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Hospital admissions and need for mechanical ventilation in children with respiratory syncytial virus before and during the COVID-19 pandemic: a Danish nationwide cohort study

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Summary

Background The incidence of respiratory syncytial virus (RSV) increased in several countries after the relaxation of COVID-19 restrictions. We aimed to investigate the age-related risk of RSV-associated hospital admissions and need for mechanical ventilation during the RSV resurgence in summer and autumn 2021 compared with the four RSV seasons preceding the COVID-19 pandemic. We also aimed to describe the clinical complications necessitating mechanical ventilation.

Methods This population-based cohort study included patients aged 0–17 years admitted to hospital with RSV in Denmark during the RSV resurgence in summer and autumn 2021, and the four pre-COVID-19 RSV seasons (2016–17, 2017–18, 2018–19, and 2019–20). We retrieved data on RSV-associated hospital admissions from the Danish National Patient Registry and demographic and clinical details of children who received mechanical ventilation through prospective real-time data collection in 2021–22 and retrospective data collection for the 2016–17 to 2019–20 RSV seasons from all eight paediatric and neonatal intensive care units in Denmark. Risk factors for severe RSV disease were as defined as age younger than 3 months or severe comorbidities. We calculated the risk of RSV-associated hospital admissions per 100 000 population in each RSV season from week 21 to week 20 of the following year. We also calculated the risk rate of receiving mechanical ventilation per 100 000 population and 1000 RSV-associated hospital admissions during each RSV season from week 21 to week 20 of the following year. We calculated risk ratios (RRs) for hospital admission and mechanical ventilation by dividing the risk rate of hospital admission and mechanical ventilation in 2021–22 by annual mean risk rates in the four pre-COVID-19 RSV epidemics (2016–17 to 2019–20). We compared RRs using Fisher's exact test. We compared complications leading to intubation between children with and without risk factors for severe RSV disease. The study is registered at ClinicalTrials.gov, NCT05186597.

Findings Among 310 423 Danish children aged younger than 5 years, the mean number of RSV-associated hospital admissions increased from 1477 (SD 226) in the 2016–17 to 2019–20 RSV seasons to 3000 in the 2021–22 RSV season (RR 2·0 [95% CI 1·9–2·1]). 54 children with RSV received mechanical ventilation in 2021–22 compared with 15–28 annually in the 2016–17 to 2019–20 RSV seasons (2·3 [1·6–3·3]). The highest increase in hospital admissions and need for mechanical ventilation occurred among children aged 24–59 months (4·1 [3·6–4·7] for hospital admission; 4·6 [1·7–12·6] for mechanical ventilation). Among children admitted to hospital, the risk of mechanical ventilation was similar in 2021–22 and the four pre-COVID-19 seasons (risk rate 14·3 per 1000 RSV-associated hospital admissions [95% CI 10·4–19·3] *vs* 12·9 [10·1–16·1]; RR 1·1 [95% CI 0·8–1·6]). Across all RSV seasons studied, among children younger than 3 months or those with severe comorbidities, respiratory failure due to bronchiolitis led to mechanical ventilation in 69 (79%) of 87 children. Of 46 children with no risk factors for severe RSV, 40 (87%) received mechanical ventilation due to additional complications, including neurological (n=16; 35%), cardiac (n=1; 2%), and pulmonary complications (n=23; 50%; eg, wheeze responsive to bronchodilator therapy, severe bacterial co-infections, and pneumothorax).

Interpretation In Denmark, RSV disease did not seem to be more severe for the individual child during the RSV resurgence in 2021 following relaxation of COVID-19 restrictions. However, hospital admissions were higher among older children, possibly due to a postponed first RSV infection or no recent reinfection. Older children without risk factors for severe RSV disease had atypical complications that led to intubation. If new RSV-preventive interventions for healthy infants delay first RSV infection, a higher number of older children might be admitted to hospital due to atypical clinical phenotypes, rather than classical bronchiolitis.

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Research in context

Evidence before this study

We searched MEDLINE on Nov 1, 2022, for studies published between Nov 1, 2020, to Nov 1, 2022, investigating paediatric respiratory syncytial virus (RSV)-associated hospital admissions and mechanical ventilation during the interseasonal RSV resurgence after COVID-19 restrictions were lifted. We used the search terms: "respiratory syncytial virus" AND "child" AND "COVID-19" OR "SARS-CoV-2" AND "intensive care unit" OR "mechanical ventilation". No language restrictions were used. We identified nine studies of RSV-associated hospital admissions, three of which reported admissions by age. No studies provided incidence of RSV-related mechanical ventilation or clinical details of RSV complications leading to intubation.

