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Acute respiratory tract infections during the first 6 years of life – results from the German birth cohort study LoewenKIDS

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ABSTRACT

Objectives: Acute respiratory tract infections (ARIs) often occur in early childhood and are mostly self-limited. However, they impose a high socioeconomic burden and can be associated with chronic diseases later in life. To date, data on self-reported ARIs beyond infancy are limited. This study aimed to describe the incidence and characteristics of self-reported ARIs in the first 6 years of life.
Methods: Data were obtained from the LoewenKIDS birth cohort study, including 782 children born between 2014 and 2018. Parents recorded daily ARI symptoms, which were classified into episodes for incidence and characteristics analysis. Regression analyses explored the influence of exposure factors on ARI incidence.
Results: This longitudinal birth cohort study of a subsample of 258 children found a mean cumulative duration of 51.5 weeks (95% confidence interval: 47.5-55.6 weeks) of respiratory symptoms in the first 6 years of life, with large individual differences. Children with frequent infections in infancy had more infections in preschool age. Exposure factors explained only a small fraction of variation in incidence (5%).
Conclusions: There is a substantial variation in susceptibility to ARIs in childhood, which is not explained by exposure factors.

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Introduction

Acute respiratory tract infections (ARIs) in childhood are very common and pose a high burden worldwide [1]. ARIs can range from asymptomatic and mild upper respiratory tract infections to life threatening diseases and death. Although most ARIs are managed at home, they also lead to socioeconomic consequences, such as parental absence from work [2], high antibiotic prescriptions [3], high numbers of doctor/clinic visits [4], and possible long-term health effects, such as impaired lung function and development of asthma at school age [5].

A recent study including inpatient and outpatient consultations estimated the economic burden due to lower respiratory tract infections in children in Germany at 213 million euros per year [6]. This burden would be even higher when upper respiratory tract infections and children treated at home alone were included. Besides economic burden, children's sickness has a considerable impact on the quality of life of the family and especially the parents [7].

Assessing the full burden of ARIs in childhood is challenging because it requires continuous recording of symptoms, and only few birth cohort studies collected this information [8]. Of them, only three previous studies analyzed the self-reported number of ARIs prospectively beyond the second year of life. The Copenhagen Prospective Studies on Asthma in Childhood 2000 (COPSAC2000) study, conducted in Denmark, reported data on infection episodes until the third birthday [9]. Another longitudinal prospective cohort study was conducted in Australia and described the number of ARIs up to the fifth birthday [10]. However, data collected in a temperate climate in the southern hemisphere might be hard to apply to populations living in Europe. In Germany, the Multizentrische Allergie Studie 1990 (MAS-90) study was conducted in 1990s and collected data on ARIs frequency up to the 12th birthday [11]. At that time, most children were cared for at home until the age of 3 years, after which most children went to kindergarten and from kindergarten to school. Since 2013, there has been a right to a place in kindergarten from the age of one year, and the proportion of children in organized childcare has strongly increased. Such processes are also likely taking place in other countries. Attendance of kindergarten is known to be associated with an increase of ARIs [12]. To address the lack of contemporary data on the occurrence of ARIs during childhood in temperate regions of the northern hemisphere, this study aimed to describe the incidence, symptom patterns, and associated factors of ARIs in children from birth until the age of six years. We used the birth cohort LoewenKIDS, which uses a symptom diary to record respiratory symptoms from birth until the age of six years. Daily recording has the advantage of capturing individual symptoms and reducing recall bias.

Methods

Study population

The detailed methods of recruitment, study design, and data collection in the LoewenKIDS cohort are described elsewhere [13]. A total of 782 newborns born between 2014 and 2018 were enrolled in four study regions in Germany (Clinicaltrials.Gov Identifier: NCT02654210). Parents of the participants were asked to complete a symptom diary for the first six years of life, submit nasal swabs in case of a respiratory infection and stool samples in case of a gastrointestinal infection, and fill in yearly questionnaires on various aspects of health. Written informed consent was obtained from the parents before recruitment, and approval for the study was obtained from the ethics committees of the Medical Faculty of the Martin Luther University Halle-Wittenberg (No. 2016-04), the Medical School Hannover (No. 6794), and the Ludwig Maximilians University Munich (No. 445-15), Germany.

