Journal of Infection 89 (2024) 106218

Contents lists available at ScienceDirect

Journal of Infection

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

Infectious Disease Practice

Age-specific SARS-CoV-2 transmission differed from human rhinovirus in households during the early COVID-19 pandemic

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ARTICLE INFO

Article history:
Accepted 26 June 2024
Available online 29 June 2024

Keywords:
SARS-CoV-2
Rhinovirus
Age factors
Epidemiology
Pandemic
Disease outbreaks
European prospective household studies

SUMMARY

Objectives: Children are generally considered main drivers of transmission for respiratory viruses, but the emergence of SARS-CoV-2 challenged this paradigm. Human rhinovirus (RV) continued to co-circulate throughout the pandemic, allowing for direct comparison of age-specific infectivity and susceptibility within households between these viruses during a time of low SARS-CoV-2 population immunity.
Methods: Households with children were prospectively monitored for ≥23 weeks between August 2020 and July 2021. Upon onset of respiratory symptoms in a household, an outbreak study was initiated, including questionnaires and repeated nasal self-sampling in all household members. Swabs were tested by PCR. Age-stratified within-household secondary attack rates (SARs) were compared between SARS-CoV-2 and RV.
Results: A total of 307 households participated, including 582 children and 627 adults. Overall, SAR was lower for SARS-CoV-2 than for RV (aOR 0.55) and age distributions differed between both viruses ($p < 0.001$). Following household exposure, children were significantly less likely to become infected with SARS-CoV-2 compared to RV (aOR 0.16), whereas this was opposite in adults (aOR 1.71).
Conclusion: In households, age-specific susceptibility to SARS-CoV-2 and RV differs and drives differences in household transmission between these pathogens. This highlights the importance of characterizing age-specific transmission risks, particularly for emerging infections, to guide appropriate infection control interventions.

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https://doi.org/10.1016/j.jinf.2024.106218

Introduction

To limit the impact of the novel SARS-CoV-2 virus on the naïve population, drastic societal measures were taken early in the COVID-19 pandemic to slow the spread of the virus in the absence of preventive or curative treatments. These non-pharmaceutical interventions led to the absence of regular epidemic peaks of common respiratory viruses like RSV and Influenza during the 2020–2021 season, followed by large rebounds in later seasons when measures were lifted.[1–3] Interestingly, the most prevalent cause of common respiratory infection, human rhinovirus (RV), was not affected in the same manner and continued to co-circulate throughout the pandemic.[4,5] This provided us with a rare opportunity to compare transmission dynamics between a novel virus in a naïve population, like SARS-CoV-2, to an established seasonal virus, like RV.

Transmission of SARS-CoV-2 predominantly occurs via droplets and aerosols, facilitating transmission under conditions where social distancing is difficult, like households.[6] Meta-analyses have shown secondary attack rates (SARs) for SARS-CoV-2 early in the pandemic ranging between 15% and 53% within households. [7–14] Initially, children were thought to play a minor role in the spread of the SARS-CoV-2 virus. They were less often identified as index case[15,16] and more often showed asymptomatic to mild disease, which is associated with decreased transmissibility.[9,17] Early literature thus suggested that children were less susceptible to SARS-CoV-2 infection and, when infected, less likely to transmit[13,18,19] and therefore early infection control measures were mainly targeted towards adults. These transmission patterns contradicted with well-established patterns for seasonal viruses, of which RV is the most common. RV is thought to transmit via droplets or aerosols like SARS-CoV-2, but also through indirect contact (i.e. via surfaces). RV infection is often found symptomatic in children and asymptomatic in adults.[20,21] The within-household SARs for RV have been estimated between 10 and 58%, and children are considered to be key transmitters within the household due to their high attack rates.[20,22] Insights on how SARS-CoV-2, a novel respiratory virus in a naïve population, deviated from transmission patterns found in established respiratory infections like RV provide a knowledge base for the development of appropriate age-specific interventions for existing versus novel emerging respiratory viruses.