Added value of this study

To our knowledge, this is the first population-based study to investigate the risk of RSV-related hospital admissions and need for mechanical ventilation, and RSV-related complications necessitating mechanical ventilation, in the RSV epidemic in 2021–22 after COVID-19 restrictions were lifted. We were able to access clinical data for all children who received mechanical ventilation in Denmark in week 21 of 2021 to week 20 of 2022 through a prospective paediatric nationwide research collaboration with a real-time enrolment of cases. Data on patients with RSV between 2016–17 and 2019–20 were obtained from the Danish National Patient Registry containing continuous surveillance data of RSV-related disease in Denmark. Compared with the four pre-COVID-19 seasons in 2016–17 to 2019–20, paediatric RSV-associated hospital admissions and mechanical ventilation doubled in the 2021–22 RSV season. The highest increase occurred among children aged 2–5 years. Clinical complications leading to intubation were mainly respiratory failure due to bronchiolitis in infants younger than 3 months and children with severe comorbidities such as chronic lung and heart disease or neuromuscular diseases. By contrast, children without risk factors for severe RSV disease had a wide range of rare complications leading to mechanical ventilation, including salbutamol-responsive wheeze, pneumothorax, severe bacterial co-infection, cardiac failure, and neurological complications.

Implications of all the available evidence

In this population-based study, an increase in paediatric RSV-associated hospital admissions and mechanical ventilation was observed during the summer and autumn of 2021 after COVID-19 restrictions were lifted. A resurgence in summer has also been reported from several other countries. Among children aged 2–5 years, the increase in RSV-associated admissions and need for mechanical ventilation was four times higher than in the four winter seasons before the COVID-19 pandemic. These findings are consistent with studies from Australia, where an increase in the median age of children admitted to hospital with RSV was reported. Similarly, in the UK in 2021, the highest relative burden of laboratory-confirmed RSV was in children aged 1–4 years. The higher age of children admitted to hospital with RSV during the interseasonal RSV epidemic in 2021 suggests that when children are older at first RSV infection, or children are not recently reinfected, a higher proportion will be at risk of hospital admission and mechanical ventilation. Furthermore, rare complications leading to mechanical ventilation in children without risk factors for severe RSV disease were identified in 2021 due to the magnitude of the RSV epidemic. These rare complications are important to be aware of in older, previously healthy children admitted to hospital due to RSV. If new preventive interventions for healthy infants result in a delay to age at first RSV infection, RSV-associated hospital admissions might change in the future, with more older children (aged 1–5 years) admitted to hospital due to complications other than bronchiolitis.

Introduction

A respiratory syncytial virus (RSV) resurgence has been reported in several countries after the relaxation of COVID-19 restrictions.[1–9] In Denmark, the interseasonal RSV resurgence in 2021 occurred during the summer and autumn. Compared with previous RSV seasons, three main differences have been identified: 1) the RSV resurgence was delayed by approximately 4–8 months and occurred out of season during summer and autumn months,[1–9] 2) the number of children admitted to hospital with RSV was higher,[1–6,8] and 3) the median age of children admitted to hospital was higher.[2,6,9] It has been postulated that the magnitude of the interseasonal 2021 RSV epidemic is due to decreased population immunity after a period of low RSV exposure following the strict public health interventions implemented due to COVID-19.[1,4,5,9,10] Studies investigating complications leading to RSV-associated hospital admission in children older than 1 year are scarce; however, Foley and colleagues reported an increase in wheeze responsive to salbutamol in the interseasonal RSV epidemic in Australia.[6]

Complications necessitating admission to intensive care units in children with RSV are typically respiratory failure due to severe bronchiolitis in young infants (aged <3 months) and children with comorbidities, such as prematurity, chronic lung diseases, congenital heart disease, and neuromuscular diseases.[11–14] Older infants and children without comorbidities are less likely to be admitted to an intensive care unit than infants aged younger than 3 months and those with comorbidities, and their complications are less well described.[15] Complications comprising severe bacterial infections, pneumothorax, neurological complications, and cardiac manifestations have primarily been reported in case series.[16–19] The rarity of severe complications in older children might indicate that most children are exposed to RSV at a younger age and have repetitive re-infections,

which are less severe due to acquired immunity.[20–22] The risk of severe complications necessitating mechanical ventilation among a cohort of RSV-naive children aged 1–2 years, and older children not recently re-infected (with possible waning of RSV immunity), remains unexplored. This risk might be of augmented importance since new RSV-preventive interventions for healthy newborn babies and infants, such as maternal RSV immunisation and long-lasting passive immunisation with monoclonal antibodies, are currently being investigated.[23–25] If such interventions increase the age at first RSV infection, more research about RSV complications in older infants will be needed.

We aimed to investigate the risk of RSV-associated hospital admissions and need for mechanical ventilation during the summer RSV resurgence in 2021 compared with four pre-COVID-19 seasons. Additionally, we aimed to describe the clinical phenotype of children with RSV-related complications leading to intubation.