Symptom diary and ARI definition

Parents were asked to record symptoms and symptom-free days of their child daily in a symptom diary for the first six years of life. The symptom diary was provided on paper, online, or as an app. The parents could choose their entry mode and were allowed to switch between those. The symptoms were classified into ARI episodes based on the definition provided by Lambert et al. [14]. An ARI episode was defined as one or more symptoms of category A (fever, wheezing, cough with sputum) or two or more symptoms of category B (runny nose or nasal congestion, sore throat, cough, chills, loss of appetite, increased need to sleep, increased attachment), as previously described. An episode continued for as long as any symptom was present. A new ARI episode could begin if there were three consecutive days without symptoms. An isolated B symptom was accepted within an episode but not as a beginning of an ARI.

Fever was defined as rectal or forehead temperature above 38°C, above 37.8°C measured in the mouth, above 37.2°C in the armpit, or above 37.5°C in the ear. In addition to indicating symptom presence, parents rated each symptom as light, medium, or severe. Parents also recorded the visits at doctor's offices, hospital admissions, and use of medication in the symptom diary.

Statistical analysis

R software (Version 4.0.5) was used for data handling and all statistical analyses. For the classification of symptoms and infection episodes, we used the R-package lkstaR [15]. Descriptive characteristics were summarized using counts and percentages, means with 95% confidence intervals (95% CIs), or medians with interquartile range. We used generalized additive regression models (GAM, Rstudio package "GAM") to assess the association between the age of the children and the incidence of ARIs [16]. Multivariable regression assessing risk factors with respect to the cumulative number of ARI at the age of six years was conducted using Poisson regression. For the main analysis, we selected participants with a symptom diary filled out for at least 80% of days within the first six years. Days with missing entries were treated as symptom-free days.

Results

Cohort characteristics

Of the 782 participants at the start of the study, 466 were actively participating until their sixth birthday. A total of 258 participants filled in the symptom diary for at least 80% of days during the six years (Supplementary Figures 1 and 2).

Demographic and social characteristics of the study participants are reported in Table 1. Most children were from the study region Braunschweig/Hannover (where the recruitment started), born vaginally, had no siblings at birth, partially or exclusively breastfeed for 7 to 12 months, began to attend childcare between one and two years, and their parents had a high socioeconomic status. The sociodemographic characteristics of the participants with six years of participation and a high completeness of records differed only slightly from the non-selected participants, with missing values less often in the selected participants.

Number and duration of ARI episodes and symptoms

A total of 8233 ARI episodes from 258 selected participants were classified based on data entered in the symptom diaries,

Table 1
Sociodemographic description of the selected sample (n = 258) and the initial study sample (n = 782).

Characteristic	Initial study sample (n = 782), n (%)	Selected participants (n = 258), n (%)
Sex		
Female	386 (49.4)	127 (49.2)
Male	386 (49.4)	131 (50.8)
Missing	10 (1.3)	0 (0.0)
Season of birth		
Spring (March-May)	186 (23.8)	60 (23.3)
Summer (June-August)	228 (29.2)	82 (31.8)
Autumn (September-November)	214 (27.4)	69 (26.7)
Winter (December-February)	147 (18.8)	47 (18.2)
Missing	7 (0.9)	0 (0.0)
Birth mode		
Vaginal	523 (66.9)	200 (77.5)
C-Section	189 (24.2)	57 (22.1)
Missing	70 (8.9)	1 (0.4)
Study region		
Braunschweig/Hannover	505 (64.6)	175 (67.8)
Bremen	97 (12.4)	33 (12.8)
Halle (Saale)	80 (10.2)	23 (8.9)
Munich	92 (11.8)	27 (10.5)
Other	8 (1.0)	0 (0.0)
Siblings at birth		
Yes	252 (32.2)	88 (34.1)
No	479 (61.3)	168 (65.1)
Missing	51 (6.5)	2 (0.8)
Socioeconomic status of the parents[a]		
Low & Middle	76 (9.7)	16 (6.2)
High	652 (83.4)	238 (92.2)
Missing	54 (6.9)	4 (1.6)
Start of attending childcare[b]		
<1 year	94 (12.0)	34 (13.2)
1-<2 years	437 (55.9)	189 (73.3)
≥2 years	75 (9.6)	31 (12.0)
No attendance until 6 years	7 (0.9)	3 (1.2)
Missing	169 (21.6)	1 (0.4)
Breast feeding (exclusive or partial)		
Never	19 (2.4)	6 (2.3)
Up to 6 months	135 (17.3)	41 (15.9)
Seven to 12 months	299 (38.3)	118 (45.7)
More than 12 months	220 (28.1)	91 (35.3)
Missing	109 (13.9)	2 (0.8)

