JAMA Network Open

Research Letter | Pediatrics

Wheeze Among Children Born During COVID-19 Lockdown

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Introduction

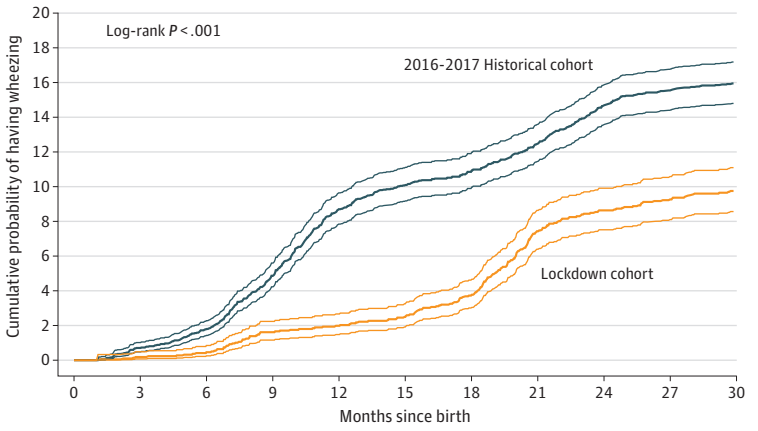
During the COVID-19 lockdown, bronchiolitis nearly disappeared.[1] Bronchiolitis, caused by respiratory syncytial virus (RSV) in 50% to 80% of cases, is a recognized risk factor for wheezing illnesses and asthma.[2,3] We compared rates of wheezing and respiratory medication use in children born during the 2020 lockdown vs those born in prepandemic winter bronchiolitis seasons.

Methods

This cohort study included all children born between February and April in 2020 (lockdown cohort) and the same months in 2016 and 2017 (historical cohort) enrolled in Pedianet, a comprehensive database of 150 family pediatricians in Italy. Wheezing was identified by *ICD-9-CM* codes (519.11 and 786.07). Antiasthma medications were identified with Anatomical Therapeutic Chemical codes (R03A* and R03BA*).

We calculated cumulative wheezing incidence using the Kaplan-Meier estimator and assessed significant differences using a log-rank test. $P < .05$ was used to indicate significance. Person-months were summed until 30 months of age. We conducted mediation analyses to evaluate the association between exposure period (lockdown vs historical) and wheezing onset and whether bronchiolitis mediated this association. The percentage mediated and percentage eliminated were calculated.[4] All models were adjusted for sex, geographic location, and area deprivation index (ADI; to account for socioeconomic status). A sensitivity analysis up to 45 months was conducted to account for potential delays in wheezing onset during lockdown. Statistical analyses were conducted in March 2023 and April 2024 using SAS, version 9.4 (SAS Institute). The eMethods in Supplement 1 provide additional information.

Figure 1. Cumulative Incidence of Wheezing



No. at risk

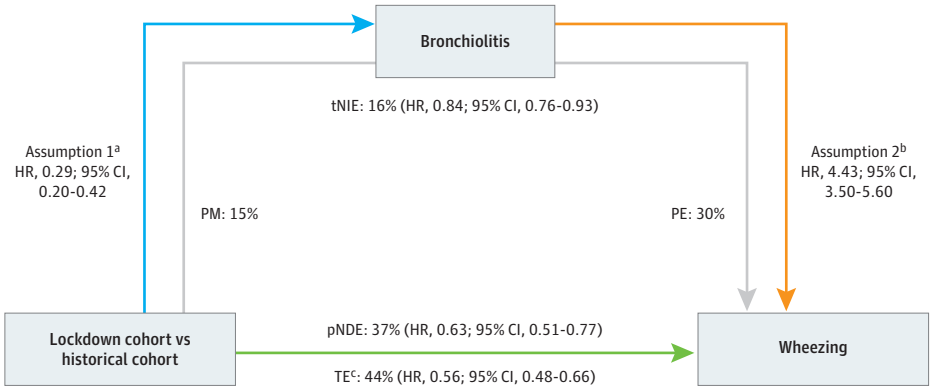
2016-2017 Historical cohort	3889	3972	3700	3515	3328	3216	3146	3046	2939	2869	2817
Lockdown cohort	2192	2176	2152	2106	2086	2058	2020	1921	1876	1849	1829

The bold lines represent the cumulative incidence of wheezing in the lockdown cohort (orange) and the prepandemic historical cohort (blue). The thin lines represent the 95% CIs.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Figure 2. Mediation Analysis of the Exposure Period (Lockdown vs Historical) and Wheezing Onset Mediated by Bronchiolitis



How much of the total effect (TE) was directly attributable to the lockdown (pure natural direct effect [pNDE]; green line) and how much was mediated by bronchiolitis (total natural indirect effect [tNIE]; gray line), a known risk factor for wheezing development, was assessed. The percentage mediated (PM) and percentage eliminated (PE) were calculated. The latter indicates how much a clinical intervention was associated with reduced wheezing if, in a counterfactual scenario, bronchiolitis had been eliminated. Model assumptions regarding the association of the exposure with the mediator (blue line, assumption 1) and the association of the mediator with the outcome (orange line, assumption 2) are shown.

