Acute respiratory infections during the first six years of life in Germany – an analysis of birth cohort data

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Abstract

Background: Acute respiratory infections (ARI) frequently occur in children with varying degrees of severity and can be associated with a high number of medical consultations, antibiotic prescriptions and socio-economic losses. To date, only a limited number of studies have investigated the burden of ARI using prospective data collection to capture also non-medically attended ARI.

The aim of this thesis is to estimate the burden of ARI in children up to the age of six in Germany, focusing on the incidence, symptom occurrence, and risk factors. For a subsample, the objective is to investigate the impact of the Coronavirus Disease 2019 (COVID-19) pandemic on ARI incidence and the underlying viral pathogens.

Methods: Data from the prospective, population-based birth cohort LoewenKIDS were used. A total of 782 children born in Germany between 2014 and 2018 were intensively followed up until the age of six. Symptoms were recorded longitudinally in a symptom diary, summarised as ARI episodes, and analysed descriptively. Data from annual questionnaires were used to assess risk factors for ARI incidence. Symptomatic nasal samples were analysed to investigate differences in viral composition before and during the COVID-19 pandemic. The analyses were conducted for subsamples up to the age of two or six with a high completeness of the symptom diary or with the highest number of participants within an age group.

Results: The children observed had a mean cumulative ARI duration of 51.5 weeks (95% Confidence Interval: 47.5-55.6 weeks) up to the age of six. The maximum yearly ARI incidence was observed in the second year of life, with a mean of 7.7 ARI. The most commonly reported symptoms were runny or congested nose, cough, and increased attachment. Participation in childcare increased the incidence of ARI both up to the age of two and up to the age of six, whereas other exposure factors showed no clear effect at both time points. In the first winter of the German lockdown (2020/2021), a strong reduction in ARI incidence was observed compared with the previous winter. Most viruses, such as Influenza viruses, disappeared in the nasal samples, whereas Human Rhinoviruses were largely unaffected by these measures.

Conclusion: This thesis analyses the burden of disease due to ARI and the impact of the COVID-19 pandemic on children up to the age of six in Germany, using data from a population-based birth cohort study.

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Referat

Hintergrund: Akute Atemwegsinfektionen (ARI) treten bei Kindern häufig und in unterschiedlicher Schwere auf. Sie können mit einer hohen Anzahl von Arztbesuchen, Antibiotikaverschreibungen und sozioökonomischen Einbußen verbunden sein. Bislang gibt es nur wenige Studien, die die Belastung durch ARI, einschließlich nicht medizinisch behandelter Fälle, mittels prospektiver Datenerhebung untersuchen. Ziel dieser Arbeit ist es, die Belastung durch ARI bei Kindern bis zum sechsten Geburtstag in Deutschland abzuschätzen, wobei der Fokus auf der Inzidenz, dem Symptomauftreten und den Risikofaktoren liegt. Anhand einer Teilstichprobe wird der Einfluss der Coronavirus Disease 2019 (COVID-19) -Pandemie auf die ARI-Inzidenz und die viralen Erreger untersucht.

Methoden: Es wurden Daten aus der prospektiven, bevölkerungsbasierten Geburtskohorte LöwenKIDS genutzt. Dabei wurden 782 Kindern, die zwischen 2014 und 2018 in Deutschland geboren wurden, bis zum sechsten Geburtstag intensiv nachverfolgt. Die Symptome wurden longitudinal in einem Symptomtagebuch erhoben, als ARI-Episoden zusammengefasst und deskriptiv ausgewertet. Daten aus jährlichen Fragebögen wurden zur Untersuchung von Risikofaktoren verwendet. Symptomatische Nasenproben wurden analysiert, um die Unterschiede in der Zusammensetzung von Viren vor und während der COVID-19-Pandemie zu untersuchen. Die Analysen wurden für Teilstichproben bis zum zweiten oder sechsten Geburtstag mit hoher Vollständigkeit des Symptomtagebuchs oder mit der höchsten Anzahl von Teilnehmenden innerhalb einer Altersgruppe durchgeführt.

Ergebnisse: Die beobachteten Kinder zeigten im Durchschnitt 51,5 Wochen (95% Konfidenzintervall: 47,5-55,6 Wochen) mit ARI bis zum sechsten Geburtstag. Das Maximum wurde im zweiten Lebensjahr mit durchschnittlich 7,7 ARI erreicht. Die am häufigsten berichteten Symptome waren eine laufende oder verstopfte Nase, Husten und erhöhte Anhänglichkeit. Die Teilnahme an der Kinderbetreuung erhöhte die ARI-Inzidenz sowohl bis zum zweiten als auch bis zum sechsten Geburtstag, während andere Expositionsfaktoren keinen eindeutigen Effekt zu beiden Zeitpunkten hatten. Im ersten Winter des deutschen Lockdowns (2020/2021) wurde ein starker Rückgang der ARI-Inzidenz im Vergleich zum vorherigen Winter beobachtet. Die meisten Viren, wie z. B. Influenzaviren, waren kaum noch nachweisbar in den Nasenproben, während Humane Rhinoviren von diesen Maßnahmen nahezu unbeeinflusst blieben.

Schlussfolgerung: Diese Arbeit analysiert die Krankheitslast durch ARI und den Einfluss der COVID-19-Pandemie bei Kindern bis zum sechsten Geburtstag in Deutschland auf Basis von Daten einer bevölkerungsbasierten Geburtskohortenstudie.

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List of abbreviations

COVID-19	Coronavirus Disease 2019
LRTI	Lower respiratory tract infections
ARI	Acute respiratory infections
URTI	Upper respiratory tract infections
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
RSV	Respiratory Syncytial Virus
RKI	Robert Koch Institute
HRV	Human Rhinovirus
AdV	Adenovirus
NPI(s)	Non-pharmaceutical intervention(s)
95% CI	95% Confidence Interval

1. Introduction and objectives

1.1. Role of acute respiratory infections (ARI) during childhood

Two respiratory conditions, Coronavirus Disease 2019 (COVID-19) and lower respiratory tract infections (LRTI), were among the top ten leading causes of death globally, as reported by the World Health Organization in 2021[1]. This highlights that, despite great advances in medicine, acute respiratory infections (ARI) continue to play a major role in the global disease burden. Children under the age of five are particularly affected by ARI due to their developing immune system and smaller airways[2]. ARI remain one of the most common causes for morbidity and mortality during childhood worldwide[3,4]. According to estimates from the Global Burden of Disease Study, the incidence of upper respiratory tract infections (URTI) showed an increasing trend between 1990 and 2021 among children under five years, particularly in high- and middle-income countries[5]. In contrast, the incidence of LRTI declined during this period, with a stronger reduction in middle- and low-income countries[5]. Nevertheless, pneumonia still caused about half a million deaths among children under five years of age and was the third common cause of childhood mortality in 2021[6]. While the burden, especially for LRTI such as pneumonia, is higher in low-income countries, high-income countries also face severe challenges related to ARI. The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has demonstrated the profound impact that emerging viruses can have. However, existing viruses, such as Respiratory Syncytial Virus (RSV), can also cause a high burden on the healthcare systems. For example, after the lifting of measures against the COVID-19 pandemic in 2022, an intensified, unseasonal increase in RSV cases among the paediatric population led to a high burden on hospitals across Europe[7].

1.2. Definition of ARI

The German Robert Koch Institute (RKI) defines ARI as ‘acute illnesses of the respiratory tract with at least one of the three symptoms fever, sore throat or cough’[8]. This definition is used for surveillance purposes, whereas clinically, ARI are classified into URTI and LRTI. URTI affect the nose, sinuses, the pharynx and the larynx while LRTI involve the trachea and the lungs including the bronchi[9].

However, in the literature, particularly in observational studies, ARI definitions are heterogenous[10]. The main differences lie in the combination of symptoms required to define an ARI. Zoch et al. compared six distinct ARI definitions used in birth cohort studies with symptom diaries[11]. Some definitions required only a single respiratory symptom, such as a runny nose for one day[12,13], whereas others required at least one or multiple symptoms to be present for two consecutive days[14,15]. The studies by Lambert et al. and Linstow et al. required a combination of symptoms (e.g. runny nose and cough), regardless of duration[16,17]. Definitions also varied on symptom-free intervals between episodes, ranging from two to six days. Zoch et al. demonstrated that the use of different ARI definitions can lead to a 1.69-fold variation in the number of reported ARI cases, making it difficult to compare study results[11]. In the following publications, the definition proposed by Lambert et al., which was applied in a birth cohort study conducted in Australia, was used[17]. This definition was found to be in the middle range of most estimates among those compared by Zoch et al.[11] and necessarily entails a trade-off between being specific enough to avoid overestimation and being generic enough to avoid underestimation.

1.3. Causes of ARI

ARI can be caused by a variety of viruses, bacteria, fungi, and parasites. However, the latter two play a minor role in ARI of healthy children; therefore, viral and bacterial infections are described in more detail.

1.3.1. Viral infections

Viruses are the most common cause for ARI in children, and considering all strains and subtypes, there is a large number of different respiratory viruses[18]. The clinical characteristics of four highly prevalent childhood viruses are described below as examples.

Human Rhinovirus (HRV) is the most common respiratory virus and can be detected throughout the year[19]. By the age of two, nearly all children have been exposed to HRV[20]. HRV typically causes mild URTI[21], although some reports indicate associations with LRTI[22,23]. Reinfections are very common due to the presence of over 150 circulating serotypes[24] and a fast waning immunity[25].

RSV is a leading cause of LRTI in infants[26,27], with almost all children experiencing at least one infection by the age of two. However, the severity can range from mild to severe symptomatic cases[28]. RSV infections peak between mid-December and early February[28] and cause high morbidity and mortality, even among healthy newborns worldwide[26]. For example, one in 56 healthy full-term infants in high-income countries is hospitalised due to RSV[29], which accounts for one in 52 deaths globally in children under five[30]. However, in addition to the passive immunisation with Palivizumab for children at high-risk, Nirsevimab has been approved since 2022 for healthy newborns, showing promising effects[31].

Adenovirus (AdV) is typically detected throughout the year, with a higher prevalence in winter[32]. There are more than 50 known serotypes of AdV, and 70-80% of five-year-old children have been exposed to at least one[33]. Due to its non-enveloped structure, AdV is highly stable and can cause outbreaks, particularly in congregate settings[34,35]. It usually causes URTI, gastrointestinal symptoms, or conjunctivitis[36].

Influenza virus typically peaks during winter months[37] and has a high attack rate among children attending childcare and school, contributing strongly to its spread into the community[38]. By the age of six, all children were seropositive for at least Influenza A[39]. Symptoms include the abrupt onset of fever, followed by cough, rhinitis, headache, muscle pain, malaise, and sometimes gastrointestinal symptoms[40,41]. While most Influenza infections are self-limiting, complications such as Otitis media or pneumonia can occur, particularly in younger children[40].

Viral infections do not provide complete immunity, and some reports have shown that reinfections with RSV and HRV are highly frequent, although comprehensive literature remains limited[42,43]. Respiratory viruses have been described in asymptomatic children in several cohorts, with studies finding that Human Bocavirus, HRV, and Human Coronaviruses are often detected without symptoms[42,44-46], whereas RSV and Influenza virus are more likely to be found in symptomatic and medically attended children[47].

1.3.2. Bacterial infections

The nasopharynx of most infants becomes colonised by various bacterial species, such as *Streptococcus pneumoniae*, *Haemophilus influenzae* or *Moraxella catarrhalis*, within the first years of life[48]. This colonisation peaks at the age of two to three and decreases thereafter[48]. Bacterial colonization is not a stable state, but rather a complex, dynamic process including acquisition, elimination and interaction between strains and the host over time[49]. If the nasal microbiome is in balance, these bacterial species do not cause symptoms and are even believed to play a beneficial role[50]. However, if host conditions change, for example after a viral infection, this can lead to bacterial overgrowth. Bacteria may then invade adjacent sites, such as lungs or middle ear, and cause disease through various mechanisms[51]. The prevalence of nasopharyngeal carriage varies widely between studies[48]. A study in Germany reported a prevalence of 35% and 24% for *S. pneumoniae* and *H. influenzae* in 1.5-year-old and 42% and 40% in 5-year-old children, respectively[52]. Major factors influencing bacterial colonization include social factors (e.g. family size, day care attendance), genetic background, age and geographical area[48].

1.3.3. Coinfections

Past studies showed that infections with more than one virus at the same time are very common in children, reaching levels of up to 40%[53,54]. Although previously controversially discussed, a meta-analysis found that viral coinfections do not impact the severity of outcomes in children, regardless of the virus combinations[55]. Explanations for this include that some viruses may be shed asymptomatically for extended periods[56], or that faster-replicating viruses can block host cells from being used by slower-replicating viruses[57].

Besides viral-viral coinfections, viral-bacterial coinfections play a substantial role, especially in LRTI. Some studies have shown that bacteria were codetected in about 40% of RSV cases[58,59]. Multiple studies showed that viral-bacterial coinfections can increase the severity of ARI[51]. It seems that bacteria and viruses interact with each other to evade and to colonise the host immune system[60]. Influenza virus and *S. pneumoniae* are a prominent example, as they can cause acute Otitis media through a synergistic relationship[60].

1.4. Characteristics of ARI

1.4.1. Frequency

There are several studies from Canada, Australia, Scandinavian countries, and Germany that report estimates ranging from three to 14 ARI episodes in the first two years of life[12,13,15,61-63]. These differences may be explained by variations in assessment methods and definitions, study regions, and associated social and cultural differences, as well as the year of the study.