The CoKids study used prospective, longitudinal monitoring of households with children of different ages for the occurrence of respiratory symptoms. The primary aim of the study was to quantify the role of children in within-household transmission of SARS-CoV-2. Respiratory samples were also tested for a panel of other respiratory pathogens, including RV, to allow direct comparison of age-specific within-household transmission of SARS-CoV-2 with other pathogens. The study was conducted in the Netherlands between August 2020 and July 2021, when the Alpha and pre-Alpha variants were dominant and vaccination for individuals < 65 years largely unavailable, except during the final months of follow-up (after April 2021).

Patients and methods

The study procedures of the CoKids study have been described elsewhere.[23] In brief, households with at least one child aged < 18 years were eligible for inclusion. Participating households were recruited from three existing birth cohorts. Following ethical approval, household enrollment took place between August 2020 and February 2021, irrespective of the presence of (prior) SARS-CoV-2 infection. Written informed consent was obtained from all participating household members and/or their legal representatives. Households were prospectively followed for a minimum of 23 weeks. During this period, participants self-reported the occurrence of new-onset respiratory symptoms and/or fever. In addition, all participants were screened every 4–6 weeks for SARS-CoV-2, irrespective of symptoms. The longitudinal follow-up was temporarily intensified when an outbreak of respiratory illness occurred in the household, which was defined as (1) new-onset respiratory symptoms and/or fever, or (2) a SARS-CoV-2 positive screening test, or (3) a positive SARS-CoV-2 test from an external testing site, in any of the household members. During an outbreak, intensified data collection took place of all household members, irrespective of symptoms. This consisted of daily recording of symptoms for 21 days or until all symptoms in the household had resolved and collection of nose-throat swabs (NTS) from all household members by self-sampling at the start of the outbreak. A retest was performed for household members who developed new or additional respiratory symptoms throughout the outbreak. Furthermore, questionnaires on household characteristics and infection control measures instated in the household were collected. A customized study App was used throughout the follow-up to guide households in study procedures and for household data collection. All samples were obtained by self-sampling following in-person instructions.

NTS samples were tested by reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2. Samples from the index case were also tested by multiplex ligation-dependent probe amplification (MLPA) for a panel of 21 respiratory viruses and atypical bacteria. Upon a positive result on MLPA in the index case, NTS samples from all household members were additionally tested by MLPA.

For the analysis in this study, we included household outbreaks with an index case positive for SARS-CoV-2, RV or both. Other respiratory viruses were not included because of their low prevalence. Outbreaks were excluded from analysis if the index case could not be identified, i.e., when it was unclear who was the first household member to present with symptoms. If the index showed coinfection with SARS-CoV-2 and RV, the outbreak was included in both groups.

Definitions

A confirmed case was defined as a positive RT-PCR or MLPA result for SARS-CoV-2 or RV. An acute respiratory illness (ARI) episode was defined as: (1) new onset of fever or (2) two consecutive days with at least one respiratory symptom (cough, sore throat, cold, or dyspnea) and one systemic symptom (headache, muscle ache, cold shivers, or fatigue) or two respiratory symptoms. For each probable or confirmed case, the severity was classified as 1) ARI episode, 2) mildly symptomatic (some symptoms but not meeting ARI threshold) or 3) asymptomatic.

Laboratory analysis

NTS samples were tested for the presence of SARS-CoV-2 by RT-PCR as described elsewhere.[24] Specimens with a cycle threshold (Cp-/Ct-values) less than or equal to 40 were defined as SARS-CoV-2 positive. For the multiplex ligation-dependent probe amplification (MLPA) analyses, we used RespiFinder® 2Smart kit 22 FAST (PathoFinder, Maastricht, the Netherlands), following the manufacturer's instructions. This MLPA kit is designed to detect 21 pathogens, including RV, adenovirus, Pertussis, Chlamydia pneumoniae, bocavirus, Human Metapneumovirus, Legionella pneumophila, Mycoplasma pneumonia, human Coronavirus OC43/NL63/HKU1/229E, Influenza A/B, Parainfluenza 1/2/3/4 and Respiratory Syncytial Virus A/B.[25]

Statistical analysis

We compared differences in household characteristics for SARS-CoV-2 versus RV outbreaks using Fisher's exact tests for categorical variables and the Kruskal-Wallis H test for continuous variables.

