The Lancet

Volume 401, Issue 10389, 20–26 May 2023, Pages 1669-1680

Articles

Respiratory syncytial virus infection during infancy and asthma during childhood in the USA (INSPIRE): a population-based, prospective birth cohort study

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https://doi.org/10.1016/S0140-6736(23)00811-5

Summary

Background

Early-life severe respiratory syncytial virus (RSV) infection has been associated with the onset of childhood wheezing illnesses. However, the relationship between RSV infection during infancy and the development of childhood asthma is unclear. We aimed to assess the association between RSV infection during infancy and childhood asthma.

Methods

INSPIRE is a large, population-based, birth cohort of healthy infants with non-low birthweight born at term between June and December, 2012, or between June and December, 2013. Infants were recruited from 11 paediatric practices across middle Tennessee, USA. We ascertained RSV infection status (no infection *vs* infection) in the first year of life using a combination of passive and active surveillance with viral identification through molecular and serological techniques. Children were then followed up prospectively for the primary outcome of 5-year current asthma, which we analysed in all participants who completed 5-year follow-up. Statistical models, which were done for children with available data, were adjusted for child's sex, race and ethnicity, any breastfeeding, day-care attendance during infancy, exposure to second-hand smoke in utero or during early infancy, and maternal asthma.

Findings

Of 1946 eligible children who were enrolled in the study, 1741 (89%) had available data to assess RSV infection status in the first year of life. The proportion of children with RSV infection during infancy was 944 (54%; 95% CI 52–57) of 1741 children. The proportion of children with 5-year current asthma was lower among those without RSV infection during infancy (91 [16%] of 587) than those with RSV infection during infancy (139 [21%] of 670; p=0·016). Not being infected with RSV during infancy was associated with a 26% lower risk of 5-year current asthma than being infected with RSV during infancy (adjusted RR 0·74, 95% CI 0·58–0·94, p=0·014). The estimated proportion of 5-year current asthma cases that could be prevented by avoiding RSV infection during infancy was 15% (95% CI 2·2–26·8).

Interpretation

Among healthy children born at term, not being infected with RSV in the first year of life was associated with a substantially reduced risk of developing childhood asthma. Our findings show an age-dependent association between RSV infection during infancy and childhood asthma. However, to definitively establish causality, the effect of interventions that prevent, delay, or decrease the severity of the initial RSV infection on childhood asthma will need to be studied.

Funding

US National Institutes of Health.

Introduction

Respiratory syncytial virus (RSV) is a ubiquitous, seasonal respiratory viral pathogen and a major cause of morbidity and mortality in infants (children younger than 12 months) worldwide.[1] 60 years of observational studies have consistently shown an association between RSV bronchiolitis and childhood asthma.2, 3, 4, 5 However, in addition to only affecting a minority of all infants with RSV infection, RSV bronchiolitis is not a true exposure, because it just represents a severe clinical manifestation of RSV infection.[6] Furthermore, we have shown that the relationship between RSV bronchiolitis and childhood asthma is likely to be confounded by the shared genetic susceptibility for early-life severe RSV infection and paediatric wheezing phenotypes.[4] Therefore, findings from previous studies focusing on the exposure of early-life severe RSV infection cannot support a causal effect of RSV infection during infancy on the onset of childhood asthma.

Understanding whether the prevention of RSV infection during infancy—a crucial period of lung and immune development—can reduce the risk of childhood asthma is key to designing successful primary preventive strategies, preventing long-term childhood respiratory morbidity, and delineating health-care policy measures. Randomised controlled trials of RSV infection in the first year of life are unethical, and current agents for RSV immunoprophylaxis decrease RSV severity but are unlikely to prevent RSV infection.7, 8, 9 To overcome these limitations, we conducted a population-based birth cohort study designed to ascertain RSV infection during infancy as an exposure, rather than only studying early-life severe RSV infection. To do this, we used a combination of passive and active surveillance with viral identification through molecular and serological techniques to ascertain RSV infection during infancy as a natural event, thereby overcoming the confounding effects of host genetics. We then examined the association between not being infected with RSV during infancy and the development of childhood asthma (figure 1).