Few studies prospectively report the frequency of ARI beyond the age of two. The 'Copenhagen Prospective Study on Asthma in Childhood' birth cohort found 2.8 URTI episodes in the third year of life[64]. An Australian birth cohort estimated two to three ARI per year from ages two to five[12], while a community-based Australian study found an average of 4.3 ARI in years two to three and 3.6 ARI in years four to five[65]. A German study conducted in the early 1990s reported 2.3 ARI per year in children aged three to five[63].

1.4.2. Duration

A systematic review showed that 90% of children recovered from a common cold within 15 days, from sore throat within two to seven days, from bronchitis within 21 days, and from an acute cough within 25 days[66]. Another review found similar results, about 50% of children were still suffering from nasal discharge and cough after one week, and between 10-20% were still affected after three weeks following consultations[67]. Besides symptoms affecting the respiratory tract, more than 90% of children reported illness-related symptoms such as disturbed sleep, decreased food or fluid intake, feeling unwell, or disruptions to daily activities[68]. The median time to recovery from these symptoms was reported to be between four and five days, while recovery from respiratory symptoms took six to eight days for URTI and LRTI, respectively[68].

1.4.3. Symptoms

The prevalence of symptoms was previously described in a British cohort study, which included more than 13,000 preschool children[69]. The symptoms of cold, cough and fever were very commonly reported between birth and 4.5 years of age[69]. Kusel et al. confirmed these observations; runny or blocked nose and cough were the most common symptoms reported by parents of children aged five years and younger[12]. This is consistent with a study from Denmark, where nasal discharge and cough were most commonly reported during the first year of life[16].

1.5. Associated factors with ARI incidence

A variety of factors are associated with the frequency and characteristics of ARI, including biological, socio-economic, and environmental factors.

Biological factors include genetic predisposition, birth mode, prematurity, age, sex, and chronic diseases of the child. There is some evidence that genetic factors influence susceptibility to ARI, but the potential mechanisms remain unexplored[70-73]. Previous studies have shown that children born prematurely[74] or by Caesarean section have a higher risk of ARI in early childhood, especially LRTI, which might be mediated through different gut microbiota compositions[75]. Male infants seem to have a higher risk for LRTI, which continues into higher age groups[76]. Children with chronic diseases are known to be at higher risk for severe ARI[77].

Children of parents with lower socio-economic status are at higher risk for ARI[78]. This association is likely mediated by factors such as inadequate nutrition, poor living conditions and limited access to healthcare.

There are established associations between an increased number of ARI cases and the cold season[13,63], day care attendance[13,79], having siblings[63,80], tobacco exposure[81] and air pollution in general[82]. Several reviews showed that breastfeeding is protective against ARI, although the optimal duration has not yet been established[83].

1.6. Association of ARI with chronic diseases

A recent meta-analysis combing the data from 150,000 children across 38 European cohorts showed that both URTI and LRTI in early-life were associated with school-age asthma, with a stronger effect for LRTI[84]. LRTI were additionally associated with lower lung function during school age[84]. Liu et al. reported similar findings in a meta-analysis, showing that wheezing due to HRV in the first three years of life is associated with a higher risk of asthma in later childhood[85]. The Finnish Espoo Cohort study followed children over a period of 20 years and found that individuals with asthma had an increased risk of ARI since childhood[86]. Other studies have used proxy markers such as the number of siblings or day care attendance to show a possible association between the exposure to infections and a lower risk for the development of asthma and atopic diseases[87,88]. The mechanisms by which ARI and the development of asthma are associated are not yet completely understood. Some researchers suggest a reverse causation, meaning that children predisposed to asthma are more likely to develop LRTI[89]. Others attempt to explain this by immunological mechanisms[90] and the disturbance of lung development by LRTI, possibly causing asthma later in life[91]. In addition to asthma, other respiratory conditions, such as chronic bronchitis or chronic obstructive pulmonary disease, are also associated with ARI during childhood, possibly caused by similar mechanisms[92,93].

1.7. Economic and societal consequences of ARI

The economic burden due to LRTI is estimated at €213 million annually in Germany for children treated in inpatient and outpatient departments up to the age of three[94]. The mean costs were €123 for outpatient treatment and €2,579 for inpatient treatment per LRTI[94]. RSV infections are highly expensive, with mean hospitalisation costs ranging from €3,001 to €3,961 per case[95]. Data on the overall costs of URTI and LRTI in Germany are missing. In addition to direct costs, the sickness of the child has a considerable impact on the quality of life of the parents. One study reported that sleep was disturbed in 72% of parents when their child suffered from acute cough[96], and 75% of parents were worried during a RSV infection[30]. A study in Finland reported that children were, on average, absent for 4.9 days from childcare, depending on the virus[97], while a review on Influenza estimated an absence between three and twelve days[98]. Schot et al. showed that 52% of children up to two years were absent from childcare for a median of two days, and 28% of mothers and 20% of fathers were absent from work with a median time of eight hours in the first week after visiting a medical doctor for ARI[68]. Similar results were found in a study in Finland, where 44% of families reported at least one day of absence from work, with a mean of 2.1 days in case of a paediatric ARI[97]. A review about the burden of Influenza in European countries showed that the mean number of days parents were absent from work ranged from 1.3 to 6.0[98].

1.8. Assessment methods for ARI

Studies investigating ARI have used various methods. Studies relying on data from healthcare reports, claims, or registers provide insights into the burden and medical costs of ARI for the healthcare system across large populations[94]. Studies in inpatient or outpatient settings can evaluate symptoms, severity, and treatment, along with laboratory and functional test results[99]. However, neither approach alone captures the full burden, as most paediatric ARI do not require medical consultation[100]. Observational studies can provide a valuable approach to overcome these limitations. While retrospective studies using, for example, questionnaires, are prone to recall bias, prospective studies can avoid this restriction by collecting data in real-time in a health diary[101]. Symptom diaries can be used as primary data source to assess non-medically attended ARI. The advantages of symptom diaries are that they provide high-quality data by minimising recall bias[101]. They also have rich analytic potential for estimating the true burden of disease[101]. On the other hand, they are time- and resource-consuming and require a high level of cooperation from participants, especially if the recording period is long; otherwise there may be high attrition[101]. Cohort studies are best suited for the prospective, longitudinal analysis of ARI. Birth cohort studies are a specific type of cohort study, following individuals born within a similar period of time[102]. The design of birth cohort studies allows researchers to draw associations between early life exposures and outcomes later in childhood or even adulthood[102]. Besides information collected through questionnaires, birth cohort studies often collect a wide range of information, such as biological material and links to health insurance data, which increases the potential for more in-depth analyses[102]. Some even include data from parents and grandparents to strengthen the life-course epidemiology approach. However, birth cohorts are prone to loss-to-follow-up, which could enhance the selection bias within the cohort[102].

1.9. LoewenKIDS birth cohort as method to identify ARI

The following publications are based on data from the LoewenKIDS study. The LoewenKIDS Birth Cohort Study uses a comprehensive study design to establish a life-term perspective[103]. Between 2014 and 2018, the study recruited 782 children at birth or shortly after in five study regions in Germany. They are followed up intensively up to the age of six and less intensively up to the age of 15. During the intensive period, parents are asked to fill in a daily symptom diary and submit yearly questionnaires. Biological samples are collected at defined time points (routine samples) as well as during ARI and gastrointestinal infections. The distinctive feature of the LoewenKIDS study is the continuous use of a symptom diary for the first six years of life. A recent scoping review found that 22 birth cohort studies worldwide used symptom diaries, and only six of these continuing up to the age of six years[104]. The greatest advantage of a health diary is the ability to receive prospective, real-time data of all symptoms that occur[101]. This approach avoids the bias of missing mild ARI, which may be underreported in hospital or outpatient studies where mostly severe ARI are treated.

The comprehensive data collection in a birth cohort study allows to understand the incidence and risk factors of ARI holistically in a lifetime approach and provides valuable insights into long-term outcomes.

1.10. Research question

ARI in childhood occur with high frequency, posing a heavy burden on children, their families, and the healthcare system, and can be associated with the development of chronic diseases later in life. While there are some prospective, longitudinal birth cohort studies monitoring the occurrence of ARI during early childhood, differences in definitions, timeframes, and locations make it difficult to generalise study results. The latest estimates for German children date back to the early 1990s[63], meaning recent data is lacking. Data from prospective studies can provide valuable insights into the expected number of mild and severe ARI, helping clinicians, public health professionals and policymakers in making informed decisions.

1. This thesis investigates the incidence of ARI within the first two and the first six years of life, using the population-based, longitudinal birth cohort study LoewenKIDS. The study analyses the incidence of ARI, including age-dependency, seasonality, symptom burden and risk factors for susceptibility from infancy to preschool age.

In addition to the factors mentioned above, the COVID-19 pandemic strongly influenced the pattern of seasonal ARI. Prospective birth cohort studies allow to study the dynamic course of ARI and can evaluate various effects, such as those of the COVID-19 pandemic, in a longitudinal perspective.

2. To understand the effect of the COVID-19 pandemic on ARI during childhood, this study analyses the impact of non-pharmaceutical interventions (NPIs) on the ARI incidence and characteristics in three- to four-year-old LoewenKIDS participants. Additionally, the occurrence and composition of nasal pathogens before and during the first German lockdown winter (2020/2021) of the COVID-19 pandemic are compared.

2. Discussion

A subsample of 288 participants with a highly complete symptom diary (≥98%) was selected for the analysis of the ARI incidence during the first two years of life. Participants reported a mean of 13.7 ARI (Interquartile Range: 10-17 ARI) with 6.0 ARI in the first and 7.7 ARI in the second year of life. ARI lasted on average 11 days (Standard deviation: 5.8 days), with runny or blocked nose and cough being the most commonly reported symptoms. A higher ARI incidence was associated with attendance at childcare, and the presence of siblings.

A subsample of 258 participants, with at least 80% completeness of the symptom dairy, was selected for the analysis during the first six years of life. Participants reported a mean of 51.5 weeks (95% Confidence Interval (95%CI): 47.5-55.6 weeks) of ARI by the age of six. The incidence peaked at the age of 14 months, with about 70 ARI per 100 children, and declined thereafter. The percentile curves showed large variations between children. While children at the 10^{th} percentile had fewer than four ARI in their second year of life, children at the 90^{th} percentile had about 13 ARI. Children, who were more or less susceptible during infancy, generally continued in the same group up to preschool age. Factors such as female sex, having no siblings at birth, early childcare attendance or being born by C-Section were associated with a higher incidence of ARI at age six. However, the investigated factors explained only around 5% of the individual variation.

To evaluate the effect of the COVID-19 pandemic, the frequency and characteristics of ARI in the first German lockdown winter (2020/2021) were analysed and compared to the pre-pandemic winter (2019/2020). For this analysis, the largest age group at this time (three to four-year-olds) was used. During the pre-pandemic period, an average of 2.8 ARI per child were reported between October and March. However, this decreased to 1.3 ARI per child in the first lockdown winter. The duration of ARI shortened from an average of 12.3 days (95%CI: 11.3-13.4 days) in the pre-pandemic winter to 8.6 days (95%CI: 7.5-9.7 days) in the pandemic winter, although the reported symptoms remained similar. Changes in monthly incidences followed the stringencies of mitigating measures. By analysing the nasal swabs with multiplex polymerase chain reaction, a strong reduction in almost all viruses, except AdV, HRV, and bacteria was observed. The proportion of detected HRV even increased. Viral coinfections decreased from 57% of all samples in the pre-pandemic period to 21% in the pandemic period.

The respective publications (P1, P2, P3) contain comprehensive discussions of the results obtained. The following sections highlight key aspects for an outlook in a broader context.

2.1. The role of ARI in a lifetime perspective

The results of the studies (P1, P3) showed a high incidence of ARI, with children experiencing respiratory symptoms for almost one year out of the first six years of life (P3). This places a considerable burden on families, potentially affecting their quality of life, work, and social activities. These findings are valuable for different stakeholders. Medical doctors can use them to guide parents on the expected frequency of ARI and to identify children at high risk. Policy makers may assess the implications for parental sick leave or productivity loss, while public health professionals can evaluate the overall burden of paediatric ARI and develop prevention strategies. The incidence rates exceed estimates from a German study conducted in the early 1990s[63], but align more closely with an Australian study from the late 1990s[65]. The difference compared to the German study might be attributed to increased daycare attendance following the expansion of kindergarten places in the mid-1990s[105]. However, within the percentile curves, large individual differences were observed, and, interestingly, children moved along their respective curves (P3). Children seem to have varying susceptibilities to ARI, raising the question of why some healthy children are more affected than others. Several studies have shown that environmental factors, such as siblings[63,80] or childcare attendance[13,79], play a role in the incidence of ARI, and most of them could be confirmed with data from the LoewenKIDS cohort (P1, P3). However, the analysis of the first six years showed that these factors accounted for only a small proportion of the individual variation (P3), suggesting that other factors might also play an important role. Some studies point to a genetic predisposition for infection susceptibility[71]. Among other genetic regulated factors, a deficiency in the Mannose-binding lectin protein, which is important for the adaptive immune response, could lead to increased susceptibility to ARI, although this is controversially discussed[106]. A previous study of a subsample of LoewenKIDS showed that lower T-cell diversity or higher clonality at age one was associated with a higher number of ARI in the first four years of life[73]. T-cell diversity is influenced by both genetic factors and environmental factors[107]. To date, the interaction between these factors and the relative contribution to infection susceptibility remains unexplored. This information could be used in the future for prevention, and therapeutic interventions. Besides exposure factors that cause ARI, it is also important to discuss the implications of having more or fewer ARI for an individual's health. The question of whether ARI have a positive or negative effect, particularly on the development of allergies and asthma, was initiated by the 'Hygiene Hypothesis'.