Methods

Study design and population

In this population-based cohort study, we identified children (aged 0–17 years) admitted to hospital with RSV in Denmark during the RSV resurgence in 2021 and the four pre-COVID-19 RSV epidemics in 2016–17, 2017–18, 2018–19, and 2019–20 from the Danish National Patient Registry. For all five seasons, data were obtained from week 21 to week 20 the following year. RSV-associated hospital admission was defined as a hospital contact of more than 12 h and a positive RSV test during hospital admission or within 5 days. In Denmark, RSV testing is only performed in hospital settings. Patients are primarily evaluated by their general practitioner in a non-hospital setting and only referred to a paediatric emergency department if the general practitioner deems it necessary due to disease severity. This practice was unchanged during the RSV resurgence in 2021. All RSV results are reported to the Danish Microbiology Database.

We prospectively enrolled patients aged 0–17 years with laboratory-proven RSV infection, who received mechanical ventilation or had an RSV-related fatal outcome in 2021–22. As part of a nationwide paediatric COVID-19 research collaboration, all paediatric departments had a principal investigator responsible for prospective identification of severe COVID-19-associated disease since March 12, 2020.[26–29] We included all eight paediatric and neonatal intensive care units in Denmark providing mechanical ventilation for children and adolescents. To ensure the completeness of cases, all patients admitted to a paediatric or neonatal intensive care unit with a positive RSV test during hospital admission or within 5 days of hospital admission, were identified through the local electronic health record systems and included if they had received mechanical ventilation. To compare the risk of mechanical ventilation and complications leading to intubation in 2021–22 with the four pre-COVID-19 RSV seasons, patients with laboratory-confirmed RSV and the national procedure code for intubation (BGDA0*) were identified through the Danish National Patient Registry.

The study was approved by the Ethics Committee of Capital Region of Denmark (H-20028631) and the Danish Data Protection Agency (P-2019–29). Informed oral and written parental consent was provided before participation. A waiver of requirement of informed consent was obtained by the Danish Patient Safety Authority (3–3013–2907/1) for patients who received mechanical ventilation in the four pre-COVID-19 RSV epidemics.

Procedures

The principal investigators responsible for the prospective inclusion of patients with RSV receiving mechanical ventilation reported real-time data to REDCap, a secure web application, including risk factors for severe RSV infection, clinical complications, treatment, and outcome. Medical records for patients receiving mechanical ventilation in the four pre-COVID-19 seasons (2016–17, 2017–18, 2018–19, and 2019–20) were retrieved through the local electronic health record systems using the unique social security number allocated to each person in Denmark and investigated for similar outcome measures as for patients in the 2021–22 RSV season. Risk factors for severe RSV infection were defined as age younger than 3 months, prematurity (gestational age <32 weeks), and chronic medical conditions, including lung and heart disease, neuromuscular diseases, inborn errors of metabolism, primary immunodeficiencies, and use of immunosuppressive therapy.

For more on the **Danish National Patient Registry** see https://econ.au.dk/the-national-centre-for-register-based-research/danish-registers/the-national-patient-register

Statistical analysis

Categorical variables are presented as numbers and percentages, and continuous variables as medians with corresponding IQRs or ranges. Non-parametric two-tailed Mann-Whitney U tests were used to compare continuous variables and Pearson's χ^2 or Fisher's exact tests to compare categorical variables. We calculated the risk of RSV-associated hospital admissions per 100 000 population in each RSV season from week 21 to week 20 of the following year. We also calculated the risk rate of receiving mechanical ventilation per 100 000 population and 1000 RSV-associated hospital admissions during each RSV season from week 21 to week 20 of the following year. The risk rates were calculated for all hospital contacts and admissions of longer than 12 h. This admission time was chosen to minimise the possible influence of changes in testing practices and health-seeking behaviours between seasons.[6] When comparing the risk rates of mechanical ventilation in 2021–22 with previous seasons, the case counts were based on numbers from the Danish National Patient Registry, since the prospective inclusion method, as used in 2021–22, has been shown to identify more cases than the Danish National Patient Registry.[26] 95% CIs were calculated using the exact method for binomial

For more on the **Danish Microbiology Database** see https://miba.ssi.dk/Service/English

proportions. We calculated risk ratios (RRs) for hospital admission and mechanical ventilation by dividing the risk rate of hospital admission and mechanical ventilation in 2021–22 by annual mean risk rates in the four pre-COVID-19 RSV epidemics (2016–17 to 2019–20). RRs were compared using Fisher's exact test. We compared complications leading to intubation in children with and without risk factors for severe RSV disease. All statistical analyses were done using R (version 4.1.2).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication.