Participants were divided into three age groups based on age at time of inclusion: 1) children < 12 years, 2) adolescents 12–17 years, and 3) adults ≥18 years. Infection control measures were divided into categories based on number of measures taken as reported by the household in case of respiratory symptoms (low < 4 measures, intermediate 4–7 measures or high > 7 measures). An overview of the infection control measures included in the questionnaire is presented in Supplementary Table 1.

We estimated within-household secondary attack rates (SARs), defined as the percentage of confirmed secondary cases out of all household members at risk (i.e. excluding index cases) using a binomial Generalized Estimating Equation (GEE) with a logit link and exchangeable correlation structure to account for within-household clustering. To explore the effect of age and virus type on the SAR, the model contained the occurrence of within-household transmission as an outcome variable with an interaction term for age and virus type (i.e. SARS-CoV-2 or RV). SARs were then computed for SARS-CoV-2 and RV outbreaks, stratified by age of the index case and by age of the household members. The model also accounted for confounding factors sex and symptom status of the index case. The latter covariates were identified by performing Quasi Information Criterion (QIC)-based covariate selection on a full GEE model considering household size, start month of the outbreak, household infection control measures, symptom status of the index case and sex of the index and susceptible case. Odds ratios (ORs) and significance of the covariates included in this full GEE model are reported in Supplementary Table 2.

Next, using the final model as described above, we quantified the effect of age on infectivity and susceptibility for each virus (SARS-CoV-2 or RV) separately and relative differences between viruses. For infectivity, age-effects per virus were based on the adjusted odds ratios (aORs) for within-household transmission by age group of the index case using adults as the reference category. For susceptibility, age-effects per virus were based on the aOR for within household transmission by age group of the household member, using adults as the reference category. For each age group, we also determined the relative differences in infectivity and susceptibility between SARS-CoV-2 versus RV as aORs.

All analyses were carried out using R Studio (version 4.0.3). P-values < 0.05 were considered statistically significant.

Results

From August 2020 until July 2021, 307 households with a total of 1209 subjects participated. In total, 183 household outbreaks of respiratory illness were studied. SARS-CoV-2 infection was present in 41 outbreaks (22.7%), of which two were excluded because the outbreak had multiple index cases (Fig. 1). RV infection was detected in 83 outbreaks (45.9%). Seven index cases showed coinfection with SARS-CoV-2 and RV and were counted in both outbreak groups. In the remaining outbreaks (n = 66), a different pathogen or combination of pathogens was identified in 15 index cases and no pathogen in 51 index cases. In five SARS-CoV-2 outbreaks, 15 RV outbreaks and one outbreak with SARS-CoV-2/RV coinfection, the index case was additionally tested positive for another pathogen than RV or SARS-CoV-2. An overview of all pathogens detected in the 181 outbreaks included in the analysis is provided in Supplementary Table 3.

Baseline characteristics of all participants included in SARS-CoV-2, and RV outbreaks are summarized in Table 1. In SARS-CoV-2 outbreaks, the index case was more often an adult (53.8%), while in RV outbreaks, most index cases were below the age of 12 years (65.1%, p < 0.001). Overall, more infection control measures were reported in the households during a SARS-CoV-2 outbreak compared to an RV outbreak. Six adults (1.2%) had received at least one dose of SARS-CoV-2 vaccination at the start of the outbreak and none of the children.