According to the 'Hygiene Hypothesis', infections during childhood protect against allergic diseases later in life[108]. This idea was firstly proposed by Strachan in 1989, who published an article showing that eczema and hay fever are less common in children with larger families[108]. He assumed that those children are more exposed to infections through their siblings. This was the first attempt to explain the rapid increase in allergic diseases in the 20th century. In the presented studies siblings also increased the incidence of ARI within the first two years of life (P1), but not within the first six years of life (P3).

In 2003, Rook proposed the ‘Old Friend Hypothesis’[109]. He stated that it is important to be early and regularly exposed to a diverse range of harmless microorganisms that co-evolved with humans[109]. He stressed that exposure to microorganisms causing infections (e.g. measles) is less important than contact with a variety of different microorganisms to train the immune system[109]. Those exposures might have decreased in recent years due to changes in sanitation, lifestyle, diet, or medical advancements[109]. In contrast to the ‘Hygiene Hypothesis’, where childhood infections seem important to protect against allergic diseases, the diversity of microbial exposure appears to be more crucial in Rook’s theory.

It seems that the interpretation of Strachan’s initial idea has evolved over time. The protective effect that has been observed is more likely to be mediated by contact with commensal microorganisms. For example, two large European studies have shown that children living on farms, who are exposed to a wide range of microbes, have a lower prevalence of asthma and atopy[110,111]. In particular, exposure to cowsheds and consumption of unprocessed cow's milk appear to be associated with a lower risk of asthma and allergies, also known as the 'farm effect'[112]. The gut microbiome is influenced by these factors, and it is possible that this plays an important role in the development of asthma and atopic diseases. Noverr and Hufnagle proposed the ‘Microflora Hypothesis’ in 2005[113]. They suggested that the gastrointestinal microbiota is disrupted due to increased antibiotic use and dietary patterns in the industrialised world[113]. Although anatomically distinct, these changes may influence the lung microbiota through the gut-lung axis, and this may contribute to the development of allergic airway diseases.

The interplay between the frequency of ARI, the immune system, microbiome composition, environmental factors, and the development of chronic diseases involves complex interactions. While recent decades have provided more insight into this topic, further research using advanced technologies such as omics approaches and high-throughput sequencing, combined with epidemiological data, is needed for a deeper understanding. One of the main aims of the LoewenKIDS study is to investigate the effect of infections, together with microbiome and genetic data on the development of asthma, allergies, and atopic diseases. Due to its comprehensive study design, the factors outlined in the aforementioned theories can be incorporated and evaluated within a lifetime perspective.

2.2. The effect of the COVID-19 pandemic on ARI

In the first phase of the COVID-19 pandemic, NPIs, such as temporary closure of day cares, dominated the public health response. The RKI reported a strong reduction in ARI rates with the beginning of the first lockdown in March 2020, and an absence of Influenza and RSV waves during the winter of 2020/2021, aligning with the second lockdown[114]. The intensity of the NPIs in 2020 was reflected in the number of ARI reported by LoewenKIDS participants (P2, P3). During the most intense NPIs, the incidence was at its lowest and increased gradually after some measures were lifted in spring 2021 (P2). Compared to the winter of 2019/2020, children experienced a strongly reduced number of ARI, with infections primarily caused by HRV, which typically results in mild disease courses (P2). Nearly all other viruses were undetectable during this period (P2), as almost all transmission routes were disrupted. For example, day cares and playgrounds were temporarily closed, contact restrictions were imposed in workplaces and private meetings, masks were mandatory for adults, and there was an overall increased focus on hygiene and distancing measures. However, in the retrospective of the pandemic, the closure of day care centres was later considered too stringent[115]. Toddlers, who typically experience a high number of ARI (P3), missed an entire winter season (P2). At that time, it was not foreseeable that the lockdown would have such a strong impact on children's immune systems. After some NPIs were eased in 2021, ARI rates remained lower than pre-pandemic levels, but an unseasonal and intense RSV wave occured[116], followed by a mild Influenza wave in early 2022[114]. By early November 2022, both RSV and Influenza waves occurred unusually early, leading to a sharp increase in paediatric hospitalisations and a strong shortage of hospital beds across many European countries[7]. The high incidence of previously undetectable viruses was attributed to the lifting of most NPIs as the COVID-19 pandemic progressed, which allowed transmission to resume. In mid-2021, the paediatrician Robert Cohen raised concerns about the impact of NPIs and introduced the concept of 'immunity debt'[117]. This theory suggests that due to the lack of exposure, the adaptive immune system is not adequately stimulated and cannot build up an immune memory[117]. This memory, which is typically developed during childhood, is crucial for providing more effective protection during subsequent exposures. The missed contact to infections and the resulting decreased capability of children's adaptive immune system might lead to higher susceptibility to infections. Following the end of NPIs, increased incidence due to higher community transmission was expected. This prediction has proven accurate, as many studies worldwide have reported the resurgence of RSV und Influenza[118-121]. Besides the immune debt theory, other researchers proposed an 'immune injury theory', which suggests that a SARS-CoV-2 infection may damage the immune system, making it more susceptible to other respiratory viruses[122,123]. However, comprehensive studies supporting this theory are lacking. Alternative explanations include viral inference between SARS-CoV-2 and other respiratory viruses, increased RSV virulence, or changing environmental factors[122]. Although children were not strongly affected by COVID-19 itself, they suffered notably from the unseasonal outbreaks and from the restrictions in terms of mental and physical health[124].

2.3. Strengths and limitations

The greatest strength of the presented studies is their population-based, prospective, longitudinal data collection. Prospective data collection provides real-time data, which reduces recall bias, while longitudinal data are particularly valuable for establishing time trends and causal relationships. While data from hospitals or medical settings are easier to collect, they can be more biased as they often include more severe cases. The population-based LoewenKIDS cohort offers the advantage on including mostly healthy children, resulting in a higher external validity. A distinct study module of the LoewenKIDS birth cohort is the symptom diary. While this could be tiring for the participants, it provides valuable insights into the symptom burden carried by the families. The combination of the different data and samples collected within the LoewenKIDS cohort allows in-depth analysis. For example, the selected nasal swabs were analysed for 25 respiratory viruses and bacteria, which exceeds medical standards. Further, this information was combined with the ARI incidence over two consecutive winter periods.

However, the study has several limitations. First, there was attrition of participants over time, likely due to the very intense study design, which involved several study elements over six years. Of the initial 782 participants, 467 actively continued until their sixth birthday, and 288 (P1) and 258 (P3) participants were included in the analyses. Study participation is time-consuming and can be an additional burden for parents, leading to dropouts. Financial compensation could not be offered, but efforts were made to keep participants motivated by sending them biannual newsletters with study results and presents for the children on their birthdays. Loss-to-follow-up is a common problem in longitudinal studies, which can lead to reduced generalisability and statistical power[125]. The main analyses were based on parents' entries in the symptom diary. However, as expected, completeness varied between participants. To increase the robustness of the results, we only used highly complete symptom diaries for the analysis. This might have introduced a selection bias if only highly motivated participants or those with a low symptom burden filled in the diary. The data in the symptom diaries were self-reported, meaning symptoms were subjectively recorded by the parents, and it cannot be ruled out that some symptoms were misclassified. However, detailed instructions for the parents and support in case of insecurities were provided. The participants were aged between two and six years when the COVID-19 pandemic started in March 2020. Although the effect of the pandemic was adjusted for in the models, it cannot be excluded that the interventions influenced parents' perception of symptoms. Lastly, parents, who participated in the study were well-educated and affluent, and thus had a high socio-economic status. This does not reflect the distribution in Germany, meaning that the sample is not fully representative for the German population.

2.4. Conclusion

This thesis provides comprehensive analyses of self-reported ARI from infancy to preschool age. The LoewenKIDS cohort is one of the very few birth cohorts to record ARI symptoms from birth to six years using a symptom diary. A high frequency of ARI during the first six years of life, with a peak in the second year, was observed. Although awareness of ARI was raised during the COVID-19 pandemic, the studies shed light on the burden primarily carried by caregivers and indirectly by society, which could help to inform medical doctors, public health professionals and policy makers. Although only few risk factors for ARI susceptibility could have been identified, future genetic and microbiome analyses may provide further insights into this complex interplay. The study is still ongoing and participants are followed up to the age of 15. Due to the longitudinal design, the impact of ARI on the development of chronic diseases, such as asthma, later in life will be studied.

As the COVID-19 pandemic demonstrated, respiratory viruses are likely to have the potential to cause both endemic and pandemic outbreaks. Although children were not severely affected by COVID-19 itself, they were indirectly impacted by strong, atypical outbreaks of RSV and Influenza. Data from the LoewenKIDS cohort demonstrated how NPIs influenced the incidence of ARI and most respiratory viruses. While disease surveillance is the responsibility of public health authorities, epidemiological studies can provide deeper insights, for example, by combining biomaterials such as nasal samples with metadata. Most LoewenKIDS participants were toddlers during the pandemic, and the longitudinal design will allow to study the effects of the pandemic in later ages.

In summary, ARI represent a substantial disease burden during childhood. Although advances in medicine and research can be expected, ARIs will likely remain one of the leading causes of morbidity and mortality worldwide due to the high number of existing and emerging pathogens, the susceptibility of children's immune systems, and the ability of these infections to spread rapidly through various transmission mechanisms.

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4. Theses

1. Within the first two years of life, participants reported a mean of 13.7 acute respiratory infections (Interquartile Range: 10–17), with 6.0 acute respiratory infections in the first and 7.7 in the second year.

2. A higher incidence of acute respiratory infections during the first two years of life was associated with participation in childcare and the presence of siblings.

3. The mean cumulative duration of acute respiratory infections up to the age of six was 51.5 weeks (95% Confidence Interval: 47.5–55.6), with large individual differences.

4. Acute respiratory infections lasted on average 10.9 days (95% Confidence Interval: 10.1–11.7), with runny or congested nose, increased attachment, and cough being the most prevalent symptoms in the first six years of life.

5. Known exposure factors associated with the increased incidence of acute respiratory infections explained only 5% of the variation in individual frequencies at the age of six years.

6. The incidence of acute respiratory infections among three- to four-year-old children decreased from 2.8 ARI per person in pre-pandemic winter months to 1.3 ARI per person in the first pandemic winter months.

7. The detection of Influenza Virus, Respiratory Syncytial Virus, Parainfluenza Virus, Human Enterovirus, and Human Bocavirus decreased strongly during the pandemic, while the prevalence of Adenovirus remained nearly unaffected, and the proportion of Human Rhinovirus even increased.

8. Codetection (the detection of more than one virus in a single symptomatic swab) was common in the pre-pandemic period (56.9%), but substantially less common during the pandemic period (21.3%).

Publications

List of included publications

1. Symptom Burden and Factors Associated with Acute Respiratory Infections in the First Two Years of Life—Results from the LoewenKIDS Cohort (P1)

Langer, S., Horn, J., Gottschick, C., **Klee, B.**, Purschke, O., Caputo, M., Dorendorf, E., Meyer-Schlinkmann, K. M., Raupach-Rosin, H., Karch, A., Rübsamen, N., Aydogdu, M., Buhles, M., Dressler, F., Eberl, W., Koch, F. E. V., Frambach, T., Franz, H., Guthmann, F., Guzman, C. A., … Mikolajczyk, R. (2022). Symptom Burden and Factors Associated with Acute Respiratory Infections in the First Two Years of Life-Results from the LoewenKIDS Cohort. *Microorganisms*, *10*(1), 111. https://doi.org/10.3390/microorganisms10010111

Personal contribution: Development of the research question, interpretation of results, writing and revision of the manuscript

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2. The impact of non-pharmaceutical interventions on community non-SARS-CoV-2 respiratory infections in preschool children (P2)

Klee, B., Diexer, S., Horn, J., Langer, S., Wende, M., Ortiz, D., Bielecka, A., Strowig, T., Mikolajczyk, R., & Gottschick, C. (2024). The impact of non-pharmaceutical interventions on community non-SARS-CoV-2 respiratory infections in preschool children. *BMC pediatrics*, *24*(1), 231. https://doi.org/10.1186/s12887-024-04686-2

Personal contribution: Development of the research question, data cleaning, data analyses, reporting of results, interpretation of results, writing and revision of the manuscript

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3. Acute respiratory tract infections during the first six years of life – results from the German cohort study LoewenKIDS (P3)

Klee, B., Diexer, S., Langer, S., Gottschick, C., Hartmann, C., Glaser, N., Horn, J., Dorendorf, E., Raupach-Rosin, H., Hassan, L., Rübsamen, N., Meyer-Schlinkmann, K. M., Guzman, C. A., Heselich, V., Battin, E., Pietschmann, T., Pieper, D. H., Pletz, M., Riese, P., Trittel, S., … Mikolajczyk, R. (2025). Acute respiratory tract infections during the first six years of life - results from the German birth cohort study LoewenKIDS. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases*, 153, 107802. Advance online publication. https://doi.org/10.1016/j.ijid.2025.107802

