# Duration of wheezy episodes in early childhood is independent of the microbial trigger

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**Background: Wheezy episodes in young children are often triggered by viral and bacterial respiratory tract infections, but there is little evidence supporting the hypothesis that symptom duration depends on the specific microbial trigger.**

**Objective: We sought to investigate whether the duration of wheezy episodes in young children depends on the microbial trigger.**

**Methods: Two hundred eighty-three children from the Copenhagen Prospective Study on Asthma in Childhood$_{2000}$ at-risk birth cohort were prospectively examined for common airway pathogenic bacteria and viruses during acute wheezy episodes in the first 3 years of life. Findings were related to symptomatic duration of episodes, as monitored in daily diary cards from birth.**

**Results: Eight hundred thirty-seven samples were investigated for viruses, bacteria, or both. Both viruses and bacteria were identified in 55% of episodes, bacteria were identified exclusively in 31% of episodes, and viruses were identified exclusively in 10% of episodes. The median duration of acute symptoms was 9 days (interquartile range, 5-16 days), and duration was independent of bacterial or viral species.**

**Conclusions: The duration of wheezy episodes was independent of pathogenic airway bacterial or viral species. This suggests that symptom burden from infections is dependent on other factors, such as environmental exposures or host factors. The common term viral wheeze seems inappropriate in view of the finding of pathogenic bacteria in 86% of wheezy episodes.**

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***Key words:*** *Respiratory tract infections, wheezy episodes, pediatrics*

*Abbreviations used*
COPSAC$_{2000}$: Copenhagen Prospective Studies on Asthma in Childhood$_{2000}$
RSV: Respiratory syncytial virus

Infections with respiratory tract viruses are known triggers of wheezy episodes in children, with reported infection rates of 62% to 95% during episodes[1-6] and 40% outside of an episode.[5] Rhinoviruses, respiratory syncytial virus (RSV), and coronaviruses seem to be the most prevalent viruses during wheezy episodes.[1-6] Several other respiratory tract viruses have been implicated, with lesser relative contributions.[1,3-6] In our recent study we highlighted that common pathogenic bacteria and respiratory tract viruses were equally closely associated with wheezy episodes,[5] suggesting that bacteria should also be considered an important trigger.

The aim of this study was to address the question of whether the duration of wheezy episodes is attributable specifically to the infecting species. If not, this would suggest host or environmental factors to be responsible for the disease course, as suggested by our recent finding of an interaction between the 17q21 gene risk variant, exposure to rhinovirus, and risk of persistent wheeze.[7] Therefore we have compared differences in the duration of wheezy episodes associated with various respiratory tract viral and bacterial species in the Copenhagen Prospective Studies on Asthma in Childhood 2000 (COPSAC$_{2000}$) at-risk birth cohort, a cohort of subjects followed from birth with daily diary cards and acute visits to our clinic during wheezy episodes.[5,8,9]

## METHODS

COPSAC$_{2000}$ is a single-center prospective birth cohort study following 411 children of mothers with doctor-diagnosed asthma.[8] Criteria for inclusion have been published previously[8,10] and are summarized in the Methods section in this article's Online Repository at www.jacionline.org.

Children in COPSAC$_{2000}$ attended the research clinic during acute wheezy episodes, at which time airway aspirates for microbiological diagnosis were collected. Wheezy symptoms were recorded in daily diaries from 1 month to 3 years of age.[8,9] Parents were taught to record their child's symptoms, with emphasis on the lower airways, at comprehensive educational sessions conducted at planned half-yearly visits. Wheezy symptoms were defined for the parents as any symptom significantly affecting the child's breathing, such as noisy breathing (wheeze or whistling sounds), shortness of breath, or persistent troublesome cough affecting the child's sleep or activity. Daily symptoms were recorded as composite dichotomized scores (yes/no) each day; parents were taught to make a global assessment. The complexity of symptoms was detailed in a book that was given to the parents (www.copsac.com/content/literature-parents). Diary cards were collected and reviewed by doctors at the planned half-yearly clinic visits.