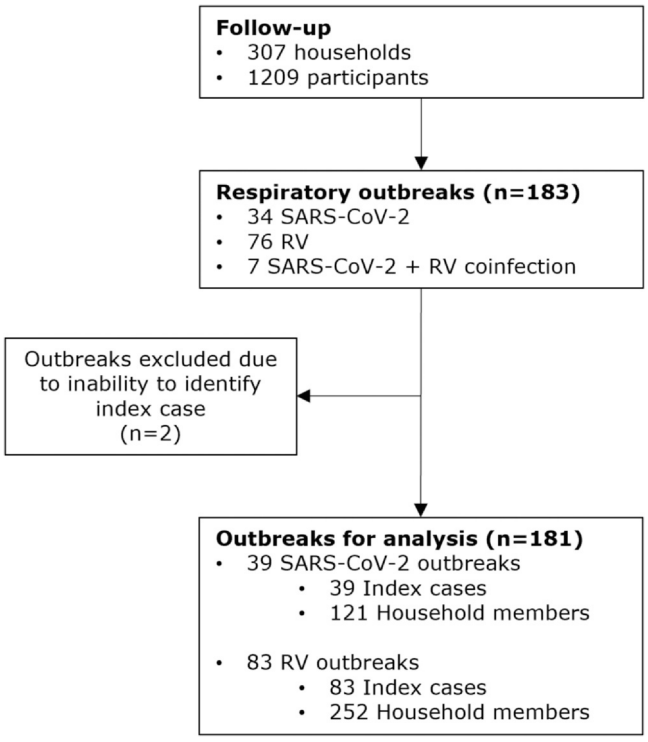

Fig. 1. Flowchart of outbreaks and participants included in analysis. RV = Human rhinovirus.

The overall SAR for SARS-CoV-2 (28.2%) was lower than for RV (40.9%), although the difference was not significant (aOR 0.55, 95% CI [0.29; 1.06]; Table 2). For SARS-CoV-2, the SAR did not vary much by age of the index case. By contrast, the SAR for RV was higher for adult index cases compared to younger age groups. The SARs among household members stratified by age was lowest for SARS-CoV-2 in children < 12 years (18.5%) and highest in the same age group for RV (63.5%).

In Fig. 2, the aORs for age-specific infectivity (a) and susceptibility (b) are plotted for SARS-CoV-2 and for RV with adults as the reference group. We did not observe significant differences in infectivity by age of the index case for SARS-CoV-2, or for RV (Fig. 2a). For susceptibility, child household members were significantly more susceptible to RV compared to adults (aOR 4.42, 95% CI [2.67–7.31]), whereas for SARS-CoV-2, they were significantly less susceptible compared to adults (aOR 0.43, 95% CI [0.19–1.00]; Fig. 2b). The same effect, though less strong, is found for adolescents compared to adults. Comparing transmission between the two viruses, the infectivity of adult index cases was lower for SARS-CoV-2 compared to RV (aOR 0.36, 95% CI: 0.17–0.92, Table 2), but this difference was not found for younger age groups ($P^{interaction} = 0.58$). Susceptibility to SARS-CoV-2 versus to RV differed significantly between age groups ($P^{interaction} < 0.001$). The youngest age group (< 12 years) had much lower susceptibility to SARS-CoV-2 compared to RV (aOR was 0.16, 95% CI [0.06;0.40).

Discussion

The CoKids study took place in the Netherlands during the time of the Alpha and pre-Alpha variants of SARS-CoV-2 when vaccination was largely unavailable and partial school closures still in place. A head-to-head comparative analysis between SARS-CoV-2 and RV shows that household transmission rates for RV are generally higher than for SARS-CoV-2 with clear differences in age-specific

Table 1
Baseline characteristics of households and participants included in SARS-CoV-2 and/or RV outbreaks.