Personal contribution: Development of the research question, data cleaning, data analyses, reporting of results, interpretation of results, writing and revision of the manuscript

Publication 1 (P1)

Langer, S., Horn, J., Gottschick, C., **Klee, B.**, Purschke, O., Caputo, M., Dorendorf, E., Meyer-Schlinkmann, K. M., Raupach-Rosin, H., Karch, A., Rübsamen, N., Aydogdu, M., Buhles, M., Dressler, F., Eberl, W., Koch, F. E. V., Frambach, T., Franz, H., Guthmann, F., Guzman, C. A., Mikolajczyk, R. (2022). **Symptom Burden and Factors Associated with Acute Respiratory Infections in the First Two Years of Life-Results from the LoewenKIDS Cohort.** Microorganisms, 10(1), 111. https://doi.org/10.3390/microorganisms10010111

microorganisms

Article

Symptom Burden and Factors Associated with Acute Respiratory Infections in the First Two Years of Life—Results from the LoewenKIDS Cohort

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Abstract: Acute respiratory infections (ARIs) are the most common childhood illnesses worldwide whereby the reported frequency varies widely, often depending on type of assessment. Symptom diaries are a powerful tool to counteract possible under-reporting, particularly of milder infections, and thus offer the possibility to assess the full burden of ARIs. The following analyses are based on symptom diaries from participants of the German birth cohort study LoewenKIDS. Primary analyses included frequencies of ARIs and specific symptoms. Factors, which might be associated with an increased number of ARIs, were identified using the Poisson regression. A subsample of two hundred eighty-eight participants were included. On average, 13.7 ARIs (SD: 5.2 median: 14.0 IQR: 10–17) were reported in the first two years of life with an average duration of 11 days per episode (SD: 5.8, median: 9.7, IQR: 7–14). The median age for the first ARI episode was 91 days (IQR: 57–128, mean: 107, SD: 84.5). Childcare attendance and having siblings were associated with an increased frequency of ARIs, while exclusive breastfeeding for the first three months was associated with less ARIs, compared to exclusive breastfeeding for a longer period. This study provides detailed insight into the symptom burden of ARIs in German infants.

Keywords: birth cohort; respiratory infection; newborn; children; symptom diary; longitudinal observation; infectious diseases; symptom burden; LoewenKIDS

1. Introduction

Acute respiratory infections (ARIs) continue to be the most common health problem during childhood worldwide. Although most ARIs are not severe [1], they contribute to a high number of outpatient visits [2], antibiotic prescriptions, hospitalizations [2,3], as well as to socioeconomic burden [4,5] and absenteeism in education and work [6]. In addition, infections with respiratory viruses (e.g., human rhinovirus, enterovirus, and adenovirus) in early childhood can influence the development of chronic and immune-mediated diseases such as asthma, type II diabetes, and obesity later in life [7,8]. Respiratory infections often heal spontaneously, and, in more than 50% of the cases, there is no doctor's consultation required, and, in even less cases, hospitalization is involved [4,5]. Therefore, it is impossible to determine the true frequency and burden of ARIs based on medical reports or hospital-based studies [9,10]. Individual information on frequency of infections can indicate particularly high susceptibility to infections, and initiate further assessment. For this purpose, contemporary norms are necessary.

Previous observational studies [11–14] used different assessment methods to determine the frequency of ARI episodes, often including a retrospective assessment. However, retrospective methods may result in under-reporting and recall problems [14], if not only a short time period is considered [15]. It is therefore highly relevant to assess the frequency of ARIs with a real-time approach, such as daily entries into a symptom diary. Symptom diaries are an excellent method to counteract under-recording and allow a detailed description of the burden of disease. Different studies found between three to seven ARIs per year in early childhood (children up to two years old) [16–19]. In Germany, frequencies of ARIs were last reported for children born in 1990 [1]. Here, only three episodes per year were recorded for children in the first year of life. Since then, no publication was published in Germany which estimated the frequencies of ARIs in children.

There are several factors which might influence the frequency of ARIs in the first two years of life. Previous studies already found out, that older age (compared to the first six months), cold seasons, childcare attendance [18,19], having older siblings, maternal smoking [20], and male sex [21] are associated with a higher number of ARIs, while full breastfeeding [22] is associated with a lower frequency of ARIs. With societal changes, the role of these factors might be changing.

Therefore, we investigated the frequency, the full burden of symptoms, as well as factors associated with ARIs in the first two years of life based on symptom diary data of the German population based on the prospective birth cohort study LoewenKIDS.

2. Materials and Methods

2.1. Study Population

A detailed description of the study design, methods of recruitment, and data collection is provided elsewhere [14]. Briefly, the LoewenKIDS-study is an ongoing population-based observational birth cohort study, which recruited 782 newborns between November 2014 and February 2018 in five study regions in Germany (Clinicaltrials.Gov Identifier: NCT02654210 (Accessed on: 1 January 2021)). Participants were recruited antenatal and postpartum until the age of three months and are followed up until the age of 15 years. In 2020, all study participants were two years old or older.

2.2. Data Collection/Symptom Diary

Parents were invited to keep a daily symptom diary in the first six years of life of their child. They recorded all the child's symptoms, symptom-free days, doctor consultations, diagnoses, medication, and absence from work or childcare on a daily basis. Participants could choose between a paper-based diary, an online version, or an app. Changes between the different modes were allowed. Symptoms such as fever, wheezing, chills, sore throat, runny/congested nose, increased need to sleep, and increased attachment were included in the symptom diary, as well as severity of the aforementioned symptoms. The symptom diary was developed on the basis of the symptom diary used by the birth cohort ORChID [15] and adapted after a feasibility study [16].

2.3. Questionnaires

Parents filled in questionnaires at the birth of their child and at the age of six months, one year, and then annually until the age of 15 years. Questionnaires contain information on social and health characteristics, pregnancy, and birth, as well as on selected diseases and environmental factors.

2.4. Classification/Definition of ARI Episode

We adapted the ARI definition proposed by Lambert et al. [23–25]. We classified ARIs by distinguishing between A- and B-symptoms. An A-symptom was defined as fever, wheezing, wet cough, and doctor diagnosed pneumonia or otitis media, whereby B-symptoms included dry cough, chills, sore throat, runny or blocked nose, increased need to sleep, loss of appetite, and increased attachment. We defined the beginning of an ARI episode as the occurrence of at least one A-symptom or a day with two B-symptoms. If there were no symptoms for three consecutive days, the episode ended and a new episode could begin. The occurrence of single/isolated B-symptoms were considered within an episode but not as the start of an episode.

2.5. Data Processing and Statistical Analyses

Data analysis was performed using R, v. 4.0.5 for Windows. Descriptive analysis included calculating frequencies and duration of ARI episodes by age, sex, and seasonality. Classification into A- and B-symptoms, as well the generation of acute respiratory episodes and the calculation of outcome variables were carried in the R-package lkstaR [26]. Summary statistics are presented as mean (standard deviation, SD) or median (interquartile range, IQR) for continuous variables and frequency (percentage) for categorical variables. We compared different strata according to the number of ARIs using *t*-Test.

ARI frequencies and associations between participant characteristics were estimated using the Poisson regression. Multivariable analysis included duration of exclusive breastfeeding, time of entry in daycare attendance, type of delivery, birth term, sex, and having older siblings. Multivariable models included all the above-mentioned associated factors. Effect estimates and their corresponding 95% confidence intervals (95% CI) are presented. This analysis is based on data collected from 2014 to February 2020.

2.6. Ethical Approval

The parents of all children participating in the study provided informed written consent. The respective Ethics Committees of the Martin-Luther-University Halle-Wittenberg, Medizinische Hochschule Hannover and Ludwig-Maximilians-Universität Munich, Germany approved the research protocol.

3. Results

3.1. Characteristics of Participants

Out of the 782 enrolled children in the LoewenKIDS study, the parents of 732 (93.6%) participants submitted daily symptom diaries. The parents of 433 (55.4%) participants provided entries for 80% of days, however, in order not to miss any potential infection events, we restricted the sample for this analysis to 288 participants (37%), who completed symptom diary on 98% of the days during the first two years of life. The present sample of 288 participants does not differ much in terms of sociodemographic factors from the 732 participants in the overall sample. Characteristics of the study population show that 85% were born at term, 70% spontaneously, 48% were male, 30% had one or more siblings, 85% attended daycare, and 65% were exclusively breastfed for at least four until six months (Table 1).

Table 1. Characteristics of 288 LoewenKIDS study participants analyzed in this study. Mean number of ARI episodes and 95% confidence intervals (mean difference) are shown.

Children	Frequency (%) or Mean (±SD)	No. of ARIs * in the First Two Years, Mean	95%CI $ Difference to Reference Group
Sex (*N* = 288)			
Male	139 (48)	13.7	0.2 (−1.00; 1.43)
Female	149 (52)	13.5	Reference
Birth term (*N* = 288) §			
Full-term birth ~	266 (92.4)	13.7	Reference
Early-term birth ~	22 (7.6)	12.4	−1.3 (−3.18; 0.54)
Birth weight (g) § (*N* = 286) §	3400 (±488)		
<2500	13 (4.5)	13.1	Reference
>2500–4000	252 (88.2)	13.6	0.5 (−1.91; 2.97)
>4000	21 (7.3)	14.1	1.0 (−2.40; 4.53)
Birth mode (*N* = 287) §			
Vaginal birth	221 (77.0)	13.7	Reference
C-section	66 (23.0)	13.1	−0.6 (−1.96; 0.84)
Number of older siblings (*N* = 286) §			
0	195 (68.2)	13.1	Reference
1	73 (25.5)	14.5	1.4 (0.01; 2.81)
2 or more	18 (6.3)	15.8	2.7 (0.76; 4.76)
Duration of exclusive breastfeeding (*N* = 267) §#			
1 to 3 months $	25 (9.4)	10.8	−3.2 (−5.08; −1.22)
4 to 6 months	165 (61.8)	14.0	Reference
7 to 13 months	62 (23.2)	14.0	0.0 (−1.52; 1.58)
No breastfeeding +	15 (5.6)	12.5	−1.5 (−4.11; 1.13)

Table 1. *Cont.*

Children	Frequency (%) or Mean (±SD)	No. of ARIs * in the First Two Years, Mean	95%CI $ Difference to Reference Group
Entry in childcare attendance (*N* = 288) §			
>0 to 12 months	98 (34.0)	13.8	2.4 (0.44; 4.42)
13 to 26 months	145 (50.4)	14.1	2.7(0.81; 4.66)
No childcare	45 (15.6)	11.4	Reference
Domestic pets (*N* = 288)			
Yes	80 (27.8)	13.0	−0.8 (−2.16; 0.41)
No	208 (72.2)	13.8	Reference
Parents			
Age mothers at birth in years (*N* = 287)	32.9 (±4.0)	-	-
Age fathers at birth in years (*N* = 285)	35.6 (±5.4)	-	-
Highest academic degree of mothers (*N* = 286) §			
Apprenticeship	77 (27.0)	12.4	−1.5 (−3.02; 0.05)
Bachelor's degree	16 (6.0)	14.0	0.1 (−2.77; 3.02)
Master's degree	131 (46.0)	13.9	Reference
PhD/ equivalent	57 (20.0)	14.3	0.4 (−1.06; 1.93)
Other	5 (2.0)	14.8	0.9 (−5.42; 7.27)
Highest academic degree of fathers (*N* = 281) §			
Apprenticeship	86 (31.0)	12.7	0.7 (−2.09; 0.70)
Bachelor's degree	9 (3.0)	16.7	3.3 (−0.06; 6.68)
Master's degree	145 (52.0)	13.4	Reference
PhD/ equivalent	37 (13.0)	15.3	1.0 (−0.12; 3.94)
Other	4 (1.0)	18.0	4.6 (−7.40; 16.68)
Monthly household net income in Euro (*N* = 287) §			
<3000	43 (15.0)	13.4	−1.1 (−3.05; 0.86)
3000 to 3999	72 (25.0)	14.5	Reference
4000 to 5000	60 (21.0)	13.1	−1.4 (−3.15; 0.33)
>5000	68 (24.0)	14.1	0.4 (−2.14; 1.31)
Did not provide any information	42 (15.0)	11.8	−2.7 (−4.76; 0.74)
At least one parent with asthma (*N* = 278)	85(30.6)	13.5	0.1 (−1.49; 1.27)
Smoking (*N* = 279) §,&			
Maternal smoking	3 (1)	9.6	-
Paternal smoking	29 (10)	13.2	-

Abbreviations: * ARI means acute respiratory infection; § participants who filled in the questionnaire, difference to 288 are missing; + 3 of 36 participants did breastfeed but not exclusively; ~ early-term birth (<38 + 4 week), full-term birth (38 + 4–41 + 3 week); # breast milk exclusively, no other nutritional products; & sample too small, difference between groups not tested. $ CI: confidence interval.

3.2. Symptom Burden

In total, 206,001 child-days with diary entries were available for analysis of the included participants. Observed symptoms included cough, wheeze, sore throat, chills, fever, attachment, high need for sleep, loss of appetite, and runny or blocked nose. One or more of these symptoms were reported on 44,441 days (21.6%), corresponding to a mean of 154.3 (IQR: 76.2–216) days with ARI symptom per child (Figure 1A). Symptoms occurred in the first six months of life on average for 19.4 days, at 7–12 months for 41.8 days, at 13–18 months for 49.5 days, and at 19–24 months for 43.4 days (Figure 1B, Table 2).

