and the missing number of performed tests in the age group of interest (See Supplementary Table S5). A total of 78 studies were included in the meta-analysis. [Supplementary references 1–78] (Figure 1).

Characteristics of included studies

All included studies can be categorized as observational studies, with cross-sectional studies being the most common study type (35/78). In total, 45 were single-centered studies, whereas 33 were performed in multiple centers. The studies were conducted in 33 different countries and one in an international setting. The European region was the best represented (35/78) followed by the Western Pacific region (22/78). An overview of the proportion of the different countries and region are shown in Figure 2. Most of the examined countries were high-income economies (45/78), 26 were upper-middle-income economies, four lower-middle, and two lower-income economies.

Viral testing was performed using polymerase chain reaction (PCR) in most studies, and rapid antigen testing in 14 studies. The testing specimens were nasopharyngeal swab/washing/aspirate, oropharyngeal swab, bronchoalveolar lavage, lung puncture aspirate, and tracheal or bronchial aspirate. Most of the included studies researched patients with acute respiratory symptoms, and only one study analyzed asymptomatic patients exclusively. Patients with confirmed SARS-CoV-2 infection were screened for viral coinfection in six studies. The larger proportion of studies were conducted in the first half of the pandemic (Supplementary Figure S1).

Most tests were performed for influenza virus (IV) (306,323 subjects), followed by human parainfluenza virus (HPIV) (281,614) and human respiratory syncytial virus (HRSV) (193,254).

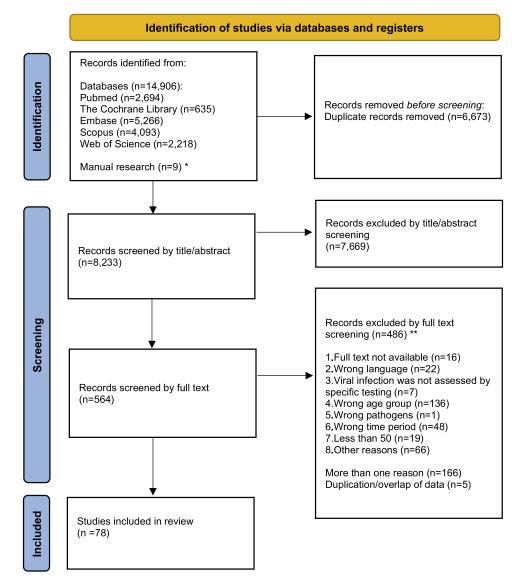


Figure 1. PRISMA flow diagram

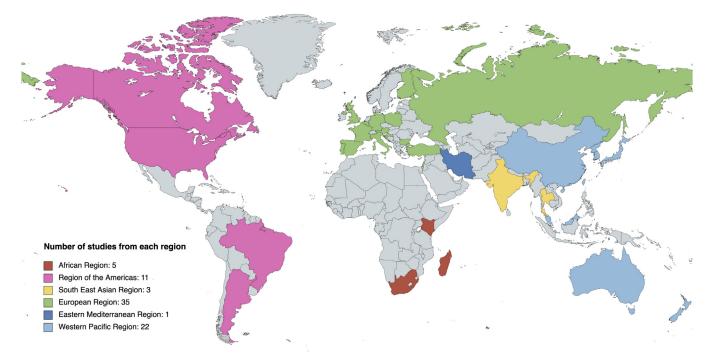


Figure 2. Proportion of WHO regions and countries among all included studies, except for one that was conducted in an international setting. The legend shows the number of studies performed in each region.

Only one study tested for Middle East respiratory-syndromerelated coronavirus (MERS-CoV) (93), human cytomegalovirus (HCMV) (93), and herpes simplex virus (HSV) (93).

The risk of bias assessment was performed using the NOS for cross-sectional studies and cohort studies. For 22 studies the quality was rated as high and 56 were graded as moderate. The characteristics of all included studies are summarized in Supplementary Table S6.