Household characteristics				
	Total	**SARS-CoV-2 outbreaks[a,b] (n = 39)**	**RV outbreaks[a,b](n = 83)**	***p-value***
Household size; n (%)				*0.839*
2	2 (1.6%)	1 (2.6%)	1 (1.2%)	
3	18 (14.8%)	5 (12.8%)	13 (15.7%)	
4	74 (60.7%)	22 (56.4%)	52 (62.7%)	
5	22 (18.0%)	9 (23.1%)	13 (15.7%)	
6	6 (4.9%)	2 (5.1%)	4 (4.8%)	
Start of follow-up; n (%)				*0.935*
Aug-Sep 2020	25 (20.5%)	7 (17.9%)	18 (21.7%)	
Oct-Nov 2020	62 (50.8%)	20 (51.3%)	42 (50.6%)	
Dec 2020-Feb 2021	35 (28.7%)	12 (30.8%)	23 (27.7%)	
Start of outbreak; n (%)				*0.040*
Sep-Oct 2020	22 (18.0%)	4 (10.3%)	18 (21.7%)	
Nov-Dec 2020	50 (41.0%)	13 (33.3%)	37 (44.6%)	
Jan-Feb 2021	17 (13.9%)	7 (17.9%)	10 (12.0%)	
Mar-Apr 2021	25 (20.5%)	9 (23.1%)	16 (19.3%)	
May-Jun 2021	8 (6.6%)	6 (15.4%)	2 (2.4%)	
Infection control measures; n (%)[c]				*< 0.001*
Low	54 (53.5%)	12 (38.7%)	42 (60.0%)	
Intermediate	38 (37.6%)	10 (32.3%)	28 (40.0%)	
High	9 (8.9%)	9 (29.0%)	0 (0.0%)	
Participant characteristics (n = 495)				
	Total	**SARS-CoV-2 outbreaks**	**RV outbreaks**	***p-value***
N Index cases	122	39	83	
N household members	373	121	252	
Age index cases; n (%)				*< 0.001*
< 12 years	65 (53.3%)	11 (28.2%)	54 (65.1%)	
12-17 years	14 (11.5%)	7 (17.9%)	7 (8.4%)	
> 17 years	43 (35.2%)	21 (53.8%)	22 (26.5%)	
Age household members; n (%)				*< 0.001*
< 12 years	134 (35.9%)	42 (34.7%)	92 (36.5%)	
12-17 years	32 (8.6%)	22 (18.2%)	10 (4.0%)	
> 17 years	207(55.5%)	57(47.1%)	150(59.5%)	
Sex; n (%)				*0.232*
Male	242 (48.9%)	72 (45.0%)	170 (50.7%)	
Female	253 (51.1%)	88 (55.0%)	165 (49.3%)	
Vaccinated before outbreak, ≥ 1 dose; n (%)	6 (1.2%)	4 (2.5%)	2 (0.6%)	*0.07*

[a] Households with an RV and SARS-CoV-2 outbreak during follow up are included in both groups.
[b] Seven outbreaks of SARS-CoV-2 and RV co-infection have been included in both groups.
[c] Column totals do not add up due to missing data.

transmission patterns between SARS-CoV-2 and RV. For SARS-CoV-2, children were only half as susceptible compared to adults, but for RV children were four times more susceptible than adults. After introduction of either virus into the household, children were five times less likely to become infected if it was a SARS-CoV-2 outbreak compared to an RV outbreak, whereas adults appeared more likely to become infected with SARS-CoV-2 than with RV.

To the best of our knowledge, this is the first study that directly compares household transmission of SARS-CoV-2 with another respiratory pathogen, while adjusting for potential confounding factors. Previous studies showed that children are often the main spreaders of common respiratory pathogens due to their increased susceptibility and infectivity.[20,21] In our study, the same pattern of increased susceptibility of children was found for RV. Interestingly, SARS-CoV-2 as novel respiratory pathogen deviated from this pattern by showing lower susceptibility among children and higher susceptibility among adults. This difference in age-specific transmission between SARS-CoV-2 and RV may be explained by differential immunity profiles across the age groups. Immunity against RV was likely mature and robust in adults but less developed in

Table 2
Age-specific secondary attack rates (SARs) for SARS-CoV-2 and RV.