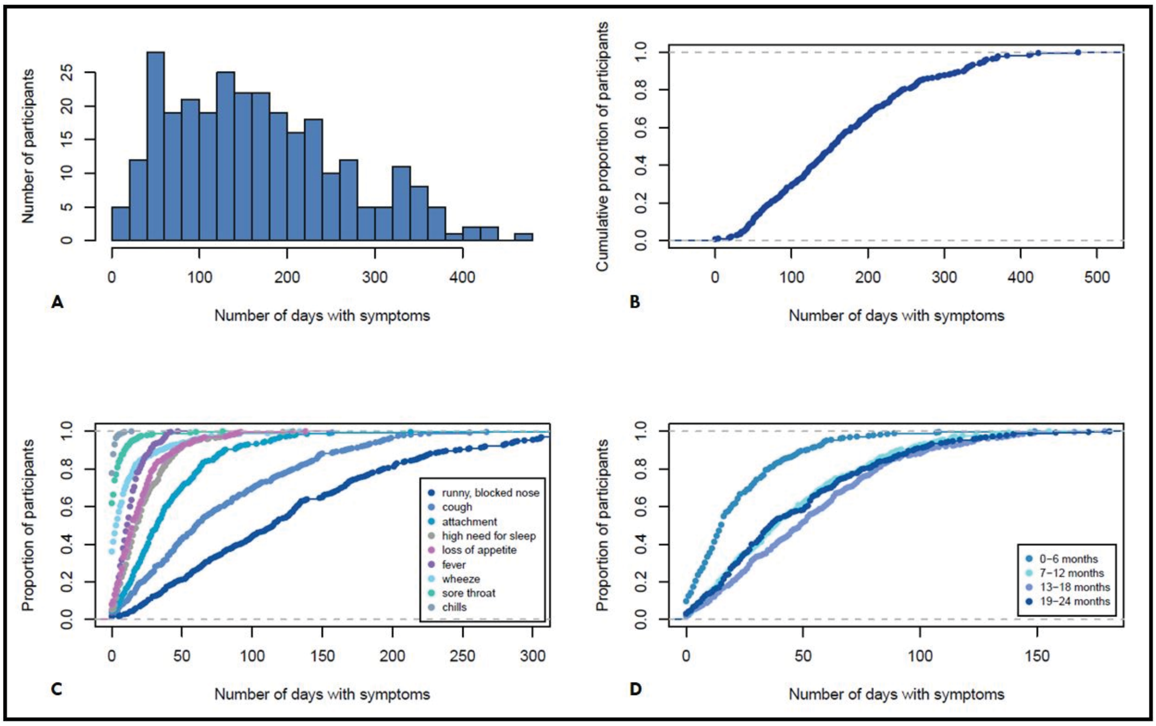

Figure 1. (**A**) Histogram of all days with symptoms within the first two years of life. (**B**) Cumulative distribution of days with symptoms within the first two years of life. (**C**) Cumulative distribution of days with specific symptoms in the first two years of life. (**D**) Cumulative distribution of days with any symptoms in the first two years of life in six months age strata.

Table 2. Days with symptoms in the first two years of life by six-month lifespans per child and days with specific symptoms.

	0–6 Months	7–12 Months	13–18 Months	19–24 Months	Overall	Cough	Runny Nose	Wheeze	Fever	Attach-ment	High Need for Sleep
Min	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1st Quantile	4.0	14.8	20.8	16.0	76.3	29.8	57.8	0.0	6.0	16.0	9.0
Median	13	33.0	41.5	33.0	132.5	60.5	115.5	3.50	11.0	33.0	18.0
Mean	19.4	41.8	49.5	43.4	154.3	76.8	125.8	11.7	13.3	41.2	23.1
3rd Quantile	27.3	60.0	71.0	62.0	216.0	115.0	176.0	13.0	18.0	57.3	34.0
Max	149	157	179	183	477.0	363.0	399.0	134.0	47.0	326.0	129.0

Figure 1C shows the cumulative distribution of days with specific symptoms in the first two years of life in percentiles. The most common symptoms were runny or blocked nose with an average of 125 days (median: 115.5, IQR: 58–176) and cough in various forms with 76.8 days (median: 60.5; IQR: 30–115). In contrast, rare symptoms such as chills occurred on average 0.5 days (median: 0, IQR: 0), sore throat 3.2 days (median: 0; IQR: 0–3), and wheezing 11.7 days (median: 3.5; IQR: 0–13) on average (Table 2, Figure 1C).

3.3. Frequency of Acute Respiratory Infections (ARI) Episodes

In the next step, we aggregated the reported symptoms to ARI episodes based on the applied definition. Among the 288 children, a total of 3911 ARIs were reported in the first two years of life (Figure 2A). On average, 13.7 ARI episodes (IQR: 10–17, SD: 5.2, 10th percentile: 7 ARIs, 90th percentile: 20 ARI)) were reported in the first two years of life (Figure 2A). The cumulative distribution of ARI frequency shows that about 25% of children have less than 10 ARI episodes and 25% show more than 17 ARI episodes in the first two years of life independent of sex (Figure 2B). The median age at first ARI episode was 91 days (IQR: 57–128, mean: 107, SD: 84.5) after birth. The mean duration of ARIs was 11 days (SD: 5.8, median 9.7, IQR: 7–14). The proportion of children with ARIs at a given day increased markedly with age (Figure 2C). The frequency of ARI episodes in the first year was slightly lower with a mean of 6.0 ARI episodes compared to the second year with a mean of 7.7 ARI episodes (Table 3).

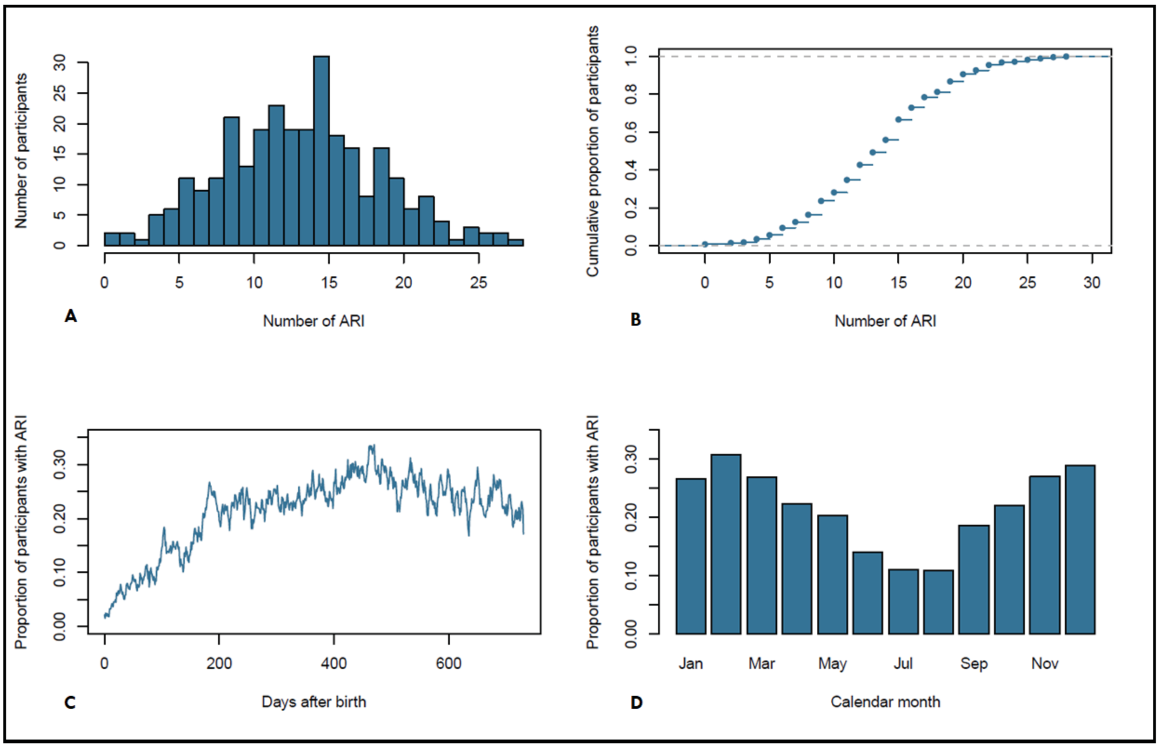

Figure 2. (**A**) ARI episodes of all children in the first two years of life. (**B**) Cumulative distribution of ARI episodes. (**C**) Proportion of children with ARIs in the first two years of life per day (in days after birth). (**D**) Proportion of children with ARIs by month (season).

Table 3. Number of acute respiratory infections (ARIs) in 288 children in the first two years of life in different age groups.

	0–6 Months	7–12 Months	13–18 Months	19–24 Months	0–12 Months	13–24 Months	0–24 Months
Min	0.0	0.0	0.0	0.0	0.0	1.0	2.0
1st Quantile	1.0	2.0	3.0	2.0	4.0	5.0	10.0
Median	2.0	4.0	4.0	3.0	6.0	8.0	14.0
Mean	2.4	3.6	4.0	3.7	6.0	7.7	13.7
3rd Quantile	3.0	5.0	5.0	5.0	8.0	10.0	17.0
Max	9.0	9.0	9.0	11.0	15.0	19.0	28.0

ARI episodes were more common in the winter months showing a well-known seasonal variation of respiratory tract infections in the northern hemisphere (Figure 2D).

3.4. Factors Associated with Acute Respiratory Infections (ARI)

The frequency of ARIs strongly depends on age and seasonality (Figure 2C,D). With increasing age, participants show a marked increase in ARI frequency in the first six months of age (Figure 2C). Furthermore, an increased ARI frequency was observed in winter months compared to the summer months (Figure 2D). In addition, the results from the multivariable analysis in Table 4 show that factors associated with a substantially increased risk of ARIs in the first two years of life are any childcare attendance and having any number of older siblings. However, neither the time point of first childcare attendance nor the exact number of siblings seem to be important for the cumulative number of infection episodes at the age of two. In contrast, the analysis shows that short-term exclusive breastfeeding (less than four months) is associated with a lower risk of ARIs 0.78 [95% CI 0.69; 0.89] within the first two years compared to exclusive breastfeeding for four to six months (Table 4). Children with a longer exclusive breastfeeding of more than six months had the same risk as those with the reference group of four to six months of exclusive breastfeeding. We did not observe any association between birth mode, birth term, or sex of the child.

Table 4. Multiple Poisson regression analysis of frequency of acute respiratory infections (ARIs) in 288 children during their first two years of life.

Variable	Crude RR $^{+}$	95% CI	adj. RR *	95% CI
Duration of exclusive breastfeeding #				
No breastfeeding	0.89	(0.77; 1.04)	0.90	(0.77; 1.05)
1 to 3 months	0.77	(0.68; 0.88)	0.78	(0.69; 0.89)
4 to 6 months	1.00	Reference	1.00	Reference
7 to 13 months	1.00	(0.93; 1.08)	1.00	(0.92; 1.08)
Birth mode				
Vaginal birth	1.00	Reference	1.00	Reference
C-section	0.96	(0.89; 1.03)	0.99	(0.92; 1.08)
Birth term				
Full-term birth ~	1.00	Reference	1.00	Reference
Early-term birth ~	1.11	(0.98; 1.25)	1.10	(0.97; 1.25)
Number of older siblings				
0	1.00	Reference	1.00	Reference
1	1.11	(1.03; 1.20)	1.08	(1.00; 1.16)
2 or more	1.21	(1.07; 1.37)	1.17	(1.03; 1.33)
Entry in daycare				
No daycare in the first two years	1.00	Reference	1.00	Reference
0 to12 months	1.21	(1.01;1.34)	1.27	(1.13; 1.42)
13 to 26 months	1.24	(1.13; 1.37)	1.27	(1.14; 1.42)
Sex				
Male	1.00	Reference	1.00	Reference
Female	1.02	(0.95; 1.08)	1.01	(0.94; 1.07)

Reference group is a duration of breastfeeding 4 to 6 months breast milk exclusively, no other nutritional products; ~ early term birth (<38 + 4 week), full-term birth (>38 + 3 week); + RR from univariable regression; CI: confidence interval; * RR from multivariable regression are adjusted for factors in Table 4.

4. Discussion

In the LoewenKIDS birth cohort study, we found that children show an average of 13.7 ARI episodes (first year 6.0 ARIs, second year 7.7 ARIs) with a median duration of 11 days in the first two years of life. ARIs increase with age and occur more frequently during the winter months compared to the summer months. Within the 13- to 18-months lifespan, children in our cohort showed the highest frequency of ARIs, days with symptoms, and occurrence of specific symptoms, such as runny nose or cough during the first two years of life. Attendance at daycare and the presence of siblings in the same household were associated with an increased risk for a higher frequency of ARIs, while exclusive short-term breastfeeding (less than four months) was associated with less ARIs compared to exclusive breastfeeding for four to six months.

The use of symptom diaries to study ARIs is rarely reported. The frequency varies widely between studies, ranging from three to seven ARIs per year in early childhood. Our results are similar to birth cohort studies in Australia [16,18], Scandinavia [27,28], and Canada [29]. However, some studies report lower frequencies such as the Perth study with 4.0 ARIs [17]/4.2 ARIs [5], the Dutch Whistler study with 4.2 [19], or the German Mas-90 Study [1] with the lowest of 3.1 ARIs in the first year of life. It should be noted that all studies took place at different times and under different conditions.