Results

The interseasonal RSV resurgence in Denmark occurred during the summer and autumn of 2021–22 (figure). The epidemic was delayed by 7 months when compared with pre-COVID-19 RSV seasons, and in the RSV season of 2020–21, fewer than ten RSV-associated hospital admissions were reported nationwide (figure). Among 310 423 Danish children younger than 5 years, the number of RSV-associated hospital admissions increased from a mean of 1477 (SD 226) in the 2016–17 to 2019–20 RSV seasons to 3000 in the 2021–22 RSV season (RR 2·0 [95% CI 1·9–2·1]; table 1). The largest increase in hospital admissions occurred among children younger than 3 months (RR 2·2 [2·1–2·4]) and in children aged 18–23 months (2·3 [1·9–2·6]), 24–35 months (3·7 [3·2–4·4]), 36–47 months (4·9 [3·7–6·6]), and 48–59 months (5·5 [3·7–8·3]). The risk

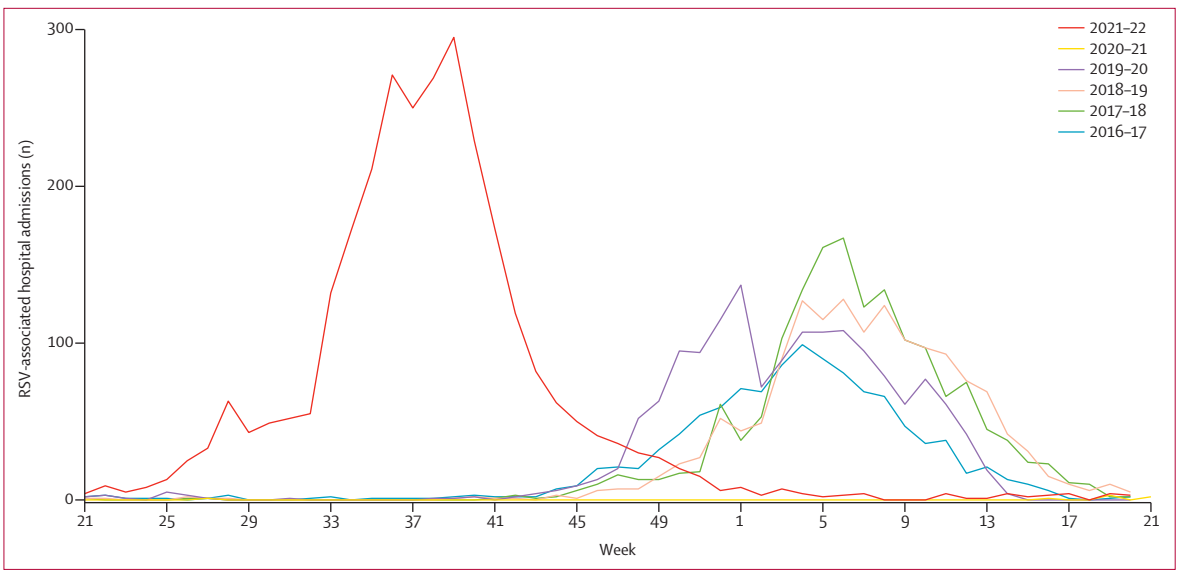

Figure: **Weekly RSV-associated hospital admissions in Danish children aged 0 to 17 years, by season**
RSV=respiratory syncytial virus.

	Population, n	RSV-associated hospital admissions, n*		Risk per 100 000 population (95% CI)		Risk ratio (95% CI)†; p value‡
		2016–17 to 2019–20§	2021–22	2016–17 to 2019–20	2021–22	
Total	310 423	1477 (226)	3000	476 (464–488)	966 (932–1001)	2·0 (1·9–2·1); p<0·0001
<3 months	15 459	529 (56)	1162	3422 (3280–3568)	7517 (7106–7944)	2·2 (2·1–2·4); p<0·0001
3–5 months	15 459	270 (43)	403	1747 (1645–1853)	2607 (2361–2870)	1·5 (1·3–1·7); p<0·0001
6–11 months	30 918	246 (46)	367	796 (747–847)	1187 (1069–1314)	1·5 (1·3–1·7) p<0·0001
12–17 months	30 937	221 (53)	396	714 (668–763)	1280 (1158–1412)	1·8 (1·6–2·0); p<0·0001
18–23 months	30 937	109 (28)	246	352 (320–387)	795 (699–901)	2·3 (1·9–2·6); p<0·0001
24–35 months	61 635	73 (20)	273	118 (105–133)	443 (392–499)	3·7 (3·2–4·4); p<0·0001
36–47 months	62 454	20 (5)	98	32 (25–40)	157 (127–191)	4·9 (3·7–6·6); p<0·0001
48–59 months	62 624	10 (4)	55	16 (11–22)	88 (66–114)	5·5 (3·7–8·3); p<0·0001

RSV=respiratory syncytial virus. *Defined as a hospital contact of >12 h and a positive RSV test during hospital admission or within 5 days. †2021–22 *vs* 2016–17 to 2019–20 winter seasons. ‡p values derived from Fisher's exact test. §Mean (SD) number of annual RSV-related hospital admissions (2016–17 to 2019–20 winter seasons).

