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A Danish nationwide cohort study

Nygaard, Ulrikka; Nielsen, Jens; Nielsen, Jeppe Sylvest Angaard; Matthesen, Astrid Thaarup; Dungu, Kia Hee Schultz; Hartling, Ulla Birgitte; Holm, Mette

Published in:
Acta Paediatrica

DOI (link to publication from Publisher):
[10.1111/apa.16877](https://doi.org/10.1111/apa.16877)

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Publication date:
2023

Document Version
Publisher's PDF, also known as Version of record

[Link to publication from Aalborg University](#)

Citation for published version (APA):
Nygaard, U., Nielsen, J., Nielsen, J. S. A., Matthesen, A. T., Dungu, K. H. S., Hartling, U. B., & Holm, M. (2023). The magnitude and severity of paediatric RSV infections in 2022-2023: A Danish nationwide cohort study. *Acta Paediatrica*, 112(10), 2199-2201. <https://doi.org/10.1111/apa.16877>

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BRIEF REPORT

The magnitude and severity of paediatric RSV infections in 2022–2023: A Danish nationwide cohort study

A summer respiratory syncytial virus (RSV) resurgence occurred in many countries in 2021 after most COVID-19 restrictions were lifted.^{1,2} In Denmark, the highest increase in hospital admissions and need for mechanical ventilation was in children aged 2–5 years.³ The magnitude of the RSV epidemic was attributed to an immunity debt caused by the COVID-19 lockdown.² In 2022, the Danish RSV epidemic started in August, in contrast to the usual start in November, and peaked in October.⁴ We aimed to describe the age-related risk of RSV-associated hospital admissions and need for mechanical ventilation in 2022–2023.

This nationwide population-based cohort study prospectively included clinical data from patients aged 0–5 years with RSV who received mechanical ventilation from week 21, 2022, to week 3, 2023. We retrieved data on RSV-associated hospital admissions from the Danish National Patient Registry during the same period. RSV-associated hospital admission was defined as admission for 12 h or more and a positive sample for RSV during admission and/or 5 days or less before. Previously reported data during the four pre-COVID-19 seasons from 2016–2017 to 2019–2020 and in 2021–2022 were used to compare RSV seasons.³ We calculated the risk of RSV-associated hospital admission and the need for mechanical ventilation per 100 000 children below 5 years in 2022–2023. Fisher's exact test was used to compare the risks to the previous RSV seasons in risk ratios (RRs). Permission to disclose patient data was obtained through oral and written parental consent or a requirement waiver.

Among 310 423 Danish children younger than 5 years, RSV-associated hospital admissions were 2435 in 2022–2023, which was 1.7-fold (95% CI, 1.6–1.7) higher than in the four pre-COVID-19 seasons (Table 1). In infants below 3 months, the risk was 1.9 (RR, 1.9; 95% CI, 1.8–2.0). The median age of hospitalised children in 2022–2023 was equal to the pre-COVID-19 RSV seasons and significantly lower than in 2021–2022 (Table 1).

Twenty-nine children received mechanical ventilation in 2022–2023, i.e., 1.2% (95% CI 0.8–1.7) of hospitalised children. This was similar to 1.2% (95% CI 1.0–1.5; $p=0.913$) in the pre-COVID-19 seasons and to 1.4% (95% CI 1.0–1.8; $p=0.629$) in 2021–2022. Among children receiving mechanical ventilation, the proportion of children with risk factors for severe RSV disease (age below 3 months and/or comorbidities) was similar in 2022–2023 compared with 2016–2017

to 2019–2020 (71% vs. 66%, $p=0.546$) and 2021–2022 (71% vs. 65%, $p=0.587$). In children younger than 3 months or those with severe comorbidities, respiratory failure due to bronchiolitis led to mechanical ventilation, while previously healthy children had respiratory failure due to additional complications, including wheeze responsive to bronchodilator therapy ($n=4$), severe bacterial coinfection ($n=1$), pneumothorax ($n=1$), and RSV-associated CNS complications ($n=2$).

In this nationwide population-based cohort study, we found an almost two-fold increase in hospital admissions during the RSV epidemic in 2022–2023, compared with the pre-COVID-19 RSV epidemics. The two-fold increase in hospital admissions was unexpected as high population immunity could have been expected following the extensive RSV resurgence in 2021. The median age among children below 5 years in 2022–2023 was similar to the pre-COVID-19 seasons. This contrasted with the 2021–2022 season, where the median age was significantly higher than in the pre-COVID-19 seasons.^{1–3} This may reflect that the proportion of RSV naïve older children, and children with waning immunity due to no recent reinfection, was significantly lower in 2022–2023 compared with 2021–2022. In addition, a high increase in hospital admissions occurred in infants below 3 months in 2022–2023, which may reflect reduced maternally derived RSV antibodies due to a specific immune debt in pregnant women.

The severity of RSV disease for the individual child was perceived to be unchanged across all RSV seasons since the risk of mechanical ventilation among hospitalised children was similar in 2022–2023 compared with previous seasons. In 2022–2023, previously healthy children with no risk factors for severe RSV infection had atypical complications leading to mechanical ventilation, eg., wheeze responsive to bronchodilator therapy, as described in previous RSV epidemics.³

The main limitation of this study was the use of RSV-associated hospital admissions as a surrogate for the epidemic. Furthermore, it cannot be excluded that the increase in hospital admissions in 2022–2023 partly was due to an increase in RSV testing practice. However, the weekly RSV testing rate in Denmark in 2022–2023 was similar to the pre-pandemic testing rates.⁴ Furthermore, the weekly positivity rate among children below 5 years was equal across RSV seasons.⁵ The main strength was the nationwide prospective research set-up in the very well-registered Danish population.