Research in context

Evidence before this study

Respiratory syncytial virus (RSV) is a major cause of morbidity and mortality in young children worldwide. In addition to the well established short-term effects of RSV, there is conflicting evidence suggesting that RSV infection during infancy (ie, during the first year of life) can have long-term effects on respiratory health and lead to the development of childhood asthma. We searched the MEDLINE database via PubMed using the terms ("respiratory syncytial virus" OR "bronchiolitis") AND ("asthma" OR "wheeze" OR "wheezing") AND ("children" OR "infant" OR "toddler" OR "early life" OR "pediatric") for articles of any study design published in English up to July 31, 2022. We found that previous studies in this field have exclusively focused on the association of early-life severe RSV infection (usually defined as the presence *vs* absence of RSV bronchiolitis requiring admission to hospital) with paediatric wheezing phenotypes. By mainly using a control group of children not admitted to hospital due to RSV bronchiolitis (a group that combines children with RSV bronchiolitis not requiring admission to hospital, children with RSV upper respiratory infections, and children with no RSV infection), these studies have all been limited by misclassification of their comparator group. Furthermore, because the association of early-life severe RSV infection with the onset of childhood asthma is probably confounded by shared genetic susceptibility, the results of these studies have been influenced by the unmeasured confounding effect of host genetics.

Added value of this study

To overcome most of the limitations of previous studies in this field we: conducted a population-based birth cohort study designed to ascertain RSV infection during infancy as an exposure, rather than only studying early-life severe RSV infection, which is a clinical phenotype and not a true exposure; used a combination of passive and active surveillance with viral identification through molecular and serological techniques to ascertain RSV infection during infancy as a natural event, thereby overcoming the confounding effects of host genetics; and examined the association between not being infected with RSV during infancy and the development of childhood asthma. 944 (54%) of 1741 children with available data had RSV infection during infancy. Not being infected with RSV during infancy was associated with 26% lower risk of 5-year current asthma than being infected with RSV during infancy (adjusted RR 0·74, 95% CI 0·58–0·94, p=0·014). The estimated proportion of 5-year current asthma cases that could be prevented by avoiding RSV infection during infancy was 15% (95% CI 2·19–26·84).

Implications of all the available evidence

To our knowledge, this is the first prospective birth cohort study to show an age-dependent and severity-dependent association between RSV infection during infancy and childhood asthma. Our findings are further supported by our previous studies showing that month of birth (in relation to seasonal RSV circulation) is associated with the risk of childhood asthma, an association that is difficult to explain by non-causal mechanisms. Our findings are also supported by in vitro and animal studies that provide evidence for potential mechanisms through which early-life RSV infection might contribute to chronic airway diseases. Our results also support the consideration of studies that prevent, delay, or decrease the severity of the initial RSV infection as strategies to reduce the prevalence of childhood asthma at the population level. Although we present multilevel evidence of a robust relationship between RSV infection during infancy and childhood asthma, our results cannot definitively establish causality because this is an observational study. Our findings highlight the need for long-term follow-up of common respiratory outcomes among children participating in ongoing and future clinical trials of RSV-prevention products.

Section snippets

Study design and participants

The Infant Susceptibility to Pulmonary Infections and Asthma Following RSV Exposure study (INSPIRE) is a large, population-based, birth cohort of healthy children born at term specifically designed to test the main hypothesis that not being infected with RSV during infancy decreases the risk of childhood asthma. Full details of the methods are available in the appendix (pp 2–4). We ascertained RSV infection status (ie, no infection *vs* infection) in the first year of life among participating…

Results

Of 1952 children enrolled in INSPRIRE, 1946 were eligible (figure 2; table 1). 1220 (63%) of all 1946 children had one or more in-person respiratory illness assessments and 1709 (88%) had a blood sample collected at age 1 year. In all 1946 enrolled children, 2093 in-person respiratory illness assessments were completed, and the median number of in-person respiratory illness assessments per child was 1 (IQR 1–2). 1760 (90%) of 1946 children completed 1-year follow-up, 1712 (88%) completed 2-year …

Discussion

In this large, population-based birth cohort of healthy infants born at term, we showed that infants without RSV infection have a substantially reduced risk of developing childhood asthma compared with infants with RSV infection. To our knowledge, INSPIRE is the first study specifically designed to test the hypothesis that not being infected with RSV during infancy decreases the risk of childhood asthma. In fact, previous studies have focused exclusively on early-life severe RSV infection…

Data sharing

Fully deidentified, individual participant data that underlie the results reported in this manuscript will be shared with other researchers beginning 12 months and ending 36 months after its publication, only for the purpose of conducting systematic reviews with meta-analyses, and upon approval by the corresponding author. For this approval, researchers requesting the deidentified individual participant data will need to have their study approved by an independent review committee (eg, an…

Declaration of interests

LJA has served on RSV vaccine advisory boards for Bavarian Nordic, Novavax, Daiichi-Sankyo, ClearPath Development Company, ADVI, Pfizer, and Jansen Pharmaceuticals. Through Emory University, LJA's laboratory currently receives funding from Pfizer for RSV surveillance studies in adults, from Advaccine Biopharmacueticals Suzhou for serological studies of RSV vaccine recipients, and from Sciogen for animal studies on RSV vaccines. LJA is a co-inventor on several Centers for Disease Control and…

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