Table 1: **Risk of RSV-associated hospital admission in children in Denmark, by age group**

	Children who required mechanical ventilation, n*		Risk of mechanical ventilation per 100 000 population (95% CI)			Risk of mechanical ventilation per 1000 RSV-associated hospital admissions (95% CI)		
	2016–17 to 2019–20	2021–22	2016–17 to 2019–20	2021–22	RR (95% CI)†; p value‡	2016–17 to 2019–20	2021–22	RR (95% CI)†; p value‡
Total	76	43	6·1 (4·8–7·7)	13·9 (10·0–18·7)	2·3 (1·6–3·3); p<0·0001	12·9 (10·1–16·1)	14·3 (10·4–19·3)	1·1 (0·8–1·6); p=0·559
<3 months	37	20	59·8 (42·1–82·5)	129 (79·0–199·7)	2·2 (1·3–3·7); p=0·007	17·5 (12·3–24·0)	17·2 (10·5–26·5)	1·0 (0·6–1·7); p=1·000
3–5 months	6	2	9·7 (3·6–21·1)	13·0 (1·6–46·7)	1·3 (0·3–6·7); p=0·664	5·6 (2·0–12·1)	5·0 (0·6–17·8)	0·9 (0·2–4·4); p=1·000
6–11 months	9	4	7·3 (3·3–13·8)	12·9 (3·5–33·1)	1·8 (0·6–5·8); p=0·308	9·1 (4·2–17·3)	10·9 (3·0–27·7)	0·9 (0·2–3·3); p=1·000
12–17 months	10	4	8·1 (3·9–14·9)	12·9 (3·5–33·1)	1·6 (0·5–5·1); p=0·500	11·3 (5·4–20·7)	10·1 (2·8–25·7)	0·9 (0·3–2·8); p=0·764
18–23 months	7	5	5·7 (2·3–11·7)	16·2 (5·2–37·7)	2·9 (0·9–9·0); p=0·073	16·1 (6·5–33·1)	20·3 (6·6–46·8)	1·3 (0·4–4·0); p=1·000
24–59 months	7	8	0·9 (0·4–1·9)	4·3 (1·8–8·4)	4·6 (1·7–12·6); p=0·004	17·0 (6·9–34·7)	18·8 (8·1–36·7)	1·1 (0·4–3·0); p=1·000

RSV=respiratory syncytial virus. RR=risk ratio. *The total number of children who received mechanical ventilation was 133; 54 in 2021–22 identified by prospective enrollment and 15–28 annually in 2016–17 to 2019–20 identified by the Danish National Patient Registry; to compare the risk of mechanical ventilation in children younger than 5 years between seasons, only patients identified through the Danish National Patient Registry were included (n=43 in 2021–22 and n=76 in 2016–17 to 2019–20). Five children aged older than 5 years were excluded (n=3 in 2016–17 to 2019–20; n=2 in 2021–22). ‡p values derived from Fisher's exact test.

Table 2: **Risk of RSV-related mechanical ventilation in Danish children aged younger than 5 years with RSV**

of any RSV-associated hospital contact, including admission for less than 12 h (eg, paediatric emergency visits), also increased by a similar magnitude when compared with hospital admission for more than 12 h (appendix). No heterogeneity was identified at the site-level regarding the increase in RSV hospitalisations in the 2021–22 RSV season (data not shown).

We identified 133 children with RSV who received mechanical ventilation: 54 children in the 2021–22 RSV season and 15–28 annually in the 2016–17 to 2019–20 RSV seasons; most of these children were younger than age 5 years. Among children younger than 5 years, the overall population-based risk of receiving mechanical ventilation was 2·3 times higher (95% CI 1·6–3·3) in 2021–22 than in previous seasons (table 2). Compared with the four pre-COVID-19 RSV seasons, in the 2021–22 RSV season, the risk was increased in infants younger than 3 months (RR 2·2 [95% CI 1·3–3·7]) and in children aged 24–59 months (RR 4·6 [1·7–12·6]; table 2). Among children aged younger than 5 years admitted to hospital due to RSV, the risk of mechanical ventilation was similar in 2021–22 and 2016–17 to 2019–20 RSV seasons (14·3 cases [95% CI 10·4–19·3] *vs* 12·9 cases [10·1–16·1] per 1000 RSV-associated hospital admissions; RR 1·1 [0·8–1·6]; table 2).

The proportion of children with risk factors for severe RSV infection was similar in 2021–22 and 2016–17 to 2019–20 RSV seasons overall (35 [65%] of 54 children who received mechanical ventilation in 2021–22 *vs* 52 [66%] of 79 children in 2016–17 to 2019–20; p=0·90), of whom 24 (69%) of 35 children in 2021–22 and 28 (54%) of 52 children in 2016–17 to 2019–20 RSV seasons were aged younger than 3 months (p=0·17). Overall, comorbidities comprised chronic neurological diseases (n=13), prematurity (n=8), congenital heart disease (n=5), chronic lung disease (n=3), metabolic diseases (n=2), airway abnormalities (n=3), and cancer (n=1).