	SARS-CoV-2	RV	aOR [95 %CI][a]	*p-value*[b]
	SAR [95% CI]	SAR [95% CI]		
Within-household SAR	28.2% [18.6; 40.3]	40.9% [34.8; 47.4]	0.55 [0.29; 1.06]	
SAR by age index case (i.e. infectivity)				*0.58*
< 12 years	26.1% [10.9; 50.4]	38.1% [30.9; 45.8]	0.68 [0.24; 1.89]	
12-17 years	20.6% [4.70; 57.4]	20.0% [7.25; 44.4]	1.06 [0.14; 8.19]	
> 17 years	32.0% [19.4; 47.9]	54.7% [44.0; 65.0]	0.36 [0.17; 0.92]	
SAR by age household member (i.e. susceptibility)				*< 0.001*
< 12 years	18.5% [8.74; 35.0]	63.5% [54.1; 71.9]	0.16 [0.06; 0.40]	
12-17 years	26.3% [13.8; 44.5]	41.4% [15.1; 73.7]	0.35 [0.07; 1.74]	
> 17 years	36.9% [23.5; 52.8]	27.4% [21.0; 35.0]	1.71 [0.75; 3.86]	

[a] Odds ratio of secondary household infection for SARS-CoV-2 in reference to RV, adjusted for sex and symptom status of the index case. Row one: overall; Row two: stratified by age of the index case (i.e. infectivity, based on SAR emerging from the index case); Row three: stratified by age of the household member at risk (i.e. susceptibility, based on the risk of becoming infected as household member exposed to the index case).
[b] Overall p-value for interaction between age group and virus (SARS-CoV-2 or RV)