Overall pooled prevalence

The analysis showed that enterovirus/rhinovirus (EV/RV) (26.06%, 95% CI: 21.59-31.09%) and HRSV (24.19%, 95% CI: 20.48-28.33%) were the most prevalent viruses since the beginning of the pandemic in the pediatric age group. The prevalence of HPIV (5.82%), human bocavirus (HBoV) (5.28%), seasonal human coronavirus (HCoV) (4.47%), human adenovirus (HAdV) (3.65%) and IV (3.41%) was distinctly lower. Human metapneumovirus (HMPV) (2.90%) was the least frequent virus (Figure 3A). The quality of evidence was rated as moderate for IV, HCoV, HAdV, EV/RV, and HMPV and low for HPIV, HRSV, and HBoV, based on GRADE (See Supplementary Table S7).

For the various virus subtypes, influenza A (IAV) was found to be more frequent than influenza B (IBV). Among the HPIV species, HPIV-3 was most common. Looking at the prevalence of HCoV, human coronavirus NL63 (HCoV_NL63) was the most prevalent virus subtype (Figure 3B).

Prevalence in the first and second half of the pandemic

When comparing the prevalence of different viruses in the first and second half of the pandemic, it is noticeable that EV/RV (30.03%, 95% CI: 20.56-41.58%) was the most prevalent virus in the first half and HRSV (56.15%, 95% CI: 37.42-73.27%) in the second. Overall, the prevalence of IV, HRSV, and HMPV increased, while that of HPIV, HAdV, and EV/RV decreased (Figure 4, Supplementary Figure S2).

The test of subgroup differences showed statistically significant results for IV, HAdV, and HRSV.

Age group distribution

Looking at the different age groups, children from 0 to 1 year old were the most affected by respiratory viruses. In this age group, the most prevalent pathogen was EV/RV (35.83%, 95% CI: 23.39-50.52%), closely followed by HRSV (35.22%, 95% CI: 27.12-44.26%). This age group was less affected by IV and HAdV, which were more prevalent in the older age groups (Figure 5A). IAV occurred more frequently than IBV in both age groups (Figure 5B).

For the age group of 7 to 12 years old, we could only include two studies that investigated IV, but the prevalence of IV in both studies was remarkably high (32.63%, 95% CI: 28.89-36.61%).

If we are looking at the infants only and divide them into the age groups of 0 to 3 months and 4 months to 1-year-old children, we saw that the IV and HRSV prevalence was higher in the 4 months to 1-year-old population (0-3 months: IV 0.27%, 95% CI: 0.03-2.19%, HRSV 11.41%, 95% CI: 4.81-26.69%, 4 months to 1 year: IV 3.78%, 95% CI: 0.29-34.38%, HRSV: 22.18%, 95% CI: 13.86-33.55%) (Supplementary Figure S3). The statistical analysis showed that the difference in prevalence between the age groups was statistically significant for IV, HPIV, HRSV, and HMPV (P < 0.01).

Viral coinfections in SARS-CoV-2 patients

The analysis found no statistically significant correlation between pooled prevalence and SARS-CoV-2-coinfection status, except for HBoV (P < 0.01). For HPIV, HAdV, HBoV, and HMPV the prevalence was higher in the group with confirmed SARS-CoV-2infection. HCoV and HRSV were more frequent in the non-COVID group. EV/RV had the highest prevalence in both groups (COVID-19-coinfection group: 25.82%, 95% CI: 10.09-51.90%, non-COVID-19 group: 26.84%, 95% CI: 22.21-32.04%). The prevalence of both groups can be found in Supplementary Figure S4. А

Virus category	# subjects (# studies)		Pooled prevalence (%) [95% Cl]	Heterogeneity (I-Squared)	P-value
Enterovirus / rhinovirus	34550 (36)	⊢ 		99%	<0.01
Human respiratory syncytial virus	193254 (57)	⊢ ∎	24.19 [20.48; 28.33]	99%	<0.01
Human parainfluenza virus	281614 (30)	⊦∎⊣	5.82 [4.51; 7.48]	99%	<0.01
Human bocavirus	7677 (14)	⊢∎−−1	5.28 [3.68; 7.50]	85%	<0.01
Seasonal human coronaviruses	14736 (20)	⊢∎I	4.47 [3.16; 6.30]	93%	<0.01
Human adenovirus	84365 (32)	HB-1	3.65 [2.60; 5.11]	98%	<0.01
Influenza virus	306323 (44)	H∎-1	3.41 [2.46; 4.72]	100%	<0.01
Human metapneumovirus	27167 (23)	H∎-I	2.90 [2.02; 4.14]	93%	<0.01
		0 2.5 5 7.5 10 12.5 15 17.5 20 22.5 25 27.5 Pooled prevalence (%)	5 30 32		