The complications leading to mechanical ventilation did not differ between the 2021–22 and the four pre-COVID-19 RSV epidemic seasons. Among the 87 patients with risk factors for severe RSV disease, 28 (80%) of 35 children received mechanical ventilation due to respiratory failure caused by classic bronchiolitis in 2021–22 and 41 (79%) of 52 in the 2016–17 to 2019–20 RSV seasons (table 3). 18 (21%) of 87 children with risk factors for severe RSV disease required mechanical ventilation due to

	Children with no risk factors		Children with risk factors	
	2016–17 to 2019–20 (n=27)*	2021–22 (n=19)†	2016–17 to 2019–20 (n=52)*	2021–22 (n=35)†
Classic bronchiolitis only	6 (22%)	0	41 (79%)	28 (80%)
Other complications	21 (78%)	19 (100%)	11 (21%)	7 (20%)
Adjacent respiratory complications				
Any	9 (33%)	14 (74%)	5 (10%)	1 (3%)
Wheeze responsive to salbutamol	3 (11%)	7 (37%)	0	0
Severe bacterial co-infection	3 (11%)	3 (16%)	5 (10%)	0
Pneumothorax	2 (7%)	3 (16%)	0	1 (3%)
Stridor	1 (4%)	1 (5%)	0	0
Acute respiratory arrest due to secretion	0	1 (5%)	0	0
Neurological complications				
Any	12 (44%)	4 (21%)	2 (4%)	5 (14%)
Prolonged or complex febrile convulsions	10 (37%)	3 (16%)	2 (4%)	3 (9%)
Acute encephalopathy or encephalitis	2 (7%)	1 (5%)	0	1 (3%)
Convulsions due to hyponatremia	0	0	0	1 (3%)
Cardiac complications	0	1 (5%)	4 (8%)	1 (3%)
Median duration of mechanical ventilation, days (IQR)	3 (2–5)	3 (2–6)	4 (3–6)	2 (1–7)
RSV-associated death	1 (4%)	0	4 (8%)	3 (9%)

Data are n (%), unless otherwise stated. Risk factors for severe RSV disease were defined as age younger than 3 months, prematurity (gestational age <32 weeks), and chronic medical conditions, including lung and heart disease, neuromuscular diseases, inborn errors of metabolism, inborn errors of immunity, and immunosuppressive therapy. RSV=respiratory syncytial virus. *79 children received mechanical ventilation during the four pre-COVID RSV-epidemic winter seasons (2016–17 to 2019–20), as identified through prospective nationwide data collection. †54 children received mechanical ventilation in the 2021–22 winter season, as identified through prospective nationwide data collection.

Table 3: **RSV-associated complications leading to intubation in Danish children aged 0–17 years**

See Online for appendix

complications in addition to bronchiolitis, including six children who had other pulmonary complications, seven with CNS complications, and five with cardiac complications. Pulmonary complications included secondary bacterial pneumonia in five patients and pneumothorax in one neonate. Cardiac complications (ie, rapidly decreasing ejection fraction) occurred in infants with congenital heart disease. CNS complications consisted of prolonged convulsions, encephalopathy or encephalitis, and severe hyponatremia.

Among the 46 children with no risk factors for severe RSV disease, complications in addition to bronchiolitis led to intubation in 19 (100%) of 19 children in 2021–22 and 21 (78%) of 27 children in the 2016–17 to 2019–20 RSV seasons (table 3). Overall, the proportion of patients with additional complications, which led to respiratory failure and necessitated mechanical ventilation, was significantly higher in children with no risk factors for severe RSV disease (40 [87%] of 46 children) than in children with risk factors (18 [21%] of 84 children; p=0·0001). Of 46 children without risk factors, 23 (50%) had pulmonary complications, 16 (36%) had CNS complications, and one (2%) had cardiac complications (table 3). The pulmonary complications included: wheeze responsive to bronchodilator therapy (n=10), of whom seven were coinfected with rhinovirus or metapneumovirus, or had previous hospital admissions with wheezing episodes responsive to bronchodilator therapy; severe bacterial coinfection with *Haemophilus influenzae, Streptococcus pneumoniae*, and Panton-Valentine Leukocidin-secreting *Staphylococcus aureus* infection (n=6); pneumothorax (n=5); stridor (n=2); and acute respiratory arrest due to secretion (n=1). One patient with Panton-Valentine Leukocidin-secreting *S aureus* had acute cardiac tamponade due to pericardial empyema and received acute rescue pericardiocentesis. The CNS complications comprised status epilepticus in 13 (81%) of 16 children and acute encephalopathy or encephalitis in three (19%) children.