To our knowledge, there is only one study about the frequency of ARIs in early childhood in Germany using symptom diaries, which was published 30 years ago [1]. The Mas-90 study examined children born in 1990 and found an ARI frequency of 3.1 in the first year of life and 3.2 in the second year, which are considerably lower than our results. This is probably because symptoms were recorded only in a kind of symptom diary, rather retrospectively (personal consultation), and additionally, half of the participants with incomplete data were included in the analysis [1]. Therefore, underestimation may be possible. In addition, the number of daycare places for children under three years has increased considerably in Germany since 1990 [30]. It is well known that children attending daycare centers have a higher risk of ARIs [13,18–20,31,32], which is in line with the findings of this study. Children in our cohort who entered daycare at the age of 13–26 months show a 1.26-fold risk of developing ARIs (RR: 1.26; CI [1.15; 1.39]) compared with children who did not attend daycare until the age of two years. A cohort study from Pittsburgh [33] as early as 1990 showed that the risk of infection increases with the number of contacts in different care settings. They showed that children in childcare with a group size of at least seven children as well as children with a care time of at least 20 h per week contracted considerably more infections than children who were in home care or in group care with three to six children. Similarly, children having siblings are more likely to have an increased number of infections, which was shown in our cohort as well as in other studies before [1,16,17,20,34]. We could not find any relationship when considering sex, birth mode, or birth term, and we were unable to measure an association between smoking exposure and ARI frequencies because an insufficient number of parents in our cohort reported smoking.

Our cohort showed that short-term exclusive breastfeeding (less than four months) without other nutritional support is associated with a lower risk for ARIs, 0.78 (95% CI 0.69; 0.89), within the first two years compared to exclusive breastfeeding for four to six months. Children with longer exclusive breastfeeding more than six months had the same risk as those with the reference group four to six months of exclusive breastfeeding. There are some studies which showed an association between breastfeeding and a lower risk of ARIs compared to no breastfeeding in early life [20,22,35,36]. However, the results are inconsistent. Cushing et al. showed a protective effect only for lower respiratory infections and no association with upper respiratory infections [22]. Frank et al. showed a protective effect between exclusive breastfeeding in the age period of three to six months compared with no breastfeeding only for ear infections and ARIs with fever and no association for ARIs in general [36]. In contrast, Wright et al. [35] also showed a protective effect of breastfeeding and a reduction in upper respiratory tract infections (URTIs), but only in the first four months of life, and Vissing et al. also showed inconclusive results [20]. On the other hand, there are studies with no evidence for a positive association [37] or even with negative effects for long breastfeeding [1,16,36]. The authors [1,16] assume that the negative effects are due to possible selection effects by, for example, over-reporting of episodes in participating families with higher social status, longer breastfeeding and less smoking.

A birth cohort study from Copenhagen [27] indicated that children in the first year of life had a runny nose an average of 16% of days, 7.9% cough, 4.9% attachment, and 1.5% wheezing. These findings are in line with our results. In comparison to the study from

Copenhagen, in our cohort there were slightly more days with runny or blocked nose (17% vs. 16% of days) and a little more cough (10% vs. 7.9% of days). In the younger age strata, we detected only a few days with sore throat and chills. Children at this age cannot yet report sore throat, and the occurrence of chills is certainly also very rare, so we did not expect high frequencies in these age strata in our cohort either.

In 2018, Sarna et al. estimated the average age of the first infection in life at a median of 2.9 months [9]. This is consistent with our estimate of a median of 91 days after birth.

There are many different ARI definitions that have been used in recent research to analyze recorded symptoms [5,16,18,25,27,38], so there is a legitimate question of whether our definition leads to more overestimation or even to underestimation of ARI episodes based on the choice of definition. We adapted the ARI definition proposed by Lambert et al. [25], which in direct comparison of different definitions provided middle estimates in a past study [24].

5. Strengths and Limitations

The strengths of this study were the prospective birth cohort study design and the presence of detailed diary data of respiratory symptoms in the first two years of life. Compared with retrospective data, symptom diaries provide more valid data, i.e., higher reporting and incidence rates, thereby mitigating recall bias [39–41]. However, the data collection is very time-consuming and challenging. Parents in our cohort were required to keep entries for each day, even if the child was asymptomatic.

It is well known that comparison of ARI episodes is very difficult when different recording methods (retrospective or by physician consultations) have been used. In addition, the studies were conducted in different regions with different environmental factors. However, it must also be said that a comparison is also difficult even with the same recording method if different definitions are used for the identification of an ARI episode based on the symptoms. This is shown by Zoch et al. [24] for six definitions for the identification of an ARI in a single dataset.

Completing a daily symptom diary can be a burden for participants and can affect compliance [42,43] and also leads to tiredness [44]. This is likely the reason why in our study only a subsample of participants submitted complete diaries. We also observed some dropout (11% dropped out of the study in the first two years and even some more stopped recording symptoms). In addition, the symptom diary as a study component likely kept many people from participation.

6. Conclusions

This study provides up-to-date, detailed data on the incidence of respiratory diseases in the first two years of life of German children and shows the effects of increasing age, seasonality, daycare attendance, breastfeeding, and the presence of siblings. This study provides pediatricians and researchers with information on the range of infection frequency in generally healthy children. It can be considered as a guideline for the normal occurrence of ARIs in the 21st century. These results show a previously undescribed high frequency and high burden of acute respiratory disease in German children in the first two years of life, which consequently can also represent a great burden for parents and should therefore receive more public attention in this phase.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committees of the Martin-Luther-University Halle-Wittenberg (protocol code 2016-04 from 20 April 2016), Hanover Medical School (protocol code 6794 from 11 November 2014) and Ludwig-Maximilians-University Munich (protocol code 445-15 from 24 September 2015).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the participants to publish this paper.

Data Availability Statement: Most of the quantitative results are provided in the tables. Distributions and individual level data in anonymized form can be obtained upon request and from the R-package lkstaR [26].

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Conflicts of Interest: The authors declare no conflict of interest.

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The impact of non-pharmaceutical interventions on community non-SARS-CoV-2 respiratory infections in preschool children

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Abstract

Background Effects of non-pharmaceutical interventions during the pandemic were mainly studied for severe outcomes. Among children, most of the burden of respiratory infections is related to infections which are not medically attended. The perspective on infections in the community setting is necessary to understand the effects of the pandemic on non-pharmaceutical interventions.

Methods In the unique prospective LoewenKIDS cohort study, we compared the true monthly incidence of self-reported acute respiratory infections (ARI) in about 350 participants (aged 3–4 years old) between October 2019 to March 2020 (pre-pandemic period) and October 2020 to March 2021 (pandemic period). Parents reported children's symptoms using a diary. Parents were asked to take a nasal swab of their child during all respiratory symptoms. We analysed 718 swabs using Multiplex PCR for 25 common respiratory viruses and bacteria.

Results During the pre-pandemic period, on average 44.6% (95% CI: 39.5–49.8%) of children acquired at least one ARI per month compared to 19.9% (95% CI: 11.1–28.7%) during the pandemic period (Incidence Rate Ratio = 0.47; 95% CI: 0.41–0.54). The detection of influenza virus decreased absolute by 96%, respiratory syncytial virus by 65%, metapneumovirus by 95%, parainfluenza virus by 100%, human enterovirus by 96% and human bocavirus by 70% when comparing the pre-pandemic to the pandemic period. However, rhinoviruses were nearly unaffected by NPI. Co-detection (detection of more than one virus in a single symptomatic swab) was common in the pre-pandemic period (222 of 390 samples with viral detection; 56.9%) and substantially less common during the pandemic period (46 of 216 samples; 21.3%).

Conclusion Non-pharmaceutical interventions strongly reduced the incidence of all respiratory infections in preschool children but did not affect rhinovirus.

Keywords Respiratory tract infections, Birth cohort study, Non-pharmaceutical interventions

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Background

The World Health Organisation declared a global pandemic on March 11, 2020, which was caused by the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) and the resulting coronavirus disease of 2019 (COVID-19) [1]. SARS-CoV-2 appeared to affect children less often during the early stages of the COVID-19 pandemic due to mostly asymptomatic or mildly symptomatic cases [2, 3]. However, subsequent studies showed that children are as likely as adults to acquire and transmit SARS-CoV-2 [4–6]. During COVID-19–related lockdown periods, the German government issued, among other non-pharmaceutical interventions (NPI) (i.e. physical distancing, stay-at-home orders, lockdown of non-essential shops, mandatory mask wearing), the closure of schools and day care centres. Given that all respiratory viruses are transmitted via similar mechanisms – aerosols or droplets – NPI targeting SARS-CoV-2 also had the potential to reduce infections by respiratory viruses other than SARS-CoV-2 [7–10]. In Germany, for example, flu season suddenly stopped in week 14 during winter 2019/20 (after the first COVID-19 lockdown was issued in week 12) [11], and an almost undetectable flu season followed during winter 2020/21 (in a period of stepwise increasing restrictions) [12]. In children, studies using data based on hospital records or registers from Australia, Austria, Finland and Japan show that the incidence decreased for different respiratory viruses, e.g. influenza, respiratory syncytial virus and metapneumovirus but not for rhino-/enterovirus and adenovirus during lockdown periods [8, 13–15].

So far, studies have shown reduced frequencies of acute respiratory infections (ARI) and changed viral and bacterial presence during COVID-19 lockdown periods using mostly hospital data or data based on registers from laboratories only. However, most ARI in children are not medically attended [16], and hospital based studies are related to severe infections, thus most of the ARI among preschool children are not included in previous research. In addition, the viral and bacterial profile might be disrupted in hospital-based studies. Furthermore, during the lockdown period, parents were reported to avoid seeing medical doctors for consultations, possibly further changing the viral spectrum detected in medical settings [9, 10, 17].

This study aimed to investigate the impact of COVID-19–related NPI during the winter period 2020/21 compared to the winter period 2019/20 on the occurrence of all ARI, i.e. also those not medically attended, and the respiratory viral and bacterial presence among 3- and 4-year-old children in a population-based cohort in Germany.

Methods

Study sample

We used data and nasal swabs from the birth cohort study LoewenKIDS (Clinicaltrials.Gov Identifier: NCT02654210) which is described in detail elsewhere [18]. Briefly, between 2014 and 2018, we enrolled 782 newborns in five German study centres (336 children in Braunschweig, 174 children in Hannover, 97 children in Bremen, 91 children in Munich and 76 children in Halle). During the first six years of their child's life, parents are asked to fill in a daily symptom diary and take nasal swabs at each event of respiratory symptoms. The Ethics Committees of the Martin Luther-University Halle-Wittenberg (No. 2016-04), the Medical School Hannover (No. 6794) and the Ludwig Maximilian University Munich (No. 445 − 15), Germany approved the study. Parents received detailed information on the objectives of the cohort study and provided written informed consent.

Symptom diary and ARI episode definition

Parents were asked to record symptoms and to rate their severity on a daily basis in a symptom diary. Symptoms included fever, wheezing, cough with sputum (category A) and runny nose or nasal congestion, sore throat, cough, chills, loss of appetite, increased need to sleep, increased attachment (category B) and were classified as previously described [19]. Participants aged three or four years in the times of interest with at least 80% completeness of daily entries for the symptoms were included in the analysis of the ARI episodes.

Nasal swabs

Parents collected nasal swabs at the beginning of an ARI, which was defined as one or more symptoms of category A or two or more symptoms of category B. Swabs were put in tubes with transport media (eNat or Amies Medium) and transported via regular mail to the laboratory within 48h of collection. Specimens were stored at -80°C until further analysis. We analysed all symptomatic nasal swabs (n=457) of 206 children aged 3–4 years in the period October 2019 to March 2020 (pre-pandemic period) and all swabs (n=261) of 162 children aged 3–4 years in the period October 2020 to March 2021 (pandemic period). Participants did not receive the results of the nasal swab testing. There were no restrictions for the selection of nasal swabs regarding the completeness of the symptom diary.

RNA extraction and qPCR analysis

Viral RNA was extracted from 200 µl of nasopharyngeal aspirate specimens using the Quick-DNA/RNATM Viral MagBeadkit (Zymo Research), according to the manufacturer's instructions. We screened the samples by multiplex PCR with the AllplexTM Respiratory Panel 2–4 and

AllplexTM SARS-CoV-2/FluA/FluB/RSV Assay (Seegene Germany GmbH) using the CFX96 Dx System (Bio-Rad). The samples were analysed using the CFX Manager™ Dx Software v3.1 and Seegene Viewer. All assays were carried out as described by the manufacturer's instructions. The four panels included assays for the following respiratory viruses and bacteria: Influenza A virus (FluA), Influenza B virus (FluB), Respiratory Syncytial Virus (RSV A & B), Adenovirus (AdV), Enterovirus (HEV), Metapneumovirus (MPV), Parainfluenza 1–4 (PIV1-4), Bocavirus (HBoV), Coronaviruses (229E, OC43, NL63), Rhinovirus (HRV), SARS-CoV-2 (N gene, RdRP gene), *Bordetella parapertussis* (BPP), *Bordetella pertussis* (BP), *Chlamydophila pneumonia*e (CP), *Haemophilus influenza*e (HI), *Legionella* pneumophila (LP), *Mycoplasma pneumonia*e (MP) and *Streptococcus pneumonia*e (SP). Invalid samples with negative internal control values ($n=2$) were not included in the analysis.