Pooled prevalence (%)

В

Virus category	# subjects (# studies)		Pooled prevalence (%) [95% Cl]	Heterogeneity (I-Squared)	P-value		
Influenza viruses							
Influenza A virus	279052 (23)	┝╼╌┥	2.43 [1.74; 3.37]	99%	<0.01		
Influenza B virus	204397 (22)	+■ -1	1.39 [0.90; 2.15]	99%	<0.01		
Human parainfluenza viruses							
Human parainfluenza virus 3	10562 (11)	۲ ۰۰۰ ه	4.86 [2.82; 8.23]	95%	<0.01		
Human parainfluenza virus 4	1303 (6)	F=1	1.14 [0.44; 2.94]	56%	0.04		
Human parainfluenza virus 1	9691 (8)	H = 1	0.96 [0.30; 3.01]	93%	<0.01		
Human parainfluenza virus 2	7880 (5)		0.36 [0.06; 2.01]	78%	<0.01		
HCoVs							
HCoV NL63	847 (5)	۲. <u>۲. ۲. ۲. ۲. ۲. ۲. ۲. ۲. ۲. ۲. ۲. ۲. ۲. ۲</u>	6.04 [2.57; 13.54]	82%	<0.01		
HCoV OC43	1265 (6)	⊢_∎ i	2.10 [0.82; 5.24]	79%	<0.01		
HCoV 229E	245 (3)	⊢∎ i	0.84 [0.21; 3.31]	0%	0.93		
HCoV HKU1	148 (2)		0.69 [0.10; 4.73]	0%	0.79		
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 Pooled prevalence (%)							

Figure 3. Pooled prevalence of respiratory viruses during the pandemic. A: Pooled prevalence of different respiratory viruses. B: Pooled prevalence of different virus species.

Regional distribution

Studies from the African region (AFR) showed the highest prevalence for most viruses. EV/RV, in particular, had a prevalence of 41.41% (95% CI: 27.59-56.73%). The least frequent virus in this region was HCoV (3.00%, 95% CI: 0.74-11.32%).

In the region of the Americas (AMR) EV/RV (33.88%, 95% CI: 21.36-49.15%) was the most frequently detected pathogen followed by HRSV (21.00%, 95% CI: 13.78-30.67%). The lowest prevalence in this region was HMPV (1.16%, 95% CI: 0.63-2.14%).

In the South-East Asian region (SEAR) the highest prevalence had HRSV (38.38%, 95% CI: 34.85-42.04%). Compared to the other

Virus category	# subjects (# studies)		Pooled prevalence (%) [95% CI]	Heterogeneity (I–Squared)	Subgroup diff. (P–value)
Influenza virus First Second	61274 (24) 1056 (4)	■-1 +=1	2.30 [1.21; 4.36] 7.49 [3.87; 14.01]	99% 75%	0.01
Human parainfluenza virus First Second	13779 (15) 529 (3)	¦æ- jæl	4.76 [2.89; 7.73] 2.86 [1.73; 4.69]	96% 0%	0.16
Human adenovirus First Second	48305 (20) 529 (3)	=- =-	4.33 [2.63; 7.06] 1.37 [0.53; 3.50]	98% 29%	0.03
Human respiratory syncytial virus First Second	62953 (29) 14107 (8)	⊦ ≖	12.12 [7.81; 18.33] 56.15 [37.42; 73.27]	99% 99%	<0.01
Enterovirus / rhinovirus First Second	13286 (20) 1116 (4)	⊢ -	30.03 [20.56; 41.58] 14.08 [6.22; 28.82]	99% 95%	0.07
Human metapneumovirus First Second	6872 (13) 529 (3)	■ ■ 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 74 Packed providence (%)	2.64 [1.56; 4.44] 3.30 [1.38; 7.70]	88% 57%	0.67

Pooled prevalence (%)

Figure 4. Pooled prevalence of respiratory viruses for which more than two studies were available for the first and second half of the pandemic.

regions SEAR had the highest IV prevalence (15.47%, 95% CI: 6.53-32.41%).