Three (6%) of 54 children who received mechanical ventilation in 2021–22 had a fatal outcome compared with five (6%) of 79 children in the 2016–17 to 2019–20 RSV seasons (table 3). All except one child had severe underlying conditions comprising neurological and neuromuscular diseases, cancer, metabolic diseases, or bronchopulmonary dysplasia. One child without comorbidities had a fatal outcome due to RSV-related encephalopathy or encephalitis. Two patients had severe sequelae: one previously healthy child with severe neurological sequelae following acute encephalopathy and one child with chronic neuromuscular disease received permanent tracheostomy.

Discussion

In Denmark, the RSV epidemic resurgence in 2021 occurred during the summer and autumn after a RSV season in 2020–21 in which fewer than ten children were admitted to hospital with RSV nationwide. The RSV resurgence was 7 months later than normal RSV seasons, and occurred after the relaxation of COVID-19 restrictions, which had included prolonged periods of daycare and school closures.

The number of paediatric RSV-associated hospital admissions and number of children requiring mechanical ventilation doubled in 2021–22 compared with the 2016–17 to 2019–20 RSV seasons. The increased risk of hospital admissions in 2021–22 coincided with a decreased population immunity after the extended period of low RSV exposure following the strict public health interventions implemented to target COVID-19.[4,9,10] Compared with the pre-COVID RSV epidemics, the highest increase in RSV-associated hospital admissions and mechanical ventilation in 2021–22 occurred in young infants (aged <3 months), possibly due to reduced levels of maternally derived RSV antibodies following diminished RSV exposure among pregnant women,[30] and in children aged 2–5 years, probably reflecting postponed primary RSV infection or waning immunity due to no recent reinfection.[20–22]

A high number of RSV-associated hospital admissions has also been reported in several other countries in 2021–22.[1–8] The magnitude of the epidemic resulted in substantial pressures on health services with overcrowded paediatric departments. However, it has been debated whether RSV disease was more severe for the individual child. Agha and colleagues reported a disproportionate increase in RSV-associated intensive care unit admissions among children admitted to hospital due to RSV during the RSV resurgence in New York (NY, USA) in 2021, indicating increased severity of the disease itself.[3] However, this single-centre study included only patients during the first months of the epidemic and six patients received mechanical ventilation. By contrast, our results indicate that the disease was not more severe for the individual child in the 2021–22 season, since the increase in number of hospital admissions and mechanical ventilation due to RSV was similar. Our results are consistent with the results of Hatter and colleagues who reported a similar increase in both RSV-associated hospital admissions and admissions to intensive care units in New Zealand. Similarly, in southeast Australia, no difference was identified in the proportion of intensive care unit admissions during their RSV resurgence in 2020 compared with previous years.[2]

In our study, the relative risk of hospital admission increased in all age groups in 2021–22 compared with the pre-COVID-19 epidemics. However, the magnitude of increase differed across age groups. The increase in relative risk of admission was smallest among children aged 3–17 months in 2021–22, and was the highest among children aged older than 24 months. Three studies (one from the UK, southeast Australia, and western Australia), have provided age-specific data on RSV-associated hospital admissions.[2,6,9] Compared with previous years, all studies found increased peak

case counts and RSV-associated hospital admissions in children aged 2–4 years in the interseasonal RSV season, which is consistent with our results. The increase in hospital admissions among older age groups could be due to immunological naivety or diminished immunity from lack of exposure to RSV in the previous seasons. This suggests that regular exposure to RSV in older children is important to maintain immunity at a level that is protective against hospital admission.

The magnitude of the epidemic, including the high number of previously healthy children receiving mechanical ventilation, allowed investigation of clinical details of complications leading to intubation. These complications did not differ between the RSV seasons. In infants younger than 3 months and children with comorbidities, respiratory failure due to classical bronchiolitis led to intubation in most cases. By contrast, children with no risk factors for severe RSV disease had a wide range of rare complications necessitating mechanical ventilation. These rare complications included CNS, cardiac, and pulmonary complications, such as severe bacterial coinfection, pneumothorax, and wheeze responsive to bronchodilator therapy.