Table 1 Socio-demographics of participants enrolled in the study

Characteristics	Pre-pandemic period *N* (%)	Pan-demic period *N* (%)
Number	323	368
Sex		
Female	164 (50.8)	176 (47.8)
Male	157 (48.6)	188 (51.1)
Missing	2 (0.6)	4 (1.1)
Age (in years)		
3	217 (67.2)	147 (39.9)
4	106 (32.8)	221 (60.1)
Study Region		
Braunschweig	147 (45.5)	144 (39.1)
Hannover	73 (22.6)	77 (20.9)
Halle (Saale)	17 (5.3)	45 (12.2)
Munich	40 (12.4)	48 (13.0)
Bremen	45 (13.9)	51 (13.9)
Other	1 (0.3)	3 (0.8)
Number of persons in household		
2	5 (1.5)	2 (0.5)
3	129 (39.9)	152 (41.3)
4	138 (42.7)	159 (43.2)
5	41 (12.7)	43 (11.7)
≥ 6	6 (1.9)	7 (1.9)
Missing	4 (1.2)	5 (1.4)
Socio economic status*		
Low	2 (0.6)	2 (0.5)
Middle	23 (7.1)	30 (8.2)
High	293 (90.7)	330 (89.7)
Missing	5 (1.5)	6 (1.6)
Total of submitted symptomatic nasal swabs	457	261

*According to Brandenburg social status index [64]

Statistical analysis

R software (Version 4.0.5) was used for data handling and all statistical analyses. For the classification of symptoms and episodes, we used the R-package lkstaR [20]. Descriptive characteristics were summarised using counts, percentages and means, with a 95% confidence interval (95% CI). For the incidence rate, we divided the number of ARI by the number of person-months in the respective period. We calculated the incidence rate ratio by dividing the incidence rate (number of ARI per person and month) during the pandemic period by the incidence rate of participants during the pre-pandemic period.

Results

Characteristics of the study population

We selected all participants aged 3–4 years in the pre-pandemic and pandemic periods resulting in 323 and 368 participants, respectively. Among those, 257 participants were included in both periods. Table 1 summarises the demographic characteristics of the participants. There is a difference of the age proportion between the pre-pandemic and pandemic period because we did not recruit the same number of children each year. We received 457 nasal swabs during the pre-pandemic period and 261 nasal swabs during the pandemic period.

Incidence and characteristics of ARI during the pre-pandemic and pandemic periods

We detected 616 ARI among 222 children during the pre-pandemic winter and 259 ARI among 144 children during the pandemic winter. In the pre-pandemic period, on average 44.6% (95% CI: 39.5–49.8%) of the participants had at least one ARI per month, whereas this number decreased to 19.9% (95% CI: 11.1–28.7%) during the pandemic period. The incidence rate of ARI among children in the pre-pandemic period was 2.8 ARI per person in six months and therefore 0.47 (95% CI: 0.41–0.54) times as high as the rate among children during the pandemic period (1.3 ARI per person in six months). This decrease in the proportion of participants with at least one ARI paralleled the start of NPI in autumn 2020 and the increasing intensity of the interventions (Fig. 1). The lowest incidence, with 6.9% of participants with at least one ARI per month, occurred in January 2021, which paralleled the strictest COVID-19 measures. After the easing of restrictions in February 2021, we observed an increase of ARI. In March 2021, the proportion of ARI reached almost the level observed before the pandemic.

During the pre-pandemic winter, an ARI episode lasted on average 12.3 days (95% CI: 11.3–13.3 days) compared to 8.6 days (95% CI: 7.5–9.7 days) during the pandemic winter (Table 2). Symptom patterns were similar for both periods. During the pre-pandemic period, 14.0% (95% CI: 10.8–17.2%) of all participants reported ARI were

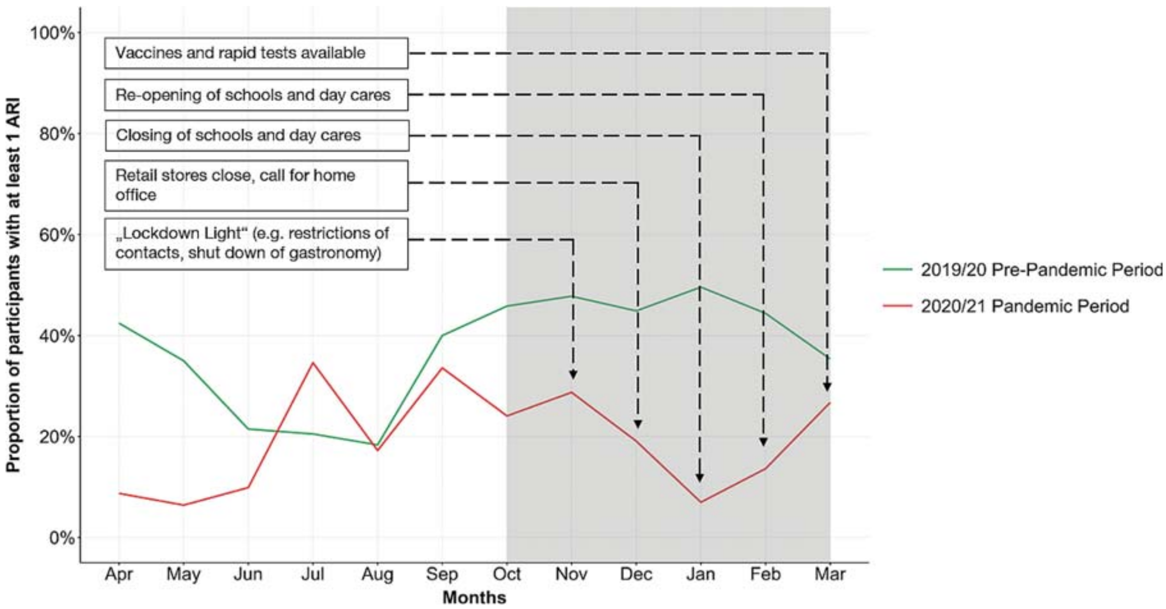

Fig. 1 Changes in incidence of ARI during the pre-pandemic and pandemic periods. The grey box indicates the winter periods, which were selected for further analysis

Table 2 Length of ARI and presence of symptoms during pre-pandemic and pandemic periods

	Pre-pandemic period	Pandemic period
Length of ARI in days (Mean, 95% CI)	12.3 (11.3–13.4)	8.6 (7.5–9.7)
Proportion of days of ARI with … (%, 95% CI)		
runny nose	71.2 (70.4–71.9)	70.8 (69.7–71.6)
cough	61.9 (59.7–63.8)	56.5 (53.2–59.1)
increased attachment	14.3 (13.7–14.9)	17.3 (16.6–20.2)
increased need to sleep	13.5 (12.8–14.1)	11.3 (9.5–12.6)
loss of appetite	12.2 (11.4–12.8)	9.7 (8.2–10.9)
fever	7.5 (6.9–7.9)	5.4 (4.6–6.1)
wheezing	3.3 (2.3–4.2)	4.1 (1.4–6.1)
sore throat	3.1 (2.5–3.6)	4.6 (3.3–5.6)
chills	0.8 (0.5–1.1)	1.0 (0.4–1.5)
Proportion of all ARI that were medically attended (%, 95% CI)	14.0 (10.8–17.2)	10.0 (3.5–16.5)
Proportion of ARI with hospital admissions	0.6%	0.0%

medically attended and 10.0% (95% CI: 3.5-16.5%) during the pandemic period.

Distribution of viruses in symptomatic nasal swabs in the pre-pandemic and pandemic periods

We analysed 455 nasal swabs from 206 children for the pre-pandemic period and 261 nasal swabs from 162 children for the pandemic period using multiplex PCR. We did not detect any bacteria or viruses in 23 samples (3.2%). While the absolute incidence for all tested viruses decreased, the fraction of adenoviruses and bacteria (non-viral) among all swabs remained at the same level, and the fraction of samples containing rhinoviruses even increased (Fig. 2). Other viruses (MPV, PIV1-4, FluA+B, HEV) were not detected during the pandemic period. We did not detect SARS-CoV-2 in any sample.

Changes in the distribution of viruses and bacteria were accompanied by a substantially decreased number of co-detections. Overall, we detected only viral strains in 57 samples (8.2%), only bacterial strains in 87 samples (12.6%) and viral plus bacterial strains in 549 samples (79.2%, Table 3). During the pre-pandemic period, we observed that 56.9% of all samples had a viral co-detection (more than one virus identified per sample); this fraction decreased to only 21.3% during the pandemic period. While we found up to six viruses in one sample during the pre-pandemic period, we only found up to three viruses in one sample during the pandemic period. The most common combinations for simultaneous presence of viruses were HRV together with MPV (21.9%) or together with AdV (20.8%). For the samples with only bacterial presence, more than 50% of samples had a double detection with HI and SP in both periods. Co-detection of viruses and bacteria were more common in the pre-pandemic period (81.9%) compared to the pandemic period (67.4%). Among them, most samples with viruses showed a co-detection with the bacteria HI and SP, followed by a co-detection with either HI or SP.

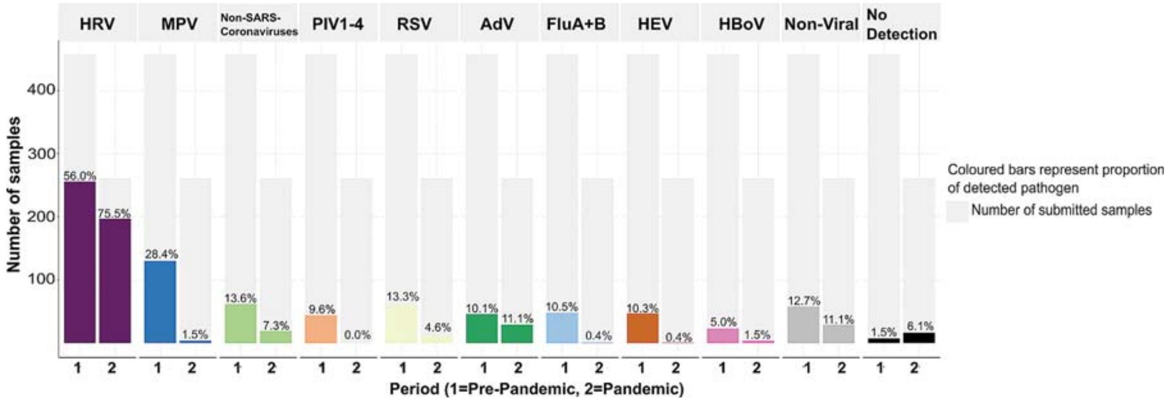

Fig. 2 Prevalence (%) of viruses and bacteria detected in both periods in relation to the number of submitted samples. (HRV: Human Rhinovirus; MPV: Metapneumovirus; Non-SARS-Coronaviruses: Human Coronaviruses 229E, OC43, NL63; PIV1-4: Parainfluenza Viruses 1–4; RSV: Respiratory Syncytial Virus; AdV: Adenovirus; FluA + B: Influenza A virus and Influenza B virus; HEV: Human Enterovirus; HBoV: Human Bocavirus; Non-viral includes all bacterial strains: Bordetella parapertussis, Bordetella pertussis, Chlamydophila pneumoniae, Haemophilus influenzae, Legionella pneumophila, Mycoplasma pneumoniae and Streptococcus pneumonia)

Table 3 Number and characteristics of viral and bacterial co-detection for analysed samples in pre-pandemic and pandemic periods (BPP: *Bordetella parapertussis*; BP: *Bordetella pertussis;* CP: *Chlamydophila pneumonia*; HI: *Haemophilus influenza*; LP: *Legionella* pneumophila; MP: *Mycoplasma pneumonia*; SP: *Streptococcus pneumonia*)

	Pre-pandemic Period	Pandemic period
Samples with ≥ 1 detected virus		
Total number / all valid samples (%)	390/455 (85.7)	216/261 (82.8)
Average number of detected viruses per sample (95% CI)	1.8 (1.7–1.9)	1.2 (1.1–1.3)
Number of detected viruses per sample (%)		
1	168 (43.1)	170 (78.7)
2	137 (35.1)	41 (19.0)
3	66 (16.9)	5 (2.3)
4	15 (3.8)	0 (0.0)
5	3 (0.8)	0 (0.0)
6	1 (0.3)	0 (0.0)
Samples with only bacterial presence		
Total number / all valid samples (%)	58/455 (12.7)	29/261 (11.1)
Number of samples with SP	21 (36.2)	8 (27.6)
Number of samples with HI	5 (8.6)	6 (20.7)
Number of samples with SP + HI	30 (51.7)	15 (51.7)
Number of samples with BPP	2 (3.4)	0 (0.0)
Samples with only viral presence		
Total number / all valid samples (%)	17/455 (3.7)	40/261 (15.3)
Samples with viral and bacterial presence		
Total number / all valid samples (%)	373/455 (81.9)	176/261 (67.4)
Virus + HI	68 (18.2)	30 (17.0)
Virus + SP	25 (6.7)	38 (21.6)
Virus + SP + HI	270 (72.4)	107 (60.8)
Virus + BPP	2 (0.5)	0 (0.0)
Virus + BPP/MP + HI	2 (0.5)	0 (0.0)
Virus + BPP/MP + HI + SP	6 (1.6)	1 (0.6)

Discussion

Our results show that the COVID-19 pandemic-related NPI strongly reduced the number of self-reported ARI in healthy 3- and 4-year-old infants in Germany. NPI suppressed the spread of most seasonal viruses except HRV.