In the European region (EUR) HRSV (33.55%, 95% CI: 26.95-40.85%) and EV/RV (25.96%, 95% CI: 21.12-31.45%) were the most frequently detected viruses, while IV (2.89%, 95% CI: 1.48-5.59%) was the least detected one. The predominant subtype was IAV (2.31%, 95% CI: 0.76-6.83%, IBV: 0.96%, 95% CI: 0.42-2.22%).

In the Western Pacific region (WPR) the highest prevalence was EV/RV (23.60%, 95% CI: 9.31-48.18%). The least detected virus was HAdV (1.99%, 95% CI: 1.02-3.83%). Influenza A and B were almost equally prevalent (IAV: 1.68%, 95% CI: 1.19 2.36, IBV: 1.38%, 95% CI: 0.73-2.60%).

There are no comparable results for the Eastern Mediterranean region (EMR).

The test for subgroup differences in the distribution of the prevalence of the viruses was significant for IV, IAV, IBV, HPIV-3, HAdV, HRSV, EV/RV, and HMPV (Supplementary Figure S5).

Distribution in countries with different country economic status

Subgroup analysis of countries with different economic status showed that IV had a higher prevalence in low-income economies (LIE) and low-middle-income economies(LMIE) (LIE: 6.53%, 95% CI: 5.54-7.68%, LMIE: 10.31%, 95% CI: 3.88-24.66%) than in upper-middle economies (UMIE) and high-income economies (HIE), (UMIE: 2.38%, 95% CI: 1.43-3.93%, HIE: 3.16%, 95% CI: 1.64-6.01%). In UMIE EV/RV (30.95%, 95% CI: 21.41-42.45%) was most prevalent and in HIE HRSV (30.54%, 95% CI: 25.44-36.16%) had the highest prevalence.

Statistically significant association between the country economic status of the countries and the viral prevalence was found for IV, IAV, IBV, HAdV, EV/RV, and HMPV (Supplementary Figure S6).

Seasonal distribution

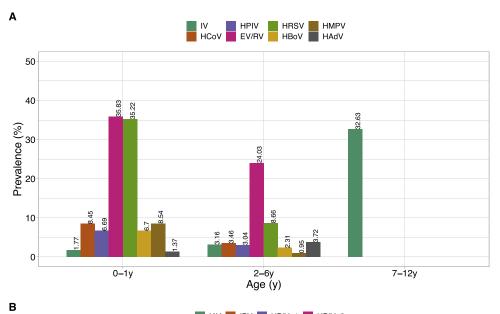
Comparing the seasons of the year, the test for subgroup differences showed a statistically significant difference between the prevalence of viruses for subjects with IV, HCoV, HAdV, HRSV, and EV/RV.

Studies showed that in the winter the most prevalent virus was IV (50.43%, 95% CI: 18.50-82.01%), while HRSV (11.99%, 95% CI: 4.26-29.43%) and EV/RV (10.73%, 95% CI: 1.95-42.08%) were less common during this season. In spring and summer, EV/RV (spring: 16.60%, 95% CI: 5.15-42.18%, summer: 47.01%, 95% CI: 29.21-65.61%) had the highest prevalence. HRSV was most detected in autumn with a prevalence of 54.89% (95% CI: 31.70-76.13%) (Supplementary Figure S7).