The rare complications of RSV bronchiolitis in children without risk factors for severe RSV disease have been described previously, but our findings identified new aspects. First, secondary bacterial infections included *S pneumoniae* and *H influenzae*,[31,32] but also Panton-Valentine Leukocidin-secreting *Staphylococcus aureus*, which has only been reported in few case reports secondary to RSV.[33] Panton-Valentine Leukocidin-secreting *S aureus* infections caused severe necrotising pneumonia. Second, pneumothorax has primarily been reported in preterm infants.[34] Among our cases, pneumothorax mainly occurred in older infants and children without risk factors for severe RSV, accounting for 13% of the complications leading to intubation. Third, cardiac complications, such as myocarditis, arrhythmias, and non-bacterial pericardiac effusion, as described previously,[35–37] were not identified in this study. However, one patient had acute cardiac tamponade due to pericardial empyema caused by Panton-Valentine Leukocidin-secreting *S aureus*. Fourth, although RSV is not generally associated with wheeze responsive to bronchodilator therapy, it was a complication of RSV bronchiolitis in a fifth of older infants and children who received mechanical ventilation, several of whom were coinfected with rhinovirus. Consistent with this finding, a significant increase in the number of children admitted to hospital with RSV had wheeze responsive to salbutamol in the summer RSV resurgence in Western Australia.[6] Therefore, bronchodilator therapy could be considered in older children with RSV and particularly in children coinfected with rhinovirus, which is a known trigger for salbutamol-responsive wheeze.[38] Fifth, CNS complications led to intubation in a high proportion of patients. Most CNS complications occurred in previously healthy children and primarily included prolonged seizures, but also severe encephalopathy and encephalitis. Other studies have also primarily reported severe RSV-associated encephalopathy and encephalitis in previously healthy children.[39] In summary, our findings indicate that clinicians should also be aware of older infants and children admitted to hospital with RSV, since treatment with antibiotics, bronchodilator therapy, antiepileptic therapy, or chest drain might be necessary for some patients.

The results of our study might be of interest if new RSV preventive interventions for all healthy infants entering their first RSV season become available. Such new interventions include maternal immunisation (ie, transplacental transfer of maternal antibodies and immunisation of infants with novel extended half-life monoclonal RSV antibodies (eg, nirsevimab and MK-1654).[23–25] If such interventions postpone the time to first RSV infection, more children might become at risk of primary RSV infection at an older age. Our results suggest that this increased risk might lead to a higher number of older infants and children requiring hospital admission and mechanical ventilation. Furthermore, the clinical picture of RSV disease in children admitted to hospital might change, since we found that older infants and children had a variety of atypical complications. However, since the overall morbidity of RSV infection in older infants and children is significantly lower than in young infants, new prevention strategies targeting all infants entering their first RSV season are expected to reduce the overall RSV burden.[20–22]

The major limitation of this study was our inability to estimate the proportion of children admitted to hospital with RSV among all RSV-infected children, since RSV testing is only performed in the hospital setting in Denmark. Thus, the total number of infected children in Denmark was unknown in the 2021–22 RSV season and all previous seasons. Therefore, we were not able to explore if the proportion of RSV-infected children who required hospital admission changed between 2021–2022 and previous seasons. Another limitation was that the threshold for hospital admissions in the 2021–22 RSV season might have been higher than previous seasons due to overcrowded paediatric departments, which might have resulted in underestimation of the increase in hospital admissions in 2021–22. This speculation is based on the fact that the proportion of admissions among all proven RSV cases, including paediatric emergency consultations, was lower in 2021–22 than previous seasons (data not shown). The major strength of our study was the well documented population of Denmark with continuous surveillance data of children admitted to hospital with RSV. An additional strength was the option to assess clinical phenotypes leading to mechanical ventilation based on real-time data and a detailed review of medical records on a population-based level during five RSV seasons.

In conclusion, we found that the number of paediatric RSV hospital admissions and children who had mechanical ventilation doubled in the interseasonal RSV epidemic in 2021–22 compared with the four pre-COVID-19 seasons. The highest increase in hospital admissions occurred among children aged 24–59 months. The study indicates that when the time for the first RSV infection is postponed or children are not recently reinfected, an increased number of older infants and children will be at risk of severe complications leading to hospital admission and mechanical ventilation. In infants younger than 3 months and children with comorbidities, the complications leading to intubation were mainly respiratory failure due to bronchiolitis, while children without risk factors for severe RSV disease had a wide range of atypical complications, including salbutamol-responsive wheeze, pneumothorax, bacterial pneumonia, cardiac failure, and CNS complications. These rare complications are important to be aware of, since new promising RSV-preventive interventions for healthy infants are currently being investigated. If such interventions postpone time to primary RSV infection, in the future, more older children might be admitted to hospital due to atypical complications, other than classic bronchiolitis.

Contributors

All authors conceptualised the study. UN obtained funding for the study. UN, UBH, ATM, JSAN, AS, and MH enrolled patients with RSV who received mechanical ventilation. JN and LSV provided nationwide numbers of RSV-associated hospital admissions and mechanical ventilation. UN, MH, JN, and KHSD had full access to all of the data in the study, verified the data, and take responsibility for the integrity of the data and accuracy of the data analysis. UN, UBH, JN, KHSD, JSAN, AS, KK, 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, revised the manuscript critically for important intellectual content, and finally approved the work. UN was responsible for the decision to submit the manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

Data will not be made available for others according to Danish data protection legislation.

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