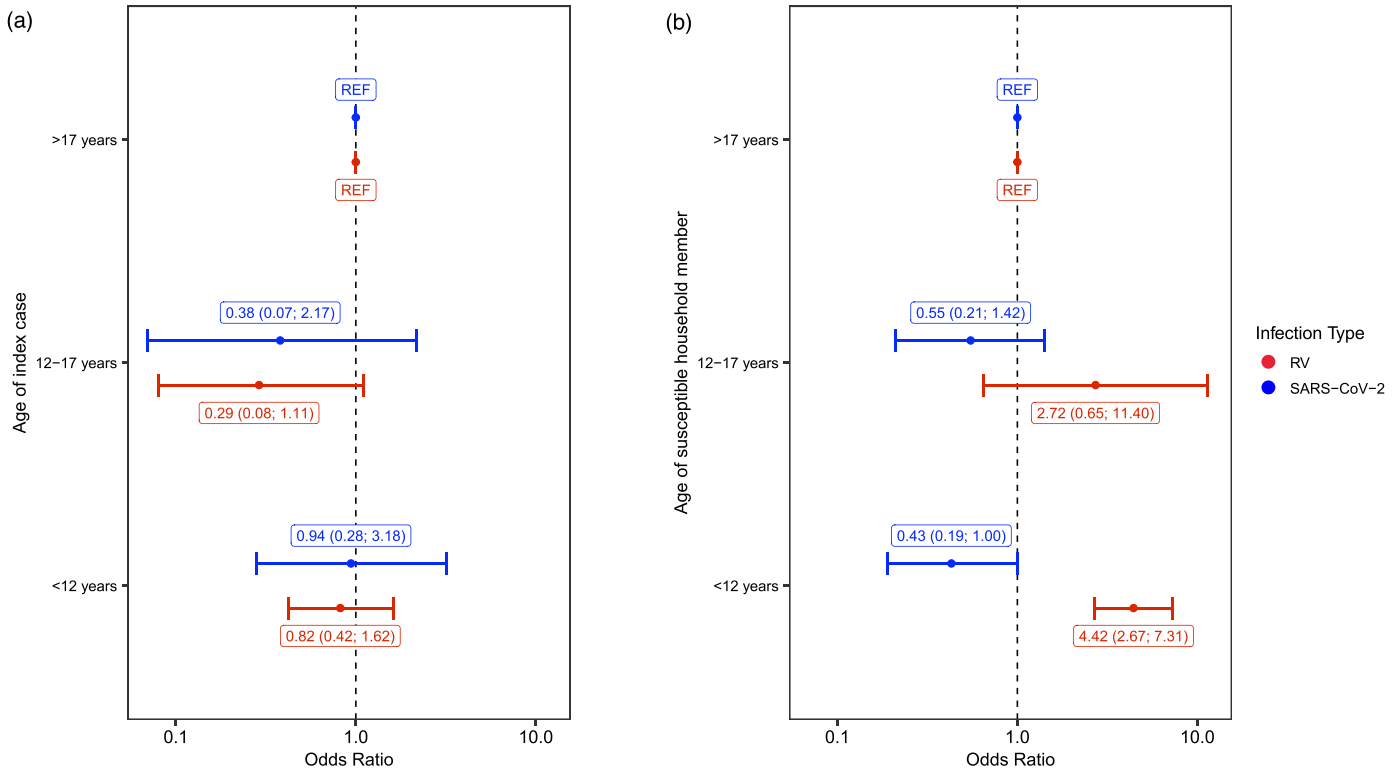

Fig. 2. a) aORs with 95% CIs for relative infectivity by age group of the index case in reference to adult index cases, stratified by virus (blue = SARS-CoV-2, red = RV). REF = Reference. Infectivity is based on SAR emerging from the index case. b) aORs with 95% CIs for susceptibility of different ages household members in reference to adult household members, stratified by infection type (blue = SARS-CoV-2, red = RV). REF = Reference. Susceptibility is based on the risk of becoming infected as household member exposed to the index case.

children, while both adults and children were naïve to the novel SARS-CoV-2 virus and susceptibility and infectivity are therefore mainly determined by the host's innate immune factors. There is ample evidence that both local and systemic innate immune responses to SARS-CoV-2 differ between children and adults, with children mounting stronger antiviral responses.[26] This enhanced innate immunity may result from frequent childhood infections, as suggested by Chou et al.[27] Our study adds to the body of evidence on differential susceptibility to a novel virus by age, which is opposite to known susceptibility patterns for established respiratory viruses. These insights illustrate that established paradigms on transmission dynamics may not hold for emerging respiratory infections and stress the importance of rapid characterization of age-specific patterns of transmission in case of a novel pathogen and the design of appropriate mitigation measures by age.

Throughout the SARS-CoV-2 pandemic, most seasonal respiratory viruses showed a decline in prevalence compared to previous seasons due to the implementation of infection control measures. RV detection rates, however, remained high throughout the pandemic.[4,5] Many have hypothesized that this could be due to RV being a non-enveloped virus, making it resistant to most ethanol-containing hand disinfectants, retaining its infectivity on inanimate surfaces for prolonged periods.[4,28] Other studies suggest that virus-virus interaction may play a role, with RV infection possibly preventing SARS-CoV-2 replication in the airways.[5,29] Based on the results from the current study, we propose two alternative explanations. Firstly, due to the higher transmissibility of RV compared to SARS-CoV-2 social distancing measures that effectively control the spread of SARS-CoV-2, fall short in controlling the spread of RV. Secondly, results from this study suggest that RV mainly circulates among children, whereas SARS-CoV-2 appears more transmissible between adults, at least early in the pandemic. Given that mitigation measures were less strict for children, with daycares remaining open for nearly the entire period and with more relaxed social distancing measures, along with the inability to install social distancing for the youngest children,[16,30] RV could continue to circulate among children, with secondary household transmission to other age groups.