Discussion

Our meta-analysis demonstrated a high prevalence of respiratory viruses besides SARS-CoV-2 in children up to 12 years of age during the COVID-19 pandemic. Overall, EV/RV (26.06%) and HRSV (24.19%) were the most common pathogens, while HMPV (2.90%) had the lowest prevalence. Other studies have already reported high EV/RV prevalence during the pandemic and found that social distancing measures in schools did not adequately prevent the transmission of human rhinovirus (HRV) [17]. The HRSV activity changed during the pandemic. At the beginning of the pandemic and with the introduction of infection control interventions a decrease in HRSV activity was seen, but the relaxation of measures in 2021 was accompanied by HRSV return [18]. This fits with our results showing that the prevalence of HRSV increased from 12.12% in the first half to as high as 56.15% in the second half of the pandemic.

The age group analysis showed that children from 0 to 1 year old were the most affected by respiratory viruses, especially by



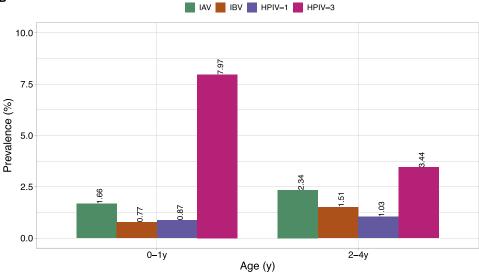


Figure 5. Virus prevalence across age groups.

Abbreviations: IV, influenza virus; HCoV, seasonal human coronavirus; HPIV, human parainfluenza virus; EV/RV, enterovirus/rhinovirus; HRSV, human respiratory syncytial virus; HBoV, human bocavirus; HMPV, human metapneumovirus; HAdV, human adenovirus.

B: Pooled prevalence of different respiratory virus species in two age groups (0-1 year; 2-6 years).

Abbreviations: IAV, influenza A virus; IBV, influenza B virus; HPIV-1, human parainfluenza virus 1; HPIV-3, human parainfluenza virus 3.

Due to the data situation, not all viruses are shown in all age groups.

EV/RV and HRSV. IV and HAdV were detected least frequently. One possible explanation could be that young children probably did not fully benefit from prevention measures, as face masks were not recommended among children under one year of age. [Supplementary references 24] Studies suggest that the possibility exists that the viral interference between influenza and SARS-CoV-2 could have led to the decrease in influenza infections [19]. Another explanation for the low IV prevalence in the age group 0 to 1 year could be the protection by maternal antibodies, which defend infants of vaccinated mothers [20].

Because of the high number of EV/RV and HRSV infections, an important question is how infections can be prevented to avoid associated morbidity. Especially for vulnerable children such as premature infants, the most important components are hygiene, passive immunization, and breastfeeding. In the future, it is likely that other preventive measures will be added, such as active immunization of children or maternal vaccination during pregnancy [21].

Older children can protect themselves through hygiene measures like hand washing or disinfection, which also reduce the likelihood of transmission [22].

The subanalysis of the SARS-CoV-2-coinfection group and the non-coinfection group found no statistically significant correlation between pooled prevalence and SARS-CoV-2-coinfection status, except for HBoV. There is no clear direction on whether one of the groups has a higher risk for respiratory viral infection. Especially rhinoviruses were equally frequent in both groups. However, studies have shown that particularly young children are more often affected by coinfection [Supplementary references 12],[23].

The regional distribution showed that EV/RV had the highest prevalence in AFR, AMR, and WPR while HRSV was the most common virus in EUR and SEAR. We had no comparable results for the EMR due to the low number of published studies from this region. The differences in the distribution of other viruses could be related to different timing of the pandemic depending on the geographi-

A: Pooled prevalence of different respiratory viruses in three age groups (0-1 year, 2-6 years, 7-12 years).

cal location and the non-uniform introduction of infection control measures.

The subanalysis of differences in viral distribution in countries with various country economic statuses revealed a higher IV prevalence in LIE and LMIE. An explanation could be that the seasonal influenza vaccination has not yet been adopted by most LIE and LMIE [24]. Furthermore, the implementation of public health measures and availability of test kits in LIE and LMIE may be insufficient.

When considered over the entire pandemic period, most viruses have maintained their usual seasonal distribution patterns among children, with HRSV being most prevalent during the autumn and IV during the winter season, while EV/RV showed the highest activity during the spring and summer [25].