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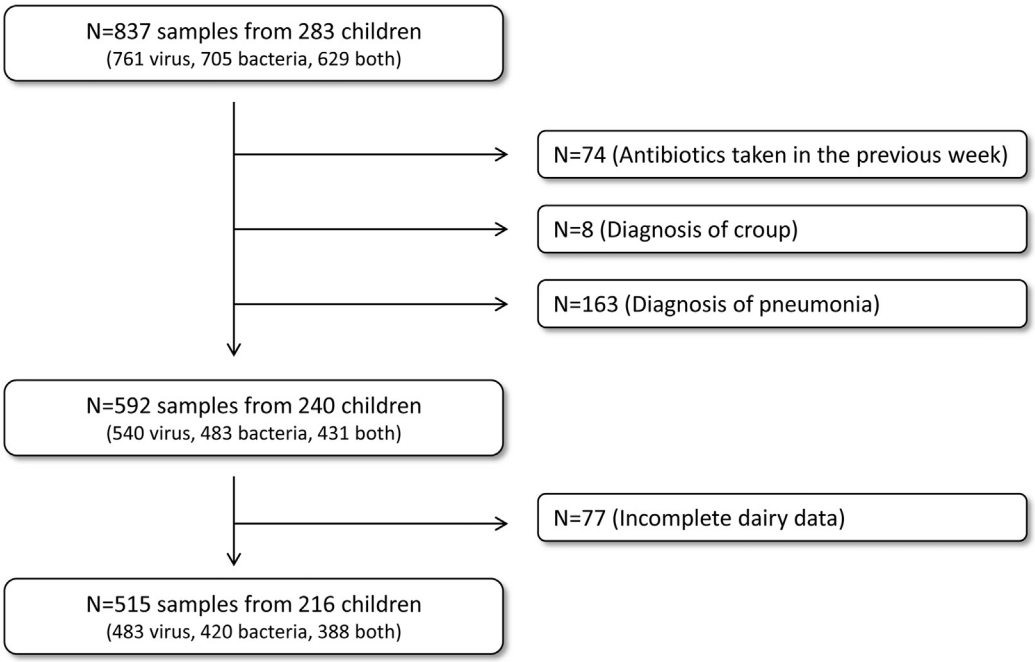


**FIG 1.** Study base selection of samples from young children with wheezy episodes analyzed for viruses and bacteria.

**TABLE I.** Viral and bacterial findings in pharyngeal aspirates obtained during wheezy episodes in young children

| | No. | Percentage |
|---|---|---|
| Viruses | | |
| Picornaviruses | 159/540 | 29 |
| RSV | 89/540 | 16 |
| Coronaviruses | 69/540 | 13 |
| Other virus (next 5) | 129/540 | 24 |
| Parainfluenza viruses | 42/540 | 8 |
| Influenza viruses | 36/540 | 7 |
| Human metapneumoviruses | 17/540 | 3 |
| Adenoviruses | 5/540 | 1 |
| Bocavirus | 43/540 | 8 |
| Any virus (of above) | 350/540 | 65 |
| Multiple virus (of above) | 183/540 | 34 |
| Bacteria | | |
| *S pneumoniae* | 229/483 | 47 |
| *H influenzae* | 200/483 | 41 |
| *M catarrhalis* | 238/483 | 49 |
| Any bacteria (of above) | 412/483 | 85 |
| Multiple bacteria (of above) | 205/483 | 42 |
| Tested for coinfection | | |
| Only virus | 42/431 | 10 |
| Only bacteria | 132/431 | 31 |
| Coinfection | 237/431 | 55 |
| No pathogens | 20/431 | 5 |

Wheezy episodes were defined as 3 consecutive days during which the child had wheezing symptoms. The parents were requested to bring the child to the clinical research unit for examination by the research physician within 24 hours after each episode (ie, on the fourth consecutive day of symptoms). For some episodes, wheezy symptoms were not recorded on the day of aspiration. These episodes were still included in the analysis if there had been symptoms up to the day before aspiration. At each acute visit, the children were examined by physicians trained in pediatrics and clinical research for the diagnosis and treatment of wheezy episodes in accordance with predefined standard operating procedures. Aspirates from acute respiratory episodes with clinical signs indicative of pneumonia or croup were excluded from this study, as described in the Methods section in this article's Online Repository.

Hypopharyngeal aspirates were obtained for routine bacterial cultures without any *a priori* species selection (we detected *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, and *Streptococcus pyogenes*) and nasopharyngeal aspirates for PCR virus identification (picornaviruses, RSV, coronaviruses, parainfluenza viruses, influenza viruses, human metapneumoviruses, adenoviruses, and bocavirus) at all acute visits, as described in the Methods section in this article's Online Repository.

Various baseline host and environmental factors were investigated for a potential confounding effect on the association between microbial triggers and duration of wheezy episodes. Allergic sensitization was determined from specific IgE measurements and skin prick tests at the ages of 6 months, 1.5 years, and 4 years. Asthma was diagnosed throughout the first 3 years of life in accordance with international guidelines, as further detailed in the Methods section in this article's Online Repository. Allelic discrimination at the *ORMDL3* locus rs7216389 at chromosome 17q21 was performed with an Applied Biosystems (Foster City, Calif) Custom TaqMan SNP Genotyping assay (c/n 4332072) on a 7700 Sequence Detection System. The variant was in Hardy-Weinberg equilibrium ($P > .05$). We collected occipital hair samples at 1 year of age for determination of trace amounts of nicotine using gas chromatography–mass spectrometry, as previously described.[11]

Microbial findings during wheezy episodes were summarized in frequency tables across all episodes with available microbial data. Coinfection was defined as identification of at least 1 respiratory tract virus and at least 1 of the investigated bacteria (*S pneumoniae*, *H influenzae*, and *M catarrhalis*).

The main outcome was duration of acute wheezy episodes during which microbial sampling was performed. The effect of various infectious agents on episode duration was investigated by using generalized estimating equations to adjust for interobservational correlations caused by multiple sampling from the same child. We assumed negative binomial distribution of the duration of episodes. Each infectious agent was investigated separately as a dichotomous variable (present/not present) independent of other findings in the sample. Results are shown both unadjusted and adjusted for confounders.