[a] According to the Brandenburg social status index [20] of the child at birth (calculated from parents' school education [three levels] and employment status [two levels], which are added to an index and then each child is assigned to a lower, middle, or higher socioeconomic status group).
[b] Childcare refers to organized childcare outside of the family home.

which corresponds to a mean cumulative number of 31.9 ARI (95% CI: 30.3-33.5) per participant in the first six years of life. The highest incidence was reported between the 7th and 24th months of life, followed by a decreasing trend up to the sixth year of life (Figure 1). On average, ARIs lasted 10.9 days (95% CI: 10.1-11.7 days), with only minor variations by age. The mean cumulative duration of ARIs up to six years was 51.5 weeks (95% CI: 47.5-55.6 weeks). In the pandemic period, starting from March 2020, the incidence of ARIs was lower, likely due to distancing measures (Figure 1).

Occurrence of individual symptoms increased from the first to the second year of life and decreased thereafter (Supplementary Figure 3, Supplementary Table 1). This pattern was similar for all symptoms.

Infection susceptibility – Individual frequency of ARI

Children with high or low infection frequency continued mostly along their percentiles (Supplementary Figure 4). Based on this, we created percentile curves for cumulative infections and for yearly infection incidence (Figure 2). Children at the 10th percentile had less than one infection, whereas those at the 90th percentile experienced eight infection episodes in the sixth year of life.

Factors associated with number of ARI

A higher cumulative number of ARIs at the age of six years was associated with female sex, having no siblings at birth, early childcare attendance, being born by cesarean section, never or non-exclusive breastfeeding more than six months, and having been born in summer (Table 2).

Given the lower completeness in year six, we repeated the analysis for the cumulative number of ARIs until the age of five years, which resulted in virtually unchanged results (Supplementary Table 2). Because in some regions of Germany, childcare is mostly offered from summer/autumn, i.e. when the oldest children leave for school, there is a systematic dependency between season of birth, age of starting childcare, and breastfeeding (which is related to childcare). Therefore, we analyzed the three factors separately but demonstrated that the estimates from the multivariable model are not affected (Supplementary Table 3). Overall, the studied exposure factors explained around 4-5% of the variation in incidence.

The estimates were unchanged when we analyzed the cumulative frequency of infections at the age of two years (Supplement Table 4), lending support to the concept that children follow their trajectory with respect to infection frequency. When using (the not fully appropriate) linear model, we could show that included variables explain about 9.4% and 8.4% of the variation in the cumula-