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TABLE 1 Risk of RSV-hospital admissions and mechanical ventilation among children below 5 in season 2022–2023 compared to pre-COVID-19 seasons from 2016–2017 to 2019–2020) and season 2021–2022.

Hospital admissions						
	Risk per 100000 population (95% CI)				Risk ratio (95% CI)	
Age (m)	2016–2017 to 2019–2020 ^a	2020–2021	2021–2022 ^a	2022–2023 ^b	2021–2022 vs. pre-COVID-19	2022–2023 vs. pre-COVID-19
Total ^c	476 (464–488)	0 ^d	966 (932–1001)	784 (754–816)	2.0 (1.9–2.1)	1.7 (1.6–1.7)
<3	3422 (3280–3568)	-	7517 (7106–7944)	6436 (6055–6835)	2.2 (2.1–2.4)	1.9 (1.8–2.0)
3–5	1747 (1645–1853)	-	2607 (2361–2870)	2374 (2139–2626)	1.5 (1.3–1.7)	1.4 (1.2–1.5)
6–11	796 (747–847)	-	1187 (1069–1314)	1329 (1205–1463)	1.5 (1.3–1.7)	1.7 (1.5–1.9)
12–17	714 (668–763)	-	1280 (1158–1412)	954 (848–1068)	1.8 (1.6–2.0)	1.3 (1.2–1.5)
18–23	352 (320–387)	-	795 (699–901)	440 (369–520)	2.3 (1.9–2.6)	1.3 (1.0–1.5)
24–35	118 (105–133)	-	443 (392–499)	213 (178–252)	3.7 (3.2–4.4)	1.8 (1.5–2.2)
36–47	32 (25–40)	-	157 (127–191)	125 (99–156)	4.9 (3.7–6.6)	3.9 (2.9–5.3)
48–59	16 (11–22)	-	88 (66–114)	35 (22–53)	5.5 (3.7–8.3)	2.2 (1.3–3.7)
Mechanical ventilation	6.1 (4.8–7.7)	0	13.9 (10.0–18.7)	9.3 (6.3–13.4)	2.3 (1.6–3.3)	1.5 (1.0–2.3)

Abbreviations: CI, confidence interval; IQR, interquartile range; m, months; RSV, respiratory syncytial virus.

^aData published previously.³

^bThe inclusion period in 2022–2023 ended in week 3, in contrast to week 20 in the previous seasons, and was estimated to account for 97.5% of the season until week 20. The numbers in 2022–2023 were adjusted to account for the different time windows.

^cThe median age of hospitalised children in 2022–2023 was 4 months (IQR 1–13), which was equal to the pre-COVID-19 RSV seasons (5 months [IQR 1–13; $p=0.086$]), but significantly lower than in 2021–2022 (5 months [IQR 1–16; $p=0.002$]) (Wilcoxon signed-rank test).

^dIn the winter season 2020–2021 (during the COVID-19 lockdown), less than 10 children were hospitalised in Denmark.

In conclusion, RSV-associated hospital admissions doubled in children in 2022–2023 compared with the pre-COVID-19 RSV epidemics. This may indicate a prolonged immunity debt caused by the COVID-19 lockdown. However, the risk of mechanical ventilation among hospitalised children was equal across all RSV seasons.

AUTHOR CONTRIBUTIONS

All co-authors conceptualised this nationwide study. UN obtained funding for the study. UN, UBH, ATM, JSAN, AS, and MH enrolled patients with RSV who received mechanical ventilation. JN provided nationwide numbers of RSV-associated hospitalizations and mechanical ventilation. UN, MH, JN, and KHSD had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. UN, UBH, JN, KHSD, JSAN, AS, and MH analysed data for the study. UN, UBH, and MH drafted the first version of the manuscript. All authors contributed to the data interpretation. All authors revised the manuscript critically for important intellectual content. All authors finally approved the work. UN is responsible for the decision to submit the manuscript.

FUNDING INFORMATION

The study was funded by Innovation Fund Denmark (0176-00020B). The funders 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.

CONFLICT OF INTEREST STATEMENT

No authors declare conflict interests.

Ulrikka Nygaard^{1,2} 

Jens Nielsen³

Jeppe Sylvest Angaard Nielsen⁴

Astrid Thaarup Matthesen⁵

Kia Hee Schultz Dungu¹

Ulla Birgitte Hartling⁶

Mette Holm⁷

¹Department of Paediatrics and Adolescent Medicine, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

²Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

³Infectious Disease Epidemiology and Prevention, Statens Serum Institut, Copenhagen, Denmark

⁴Department of Paediatric and Neonatal Intensive Care, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

⁵Department of Paediatrics and Adolescent Medicine, Aalborg University Hospital, Aalborg, Denmark

⁶Department of Paediatrics and Adolescent Medicine, Hans Christian Andersen Children's Hospital, Odense, Denmark

⁷Department of Paediatrics and Adolescent Medicine, Aarhus University Hospital, Aarhus, Denmark

Correspondence

Ulrikka Nygaard, Department of Paediatrics and Adolescent
Medicine, Copenhagen University Hospital, Rigshospitalet,
Blegdamsvej 9, DK-2100 Copenhagen, Denmark.
Email: ulrikka.nygaard@regionh.dk

ORCID

Ulrikka Nygaard  <https://orcid.org/0000-0002-2093-5909>

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