A meta-analysis [26] including 186 articles examining the prevalence of viruses in children with community-acquired pneumonia up to 18 years of age between 1995 and 2019 showed the highest prevalence for HRSV 22.7% (95% CI: 20.9-24.5%) and HRV 22.1% (95% CI: 19.5-24.7%). The prevalence of both viruses is a little lower than those found in our analysis during the pandemic.

Another meta-analysis [27] that included 42 studies on the topic of children up to 18 years old with acute respiratory tract infection assessed the viral and bacterial prevalence before and during the COVID-19 pandemic. The period before the pandemic covered from 2010 to 2020 revealed the following prevalence: HRV 16.98% (95% CI: 10.42-24.62%), HRSV 11.12% (95% CI: 8.78-13.7%), IV 8.85% (95% CI: 5.04-13.59%), HPIV 5.36% (95% CI: 4.49-6.31%), HAdV 4.66% (95% CI: 2.78-7.0%), HBoV 4.2% (95% CI: 2.89-5.74%), HMPV 2.41% (95% CI: 1.42-3.64%), HCoV 2.4% (95% CI: 1.66-3.26%). Worth noting here are the higher IV prevalence and lower HCoV prevalence in the prepandemic period compared to our results. HRV and HRSV are also the leading viruses here but with lower prevalence than in our analysis.

A meta-analysis [28] that focused on children under 2 years of age with bronchiolitis, examined the prevalence between 2019 and 2020 and included 50 studies. Here, HRSV (59.17%, 95% CI: 54.66-63.6%) and HRV (19.29%, 95% CI: 16.67-22.04) were the most frequently detected viruses, followed by HBoV 8.23% (95% CI: 5.65-11.24%), HAdV 6.08% (95% CI: 4.37-8.03%), HPIV 5.39% (95% CI: 3.78-7.26%), HMPV 5.38% (95% CI: 4.4-6.44%), IV 3.17% (95% CI: 2.17-4.34%), HCoV 2.91% (95% CI: 1.96-4.03%). In these studies, too, a lower HCoV prevalence is noticeable compared to the pandemic period.

Nevertheless, we should highlight that the inclusion criteria differ from those in our analysis and comparisons should be made with caution.

Strengths and limitations

This systematic review and meta-analysis is subject to several strengths and limitations. One strength of our review is that we looked at almost the entire pandemic period and due to this large period, we had the opportunity to analyze seasonal changes. Furthermore, we only included studies that used molecular testing methods for virus detection to ensure that the correct virus was assigned to the infection. The large number of studies from the database search allowed us to screen and include many studies to create an accurate representation of the pandemic period.

The limitations of this review were that we included studies with almost exclusively symptomatic patients, which may have influenced the observed prevalence of respiratory viruses. Including only symptomatic patients does not allow us to draw robust conclusions on the prevalence in the general population and may rather represent a distribution of the viruses that cause symptomatic infection. Moreover, the different viral testing methods used could differ in sensitivity and specificity and may be varied in their ability to detect infections, which may have affected the observed prevalence. Third, we could not include in our analysis data such as vaccination status, comorbidities, and gender due to the lack of reporting them among original studies. In addition, the regional distribution of the studies was inconsistent therefore some countries are well represented and some not at all. The different seasons were only considered over the entire period, but the prevalence might have differed in the different years. In some subanalysis we could only include a few studies and the risk of publication bias could not be excluded for all viruses.

Conclusion

In conclusion, EV/RV and HRSV showed the highest prevalence among all respiratory viruses in children aged 12 years and younger during the pandemic. The time course analysis showed an increase in HRSV in the second half of the pandemic period. Most affected were children younger than 1 year of age. Patients with and without SARS-CoV-2-coinfection were both predisposed to other respiratory viral infections. The prevailing viruses vary according to geographic region and economic status of the country. Considering the whole period, the seasonal characteristics of the viruses have remained the same compared to the prepandemic era.