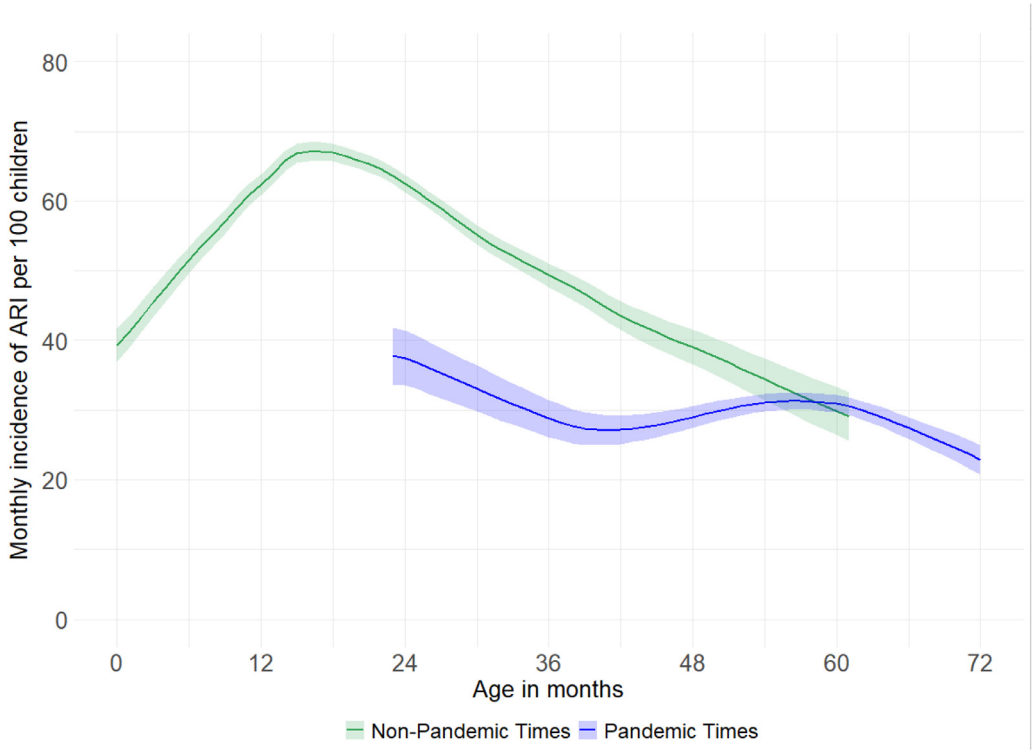

Figure 1. Monthly incidence of ARIs per 100 children by months of life, with 95% confidence interval (generalized additive model). (At the start of the pandemic, children were between 22 and 62 months old; the oldest age group in the blue curve corresponds to the post-pandemic period).
ARI, acute respiratory infection.

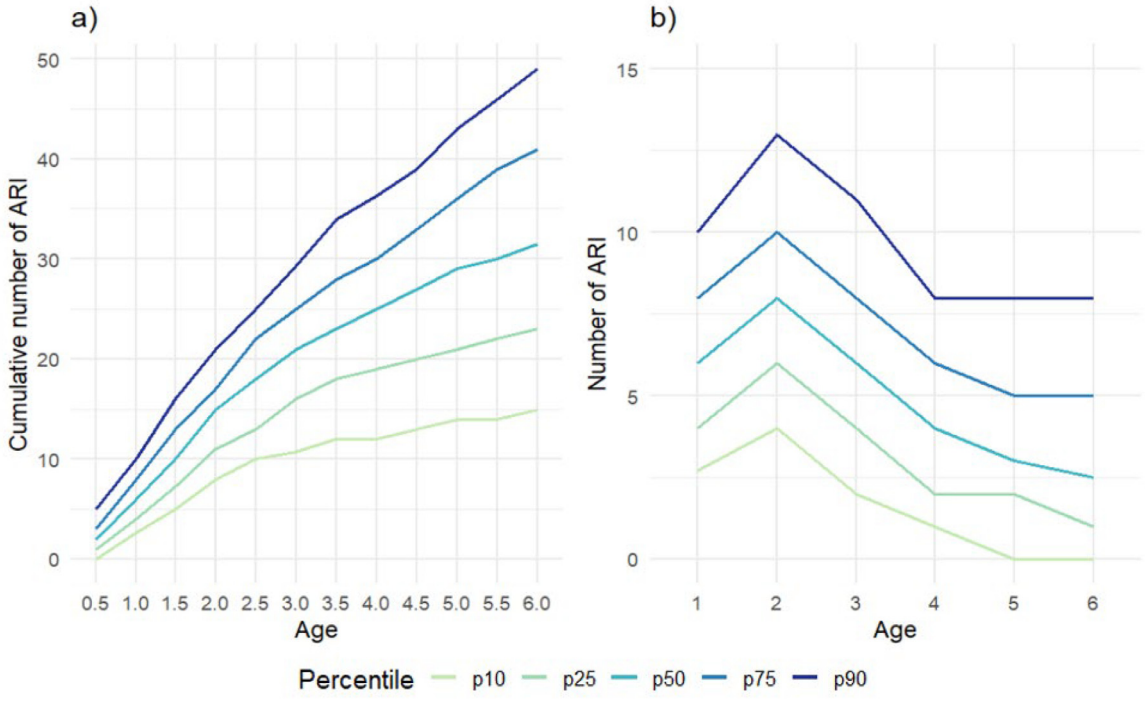

Figure 2. Cumulative (a) and annual (b) percentile curves by age; numbers for the sixth year are potentially biased downward due to a lower completeness of records.