The observed reduction of ARI incidence during the NPI is in line with other studies focusing on the paediatric population in hospitals or using register data [8, 21, 22]. The reduction is likely to be caused by various NPI, although the impact of individual components is unclear. Respiratory infections, especially in early childhood, are very common and cause not just high socioeconomic burdens [23] but are also associated with the development of chronic diseases later in life [24]. However, fewer infections during NPI likely mean a reduced immunity afterwards. In some parts of the world, a strong atypical resurgence of respiratory infections, like RSV, was observed during summer months for children after easing NPI [25–27]. The high proportion of susceptible individuals and the lack of exposure to certain viruses and bacteria could affect timing and severity of future ARI seasons [28].

We found that the prevalence of viral strains changed before and during NPI with suppression of severe viruses such as FluA + B, PIV1-4, RSV and MPV. The natural season period of some viruses was interrupted through the NPI. For example MPV, which is normally detected in late winter and spring [29], was no longer detectable during the pandemic period [30, 31]. However, some studies reported an off-season outbreak of MPV from May to July 2021 [32, 33]. Similarly, RSV, which mostly occurs between December to March each year [29], could rarely be found during the pandemic period [30, 34–36]. Many hospitals, however, registered a massive off-season outbreak during summer months [27, 30, 34]. Interestingly, influenza virus infection incidence remained low during summer months [37, 38], this could indicate that climatic conditions and seasonality differentially affects the various viruses. In contrast, HRV was less affected by the NPI. HRV infections are highly common in children [39] and can cause light symptoms, which are usually associated with a common cold [40]. However, HRV can also cause severe symptoms leading to lower respiratory tract infections such as bronchitis [41]. In our study, HRV infections usually showed only mild symptoms.

Our findings from a population-based setting are in line with recent reports of registers or hospital data published in various countries which all describe that HRV circulation was unchanged during NPI to control the spread of SARS-CoV-2 [9, 13, 42, 43], but we also detected similar levels of AdV before and during the pandemic. This suggests that non-enveloped viruses were less affected by NPI. A major reason could be the stability of non-enveloped viruses, (e.g., HRV has been proven to be more resistant to detergents for hand washing [44] or disinfectants [45]). HRV and AdV are more effective than other airborne viruses at using the indirect transmission pathway (e.g. hand-to-hand contact followed by self-inoculation) [46–48]. This might explain the high prevalence of HRV in children, as the hygiene behaviour is not yet well established [49]. However, we detected a strong decline in HEV, which also belongs to the non-enveloped viruses. Thus, a comprehensive explanation of our findings is still lacking, and further research is needed to better understand the circulation of enveloped and non-enveloped viruses during NPI. It has been also proposed that surgical masks might not prevent the transmission of HRV [50]. On the other hand, it was discussed that HRV might display some form of colonization and thus be present independently of infection symptoms [51, 52]. If HRV were part of the microbiome, then the fraction of symptomatic swabs without a responsible virus would substantially increase, particularly during the pandemic period when fewer co-detections were present. However, we detected HRV without co-detections in the symptomatic nasal swabs especially during the pandemic period, which points towards HRV being the causative virus in our samples. There is also the possibility that we detected different HRV species. There is evidence that HRV-A and HRV-C are frequently associated with more severe infections, while HRV-B is often associated with asymptomatic infections [53, 54]. However, we did not analyse the species.

The proportion of viral co-detections before the pandemic was surprisingly high compared to most previous studies where co-detection rates up to 40% [55, 56] were reported. However, most of those studies were conducted in hospital settings with severely infected children so that virus patterns might be altered compared to the LoewenKIDS' community setting. In healthy children, higher co-detections may be normal; however, literature about co-detection in community settings is very limited. An explanation for co-detection could be that some viral shedding is prolonged although the infection already passed. It was also shown that some viruses (e.g., HRV) are able to colonise the nasal microbiome and are therefore non-pathogenic [51, 52]. During the pandemic period, viral co-detection was markedly reduced, which reflects the decline of most viruses.

A recent systematic review and meta-analysis showed that viral co-detections in children do not have an impact on the severity of the disease, where mostly hospital-based studies with clinical outcomes were included [57]. In our analysis, we also did not observe any change in severity of symptoms.

The bacterial presence was not affected by NPI, which is supported by findings for pneumococcal carriage [58, 59]. Detection of viral and bacterial strains in the same sample was rather common, and among them, almost all samples yielded bacterial co-detections with SP and HI. Asymptomatic nasopharyngeal carriage in healthy preschool children has been documented, 64% for HI [60] and at least 50% for SP [61], meaning that children are mostly colonised with those acting commensals after entering daycare [62]. Most of the children in our cohort entered day care in the second year of life [19] potentially explaining the high prevalence of HI and SP in our samples.

Strengths and limitations

This study has several strengths, including the utilisation of data from the prospective, longitudinal birth cohort study LoewenKIDS in a community setting [63]. Parents reported symptoms on a daily basis making it possible to evaluate the true disease burden, because mild diseases are recorded even if a physician was not consulted. Furthermore, parents provided symptomatic nasal swabs whenever the child had symptoms of ARI. Multiplex PCR including 25 major respiratory viruses and bacteria is unusual for regular care; therefore, our study provides a valuable insight into the viral prevalence of ARI during both winter seasons in a healthy paediatric cohort.

This study also has several limitations. First, we cannot exclude that the NPI and the pandemic situation in general had an impact on our participants. It might be possible that parents were more sensitive to perceive symptoms, and we overestimated the number of ARI during the pandemic period. However, participants of our study have been trained for several years to record symptoms routinely. Second, we included nasal swabs which were taken by the parents of the children and not from a health care worker. However, we provided a detailed description on how to take the swab to minimise individual sample techniques and ensure that detection rates were equal. Third, there were ARI episodes in the symptom diary without nasal swabs, and sometimes parents sent nasal swabs without corresponding entries in the symptom diary. However, the numbers were similar in both periods. ARI characteristics of the episodes with nasal swabs did not differ from the episodes without swabs (data not shown), so the missing information should not have an impact on the results. Fourth, the participants of the LoewenKIDS cohort are mostly well educated and affluent [13], (e.g., most of the parents have high academic degrees and could probably work in a home office to avoid contact to other people). This does not reflect the majority of the population in Germany, so our results could be biased by the high socio-economic status of our study population.

Conclusion

The introduction of strict public health measures to control the COVID-19 pandemic in Germany reduced the number of self-reported ARI. Various respiratory viruses and bacteria were differentially affected and might indicate the possibility of various pathways to improve infection control among preschool children. Effects of co-detections should be further studied.

Abbreviations

95% CI	95% confidence interval
AdV	Adenovirus
ARI	Acute respiratory infections
BP	Bordetella pertussis
BPP	Bordetella parapertussis
COVID	19 Coronavirus disease 2019
CP	Chlamydophila pneumoniae
FluA	Influenza A virus
FluB	Influenza B virus
HBoV	Human Bocavirus
HEV	Enterovirus
HI	Haemophilus influenzae
HRV	Human Rhinovirus
LP	Legionella pneumophila
MP	Mycoplasma pneumoniae
MPV	Metapneumovirus
NPI Non	Pharmaceutical interventions
PIV1-4	Parainfluenza virus 1–4
RSV	Respiratory Syncytial Virus
SARS	CoV-2 Severe acute respiratory syndrome coronavirus type 2
SP	Streptococcus pneumoniae

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Author contributions

BK conceptualised and designed the study, carried out the analyses, interpreted the data, drafted the initial manuscript and critically reviewed and revised the manuscript. SD, JH and SL interpreted the data and critically reviewed and revised the manuscript. MW, DO and AB collected data, provided technical assistance and critically reviewed and revised the manuscript. TS, RM and CG conceptualised and designed the study, supervised the data analysis and interpretation and critically reviewed and revised the manuscript. All authors approve the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study followed guidelines stated in the declaration of Helsinki. The study protocol was approved by the Ethics Committees of the Martin Luther University Halle-Wittenberg (No. 2016-04), the Medical School Hannover (No. 6794) and the Ludwig Maximilian University Munich (No. 445 – 15), Germany. Parents received detailed information on the objectives of the cohort study and provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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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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A B S T R A C T

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-

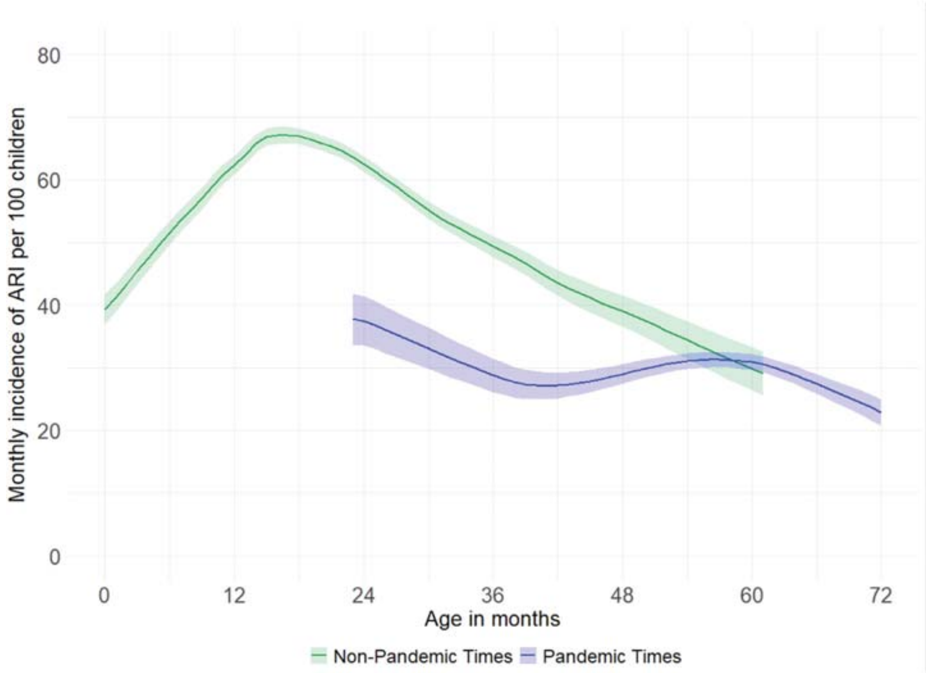

Figure 1. Monthly incidence of ARIs per 100 children by months of life, with 95% confidence interval (generalized additive model). (At the start of the pandemic, children were between 22 and 62 months old; the oldest age group in the blue curve corresponds to the post-pandemic period).
ARI, acute respiratory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

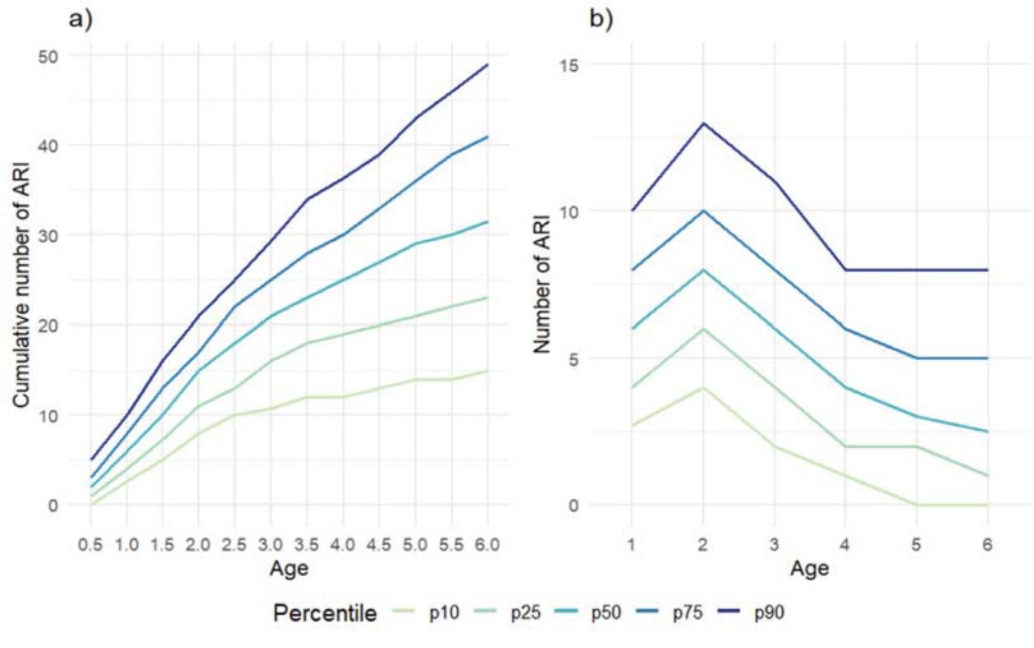

Figure 2. Cumulative (a) and annual (b) percentile curves by age; numbers for the sixth year are potentially biased downward due to a lower completeness of records.

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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Declaration of previous doctoral attempts

(1) I declare that I have not undergone a doctoral procedure or started a doctoral program at any other university.

(2) I declare that the information I have provided is true and that I have not submitted the scientific work to any other scientific institution for the purpose of obtaining an academic degree

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Declaration of independence

I declare in lieu of an oath that I have written this thesis independently and without outside help.

All rules of good scientific practice have been observed; no sources and aids other than those indicated by me have been used and passages taken verbatim or in terms of content from the works used have been identified as such. I assure that I have not used the paid help of mediation and consulting services (PhD advisors or other persons) for the preparation of the content of this thesis. No one has directly or indirectly received monetary benefits from me for work related to the content of the submitted dissertation.

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