Our results provide an overview of the distribution of respiratory viruses in children since the beginning of the pandemic. Even though the WHO has declared an end to COVID-19 as a public health emergency, the topic remains highly relevant. Other respiratory viruses are increasingly coming to the forefront and SARS-CoV-2 is a virus that circulates and can have an impact on the spectrum of respiratory pathogens. At least some of the measures introduced during the COVID-19 pandemic may be taken up again in future pandemics or new SARS-CoV-2 outbreaks, and it is, therefore, important to know how other viruses behave under such measures.

To confirm our observations and to explain some findings such as the virus distribution in different age groups, further research and studies are needed.

Declaration of competing interest

Chrysanthi Skevaki: Consultancy and research funding, Bencard Allergie and Thermo Fisher Scientific; Research Funding, Mead Johnson Nutrition (MJN).

Funding

This research did not receive any specific grant from funding agencies in the public commercial, or not-for-profit sectors.

Ethical approval

Ethical approval was not necessary because the meta-analysis consists only of previously published studies.

Acknowledgments

We would like to thank the following authors for providing us with information about their articles:

Zhengrong Chen, Department of Respiratory Medicine, Children's Hospital of Soochow University, Suzhou, China

Wei Li, Department of Clinical Laboratory, The Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health. Hangzhou 310052, PR China Gültaç Evren, Manisa City Hospital, Pediatric Intensive Care Unit, Manisa, Türkiye

Ilari Kuitunen, School of Medicine, University of Eastern Finland, Kuopio, Finland and Department of Pediatrics, Mikkeli Central Hospital, Finland

Angela Dramowski, Department of Paediatrics and Child Health, Stellenbosch University, Cape Town, South Africa

Gioacchino Andrea Rotulo, Pediatric Emergency Unit, IRCCS Istituto Giannina Gaslini, Genoa Italy and Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), University of Genoa, Genoa Italy

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2023.10.023.

References

- World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020, https://www.who.int/directorgeneral/speeches/detail/who-director-general-s-opening-remarks-at-themedia-briefing-on-covid-19-11-march-2020; 2020 [accessed 04 July 2023].
- [2] Güner R, Hasanoğlu I, Aktaş F. COVID-19: prevention and control measures in community. *Turk | Med Sci* 2020;50:571–7. doi:10.3906/sag-2004-146.
- [3] GBDEstimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Infect Dis* 2018;**18**:1191–210. doi:10.1016/S1473-3099(18)30310-4.
- [4] Nair H, Nokes DJ, Gessner BD, Dherani M, Madhi SA, Singleton RJ, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. *Lancet* 2010;**375**:1545–55. doi:10.1016/S0140-6736(10)60206-1.
- [5] Pierce CA, Herold KC, Herold BC, Chou J, Randolph A, Kane B, et al. COVID-19 and children. *Science* 2022;**377**:1144–9. doi:10.1126/science.ade1675.
- [6] Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;**372**:n71. doi:10.1136/bmj.n71.
- [7] ICTV. Current ICTV taxonomy release 2023. https://ictv.global/taxonomy [accessed 05 July 2023].
- [8] World Population Review. Total population by country 2023, https:// worldpopulationreview.com/countries; 2023 [accessed 05 July 2023].
- [9] World Health Organization Countries overview; 2023 https://www.who.int/ countries [accessed 05 July 2023].
- [10] World Bank data help desk World Bank country and lending groups World Bank data help desk; 2023 https://datahelpdesk.worldbank.org/knowledgebase/ articles/906519-world-bank-country-and-lending-groups [accessed 05 July 2023].
- [11] Herzog R, Álvarez-Pasquin MJ, Díaz C, Del Barrio JL, Estrada JM, Gil Á. Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? a systematic review. BMC Public Health 2013;13:154. doi:10.1186/1471-2458-13-154.