[a] Exposure as fixed-exposure variable.

[b] Exposure as time-varying exposure.

[c] HR for TE = HR for tNIE × HR for pNDE.

We followed the STROBE reporting guideline. The Internal Scientific Committee of Società Servizi Telematici Srl, the legal owner of Pedianet, approved the study and access to the database. According to Italian law, observational, retrospective, noninterventional studies do not require the approval by an ethics committee in Italy. Written informed consent was provided by participants' legal guardians or next of kin.

Results

There were 2192 births during the lockdown period and 3889 in the historical period, with no differences in sex, ADI, gestational age, and presence of atopic disease in the family. During the 30-month follow-up, 206 children (9.4%) in the lockdown cohort experienced at least 1 wheezing episode, vs 582 (15.0%) in the historical cohort ($P < .001$). Wheezing episode rates were 67.6 (95% CI, 61.2-74.0) and 110.0 (95% CI, 103.8-117.8) per 10 000 person-months in the lockdown and historical cohorts, respectively. Bronchiolitis cases were nearly absent during lockdown (6.6 [95% CI, −0.9 to 14.0] vs 82.4 [95% CI, 62.7 to 102.2] episodes per 10 000 person-months in the lockdown and historical cohorts, respectively). Thirty-month cumulative wheezing incidence curves showed a significant difference between cohorts (**Figure 1**), confirmed at 45 months with a cumulative wheezing risk of 16% (95% CI, 15%-18%) in historical cohort and 13% (95% CI, 12%-15%) in the lockdown cohort (log-rank test, $P = .002$).

Wheezing risk dropped by 44% in children born during lockdown (**Figure 2**). Thirty percent of wheezing was eliminated by the lockdown preventive measures alone, assuming bronchiolitis had no additional positive association with wheezing risk (HR, 4.43; 95% CI, 3.50-5.60; $P = .01$). Children in the lockdown cohort received fewer nebulized β_2 agonists (5.1 [95% CI, 4.6-5.7] vs 7.9 [95% CI, 7.4-8.5] per 1000 person-months; $P < .001$) and nebulized glucocorticosteroids (19.5 [95% CI, 18.4-20.5] vs 23.5 [95% CI, 22.6-24.4] per 1000 person-months; $P < .001$) vs the historical cohort during follow-up.

Discussion

In this study, children born during the COVID-19 lockdown had fewer wheezing episodes and less use of respiratory medicines compared with the prepandemic cohort. Limitations include the study's retrospective nature and the impossibility of assessing RSV infection. In line with a large birth cohort study[5] demonstrating that not being infected with RSV during the first year of life is associated with a 26% lower risk of 5-year current asthma, this study underscores the potential role of a universal RSV immunoprophylaxis in preventing postbronchiolitis wheezing.[6]

ARTICLE INFORMATION

Accepted for Publication: May 7, 2024.

Published: July 9, 2024. doi:10.1001/jamanetworkopen.2024.20792

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Author Contributions: Drs Boracchini and Cantarutti had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Barbieri, Cantarutti, Baraldi.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Barbieri, Cantarutti, Donà, Baraldi.

Critical review of the manuscript for important intellectual content: All authors.

Statistical analysis: Cantarutti, Boracchini.

Obtained funding: Giaquinto.

Administrative, technical, or material support: Cantarutti.

Supervision: Giaquinto, Baraldi.

Conflict of Interest Disclosures: Dr Barbieri reported receiving a travel grant from AstraZeneca and grants from MIUR (her salary is supported by the European Union–Next Generation EU under the National Recovery and Resilience Plan, project INF-ACT, One Health Basic and Translational Research Actions addressing Unmet Needs on Emerging Infectious Diseases) during the conduct of the study and a travel grant from Sanofi outside the submitted work. Dr Boracchini reported receiving travel grants from AstraZeneca during the conduct of the study. Dr Baraldi reported receiving personal fees from AstraZeneca, Sanofi, and Chiesi for participating as a speaker at sponsored lectures/symposia and as a scientific expert at advisory board meetings during the conduct of the study. No other disclosures were reported.

Funding/Support: This study was supported by an unrestricted grant from AstraZeneca.

Role of the Funder/Sponsor: AstraZeneca had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Meeting Presentations: Part of the results from this study were presented as a poster at the 41st Annual Meeting of the European Society for Paediatric Infectious Diseases; May 11, 2023; Lisbon, Portugal; and at the 9th ESWI Influenza Conference; September 18, 2023; Valencia, Spain.

Data Sharing Statement: See Supplement 2.

Additional Contributions: The authors thank all of the family pediatricians who collaborate in Pedianet, as well as Dr Luigi Cantarutti, MD, and Antonio Scamarcia, MSc, from Società Servizi Telematici for their support in data extraction. They were not compensated beyond their regular salary for their work.

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SUPPLEMENT 1.
eMethods.
eReferences.

SUPPLEMENT 2.
Data Sharing Statement