Table 2
Factors associated with individual frequency of ARIs (multivariable mixed Poisson regression for cumulative number of ARIs until the sixth birthday).

	N	RR (unadjusted)	95% CI	RR (adjusted[a])	95% CI
Sex					
Female	127	Ref.		Ref.	
Male	131	0.97	0.93-1.01	0.96	0.91-1.00
Siblings at birth					
No	168	Ref.		Ref.	
Yes	88	0.98	0.94-1.03	0.96	0.92-1.01
Start of attending childcare[b]					
<1 year	34	Ref.		Ref.	
1-2 years	189	1.03	0.97-1.11	1.03	0.97-1.11
>2 years	31	0.90	0.82-0.98	0.87	0.79-0.96
No attendance	3	0.64	0.49-0.82	0.65	0.50-0.85
Birth mode					
Vaginal	200	Ref.		Ref.	
C-Section	57	1.09	1.04-1.15	1.12	1.06-1.18
Breastfeeding (exclusive or partial)					
Never	6	1.40	1.21-1.60	1.39	1.21-1.61
Up to 6 months	41	Ref.		Ref.	
Seven to 12 months	118	1.21	1.13-1.29	1.20	1.12-1.28
More than 12 months	91	1.13	1.05-1.21	1.15	1.07-1.23
Season of Birth					
Spring (March-May)	60	1.06	0.99-1.12	1.06	0.99-1.13
Summer (June-August)	82	1.12	1.06-1.19	1.18	1.11-1.25
Autumn (September-November)	69	Ref.		Ref.	
Winter (December-February)	47	1.04	0.97-1.11	1.03	0.96-1.11

ARI, acute respiratory infection; CI, confidence interval; RR, relative risk.
[a] Mutually adjusted for all variables in the table and for the study center as a random effect.
[b] Childcare refers to organized childcare outside of the family home.

tive number of infections at the age of two and five years, respectively.

Discussion

Our results confirm that children experience a high number of ARIs in the first six years of life, with the highest burden during the second year of life. On average, children in our sample were sick for one of the first six years; however, there was a substantial individual variation, with children in their sixth year of life having no infections at the 10th percentile to eight infections at the 90th percentile. Although the numerical results can depend on the specific situation in each country, for example, in terms of childcare and sample composition, the variability is likely to be a more general feature. Known variables associated with an increased frequency of infections had persistent effects on the cumulative scale until the age of six years but explained only 4-5% of the observed variation in the individual frequency of infections.

To the best of our knowledge, there are only three cohort studies reporting ARIs estimates beyond infancy using prospective data collection, showing that longitudinal, self-reported data on ARIs during childhood is limited. All those studies reported lower values than our results. In the birth cohort conducted in Perth, Australia, two to three ARIs were reported per year in the second to the fifth year of life [10]. Similarly, the COPSAC2000 study (Denmark) reported a mean incidence of upper respiratory tract infections in the first two to three years of life of 2.8 episodes (median 2; interquartile range: 1-4) [9]. The study by Grüber et al. found a mean annual number of 3.4 episodes in infancy (0-2 years old), 2.3 episodes in pre-school age (3-5 years old), and 1.1 episodes in school age (6-12 years old) for children born in Germany in 1990 [11]. The different estimates might be explained through differences between countries (e.g. climate zone), as well as societal changes. In Germany, mothers, especially in former western regions, often stayed home until their child turned three years old [17]. The study by Grüber et al. [11] was conducted in these areas where the childcare typically started afterwards. Currently, early start of childcare is much more common in Germany [18].

In one of our previous analyses of the LoewenKIDS data [19], we showed a strong reduction in ARI frequency and altered pathogen profiles during the COVID-19 pandemic, which is consistent with other studies [20]. The COVID-19 pandemic had a major impact on paediatric ARIs due to non-pharmaceutical interventions, such as the closure of daycares or social distancing orders. Children were less exposed to common viruses during the first 1.5 years of the pandemic and missed out on gaining immunity [20]. However, after some restrictions were lifted, there was a sharp increase in ARIs, with some unusual resurgences of specific viruses, leading to a high health care burden in some European countries [21].