- [12] Ottawa Hospital Research Institute. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, https://www. ohri.ca/programs/clinical_epidemiology/oxford.asp; [accessed 05 July 2023].
- [13] Granholm A, Alhazzani W, Møller MH. Use of the GRADE approach in systematic reviews and guidelines. Br J Anaesth 2019;123:554–9. doi:10.1016/j.bja. 2019.08.015.
- [14] R Software. R: the R Project for Statistical Computing, https://www.r-project. org/; 2023 [accessed 05 July 2023].
- [15] Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. J Stat Soft 2010;36:1–48. doi:10.18637/jss.v036.i03.
- [16] Lin L, Chu H. Quantifying publication bias in meta-analysis. Biometrics 2018;74:785-94. doi:10.1111/biom.12817.
- [17] Poole S, Brendish NJ, Tanner AR, Clark TW. Physical distancing in schools for SARS-CoV-2 and the resurgence of rhinovirus. *Lancet Respir Med* 2020;8:e92– 3. doi:10.1016/S2213-2600(20)30502-6.
- [18] Qiu W, Zheng C, Huang S, Zhang Y, Chen Z. Epidemiological trend of RSV infection before and during COVID-19 pandemic: a three-year consecutive study in China. *Infect Drug Resist* 2022;15:6829–37. doi:10.2147/IDR.S388231.
- [19] Groves HE, Papenburg J, Mehta K, Bettinger JA, Sadarangani M, Halperin SA, et al. The effect of the COVID-19 pandemic on influenza-related hospitalization, intensive care admission and mortality in children in Canada: A population-based study. *Lancet Reg Health Am* 2022;7:100132. doi:10.1016/j. lana.2021.100132.
- [20] Shakib JH, Korgenski K, Presson AP, Sheng X, Varner MW, Pavia AT, et al. Influenza in infants born to women vaccinated during pregnancy. *Pediatrics* 2016;**137**:e20152360. doi:10.1542/peds.2015-2360.
- [21] Messina A, Germano C, Avellis V, Tavella E, Dodaro V, Massaro A, et al. New strategies for the prevention of respiratory syncytial virus (RSV). *Early Hum Dev* 2022;**174**:105666. doi:10.1016/j.earlhumdev.2022.105666.
- [22] Allan GM, Arroll B. Prevention and treatment of the common cold: making sense of the evidence. CMAJ 2014;186:190-9. doi:10.1503/cmaj.121442.
- [23] Scott SJ, Pfotenhauer B, Weiner JJ, Hilleshiem J, Khubbar M, Bhattacharyya S. Respiratory pathogen coinfections in SARS-CoV-2-Positive patients in Southeastern Wisconsin: a retrospective analysis. *Microbiol Spectr* 2021;9:e0083121. doi:10.1128/Spectrum.00831-21.
- [24] Mantel C, Chu SY, Hyde TB, Lambach P. IPIE Pilot Implementation Group. Seasonal influenza vaccination in middle-income countries: assessment of immunization practices in Belarus, Morocco, and Thailand. *Vaccine* 2020;38:212–19. doi:10.1016/j.vaccine.2019.10.028.
- [25] García-Arroyo L, Prim N, Del Cuerpo M, Marín P, Roig MC, Esteban M, et al. Prevalence and seasonality of viral respiratory infections in a temperate climate region: a 24-year study (1997–2020). *Influenza Other Respir Viruses* 2022;**16**:756–66. doi:10.1111/irv.12972.
- [26] Pratt MTG, Abdalla T, Richmond PC, Moore HC, Snelling TL, Blyth CC, et al. Prevalence of respiratory viruses in community-acquired pneumonia in children: a systematic review and meta-analysis. *Lancet Child Adolesc Health* 2022;6:555–70. doi:10.1016/S2352-4642(22)00092-X.
- [27] Tang Y, Dang X, Lv M, Norris SL, Chen Y, Ren L, et al. Changes in the prevalence of respiratory pathogens in children due to the COVID-19 pandemic: a systematic review and meta-analysis. J Infect 2023;86:154–225. doi:10.1016/j. jinf.2022.11.023.
- [28] Kenmoe S, Kengne-Nde C, Ebogo-Belobo JT, Mbaga DS, Fatawou Modiyinji A, Njouom R. Systematic review and meta-analysis of the prevalence of common respiratory viruses in children < 2 years with bronchiolitis in the pre-COVID-19 pandemic era. *PLoS One* 2020;15:e0242302. doi:10.1371/journal. pone.0242302.