This study has several limitations. Firstly, results of this study are based on a testing scheme including NTS samples at the start of the outbreak in all household members and a second sample upon new onset ARI symptoms, but no repeated sampling in the absence of symptoms. A large meta-analysis performed by Fung et al. shows that there is on average an over two-fold increase in estimated SAR when including more than one test result per household member.[7] Thus, the SARs detected in our study may be underestimated (28.2% for SARS-CoV-2, 40.9% for RV). As an earlier analysis of the study data found that asymptomatic SARS-CoV-2 infections occurred more frequently in children compared to adults,[31] some differential underdetection by age cannot be excluded and may contribute to the lower susceptibility estimate found for SARS-CoV-2 in children. However, we consider it unlikely that that this would fully explain our observations, given the strength of this association between age and SARS-CoV-2 susceptibility. Secondly, the GEEs in this study assume direct transmission from the index case to all secondary cases, without accounting for potential indirect transmission routes. A transmission modeling study is required to account for all indirect routes of transmission. Thirdly, at the time of the study, household infection control measures were recommended for symptomatic subjects until SARS-CoV-2 infections had been ruled out. Most likely, measures were therefore discontinued earlier in SARS-CoV-2 negative outbreaks, which in theory could enhance transmission. However, we found no significant effect of the stringency of infection control measures reported by the household on the SAR for either SARS-CoV-2 or RV. Possibly, this is explained by the fact that most household transmission occurred already before the diagnosis in the

index case was confirmed as also suggested by Verberk et al.[14] Fourth, the study population consisted of households with children and participating adults were mostly between 30–60 years of age. The study findings may therefore not be generalizable to the elderly. Finally, this study was performed during the Alpha and pre-Alpha period in a largely naïve and unvaccinated population. Hence, results on SARS-CoV-2 household transmission cannot be extrapolated to the current era with high population immunity against SARS-CoV-2 and different circulating variants. Rather, it reflects the age-specific transmission characteristics of a novel viral respiratory pathogen in a naïve population.

Conclusion

Early in the SARS-CoV-2 pandemic, there were clear differences in age-specific transmission patterns between SARS-CoV-2 and RV, with higher susceptibility to SARS-CoV-2 in adults, both compared to RV and relative to younger household members. The relatively high susceptibility to RV infection in young children may have contributed to the continued circulation of RV throughout the pandemic. Findings from this study provide insight into age-specific transmission characteristics of novel versus established respiratory pathogens and can guide the age-specific research response and design of interventions in case of a future outbreak of a novel respiratory pathogen.

Funding

The CoKids study, from which the data presented in this manuscript derived, was supported by ZonMW (grant 10150062010006). ZonMW is the Netherlands Organisation for Health Research and Development and had no involvement in study design, data collection, data analysis, data interpretation, the writing of the report or the decision to submit the article for publication. This research did not receive other specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Bont has regular interaction with pharmaceutical and other industrial partners. He has not received personal fees or other personal benefits. UMCU has received major funding (> €100,000 per industrial partner) for investigator-initiated studies from AbbVie, MedImmune, AstraZeneca, Sanofi, Janssen, Pfizer, MSD and MeMed Diagnostics. UMCU has received major funding for the RSV GOLD study from the Bill and Melinda Gates Foundation. UMCU has received major funding as part of the public–private partnership IMI-funded RESCEU and PROMISE projects with partners GSK, Novavax, Janssen, AstraZeneca, Pfizer and Sanofi. UMCU has received major funding by Julius Clinical for participating in clinical studies sponsored by MedImmune and Pfizer. UMCU received minor funding (€1000–25,000 per industrial partner) for consultation and invited lectures by AbbVie, MedImmune, Ablynx, Bavaria Nordic, MabXience, GSK, Novavax, Pfizer, Moderna, AstraZeneca, MSD, Sanofi, Janssen. Dr. Bont is the founding chairman of the ReSViNET Foundation. All other 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.

Acknowledgements

We gratefully acknowledge all participants of the study.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106218.

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