There was a substantial variation in individual ARI incidence among the studied children. We confirmed some known factors associated with a higher incidence; however, they explained only a small fraction of the individual variation. Although it is possible that the effects were diluted by measurement error (for example, we combined partial and exclusive breastfeeding), it is unlikely that this effect is very strong. Thus, we assume that the observed differences in frequency of infections result from differences in susceptibility as an individual characteristic, in line with previous research [11,22]. In an earlier analysis, we could show a correlation with T-cell repertoire in a subsample from our study with blood samples at the age of one and two years [23]. The effect of a higher infection number to increase T-cell diversity did not override preexisting differences in diversity or, possibly, the reactions to subsequent infection were less pronounced. It is possible that this is an effect of the initial infection; however, more likely, it is a predisposition.

The season of birth has been previously shown to have an impact on respiratory infections [24]. Children born in autumn or winter can be protected by maternal antibodies during their first season of increased infections, and children born in the spring are already older when entering autumn/winter season, leaving children born in the summer in the least favorable situation. We were not able to investigate this aspect further (e.g. whether the difference originated in the first winter or whether experiencing more infections at an early age resulted in higher susceptibility in the subsequent years) due to the limited sample size. Although it is

known that for infections caused by the respiratory syncytial virus, the risk of hospitalisation varies up to factor ten, depending on the season of birth [25]; for the mild infections, we mostly found that the difference was around 10%.

With respect to individual susceptibility, for genetic factors, an important role in the host defense was proposed [26]. Some studies showed that the mannose-binding lectin serum protein is particularly important in the vulnerable period of infancy [27,28], whereas others failed to demonstrate an association between the protein and higher susceptibility [29]. The extent to which genetic and environmental factors contribute to and interact with the susceptibility to ARI is still under debate.

Strengths and limitations

The strengths of our prospective study include a community-based sample with longitudinal, detailed reporting of respiratory symptoms for the first six years of life. Although hospitalisation records should be available for many settings, capturing infections not requiring medical treatment is much more demanding. The use of a symptom diary has the advantage of assessing the burden of ARIs in real time, thus avoiding recall bias. The analysis in the study focused on participants with high completeness to increase the robustness of the results. The enrollment of our study was throughout the year so that we could account for seasonal effects.

Our study has some limitations. Parents may have overlooked mild symptoms, and under-reporting and misinterpretation of allergic symptoms cannot be completely ruled out. Some parents might have been more prone to report symptoms, thus artificially creating differences in susceptibility. At the same time, we made efforts to standardize reporting, and the correlation with analyses of blood samples suggested that there is some information in the data. Furthermore, although previous analyses demonstrated that different definitions of ARIs can lead to deviating estimates [30], we used only symptom records and classified the episodes based on those and not what parents perceived as an infection episode. We only selected children who participated until their sixth birthday, with a high completeness. It may be that we have a higher proportion of healthier children whose parents did not have the burden of reporting many symptoms. It should be noted that participants of the LoewenKIDS birth cohort study are mostly well-educated with a high socioeconomic status, not reflecting the whole of the German population.

Conclusion

We showed a high frequency of ARIs during the first six years of life. Our estimates exceeded those previously published, possibly due to changes in childcare. Furthermore, we described substantial inter-individual variation, of which only a small fraction could be explained by known exposure variables, and the remaining differences in susceptibility are likely an individual constitution. It is unknown how this susceptibility is linked to health in adult life.

Declarations of competing interest

The authors have no competing interests to declare.

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Ethical approval statement

Written informed consent was obtained from the parents before recruitment, and approval for the study was obtained from the ethics committees of the Medical Faculty of the Martin Luther University Halle-Wittenberg (No. 2016-04), the Medical School Hannover (No. 6794), and the Ludwig Maximilians University Munich (No. 445-15), Germany.

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Author contributions

Bianca Klee and Rafael Mikolajczyk developed the concept and the design for the analyses and the manuscript. Bianca Klee conducted the analyses and drafted the manuscript. All authors were involed in the acquisition or interpretation of the data. All authors provided comments on the manuscript and all authors accepted the final version.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2025.107802.

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