
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Vaccine 41 (2023) 3796–3800

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

# The increasing age of respiratory syncytial virus-related hospitalisation during COVID-19 pandemic in Lyon was associated with reduced hospitalisation costs

Álvaro Roy [a,b,*], Stéphanie Polazzi [c], Dominique Ploin [d], Yves Gillet [d], Etienne Javouhey [d], Bruno Lina [a], VRS study group in Lyon [d]Anne-Florence Myard-Dury [e], Sandrine Couray-Targe [e], Antoine Duclos [c], Jean-Sébastien Casalegno [a]

[a] Hospices Civils de Lyon, Hôpital de la Croix-Rousse, Centre de Biologie Nord, Institut des Agents Infectieux, Laboratoire de Virologie, Lyon 69004, France
[b] ECDC Fellowship Programme, Public Health Microbiology Path (EUPHEM), European Centre for Disease Prevention and Control (ECDC), Solna 169 73, Sweden
[c] Hospices Civils de Lyon, Service des Données de Santé, Lyon 69003, France
[d] Hospices Civils de Lyon, Hôpital Femme Mère Enfant, Service de Réanimation Pédiatrique et d'Accueil des Urgences, Bron 69500, France
[e] Hospices Civils de Lyon, Département d'Information Médicale, Lyon 69003, France

ARTICLE INFO

*Article history:*
Received 20 February 2023
Received in revised form 3 May 2023
Accepted 5 May 2023
Available online 10 May 2023

*Keywords:*
Respiratory syncytial virus
Age shift
Hospitalisation costs
Lyon

ABSTRACT

*Background:* Preventive measures applied during the COVID-19 pandemic have modified the age distribution, the clinical severity and the incidence of Respiratory Syncytial Virus (RSV) hospitalisations during the 2020/21 RSV season. The aim of the present study was to estimate the impact of these aspects on RSV-associated hospitalisations (RSVH) costs stratified by age group between pre-COVID-19 seasons and 2020/21 RSV season.

*Methods:* We compared the incidence, the median costs, and total RSVH costs from the national health insurance perspective in children < 24 months of age during the COVID-19 period (2020/21 RSV season) with a pre-COVID-19 period (2014/17 RSV seasons). Children were born and hospitalised in the Lyon metropolitan area. RSVH costs were extracted from the French medical information system (*Programme de Médicalisation des Systémes d'Information*).

*Results:* The RSVH-incidence rate per 1000 infants aged < 3 months decreased significantly from 4.6 (95 % CI [4.1; 5.2]) to 3.1 (95 % CI [2.4; 4.0]), and increased in older infants and children up to 24 months of age during the 2020/21 RSV season. Overall, RSVH costs for RSVH cases aged below 2 years old decreased by €201,770 (31 %) during 2020/21 RSV season compared to the mean pre-COVID-19 costs.

*Conclusions:* The sharp reduction in costs of RSVH in infants aged < 3 months outweighed the modest increase in costs observed in the 3–24 months age group. Therefore, conferring a temporal protection through passive immunisation to infants aged < 3 months should have a major impact on RSVH costs even if it results in an increase of RSVH in older children infected later in life. Nevertheless, stakeholders should be aware of this potential increase of RSVH in older age groups presenting with a wider range of disease to avoid any bias in estimating the cost-effectiveness of passive immunisation strategies.



## 1. Introduction

Respiratory syncytial virus (RSV) is, worldwide, the leading cause of lower respiratory tract infections (LRTI) in infants and the leading cause of hospital admissions in children < 1 year of age [1]. It can cause severe complications such as bronchiolitis and pneumonia, and patients may present acute respiratory distress that could require hospitalisation [2]. The risk of complications is higher in infants < 3 months of age [3–5].

*Abbreviations:* RSVH, respiratory syncytial virus-associated hospitalisations; mAb, monoclonal antibody; NPIs, non-pharmaceutical interventions; HCL, Hospices Civils de Lyon; LRTI, lower respiratory tract infections.

* Corresponding author at: Laboratoire de Virologie, Institut des Agents Infectieux, Laboratoire associé au Centre National de Référence des virus des infections respiratoires, Hospices Civils de Lyon, 103 Gd Rue de la Croix-Rousse, Lyon 69004, France.
*E-mail address:* alvaro.roy-cordero@chu-lyon.fr (Á. Roy).

https://doi.org/10.1016/j.vaccine.2023.05.021
0264-410X/

The annual RSV epidemic in France resulted in a mean 45,225 RSV-associated hospitalisations (RSVH) in children < 5 years of age per season (October-March) during the 2010–2018 period, resulting in high direct costs per season to the healthcare system [6]. Direct costs of RSVH during the 2017–18 RSV season in France were estimated to be €124.1 million, with infants < 1 year of age accounting for 80 % of the economic burden and half of them were infants < 3 months of age [6]. This finding may be explained by the greater number of cases in these age groups and longer hospital stay, as described elsewhere [4,6–7]. The mean cost for RSVH per infant < 1 year of age in the Lyon metropolitan area (approximately 1.4 million inhabitants) was previously estimated to be €3,973 in the 2014–2017 period [8]. These costs were even higher for infants younger than three months of age or born prematurely (<37 weeks of gestational age) [8], which can be explained by disease risk being partly age-dependant, related to the development of respiratory tract and maturity of immune system [7,9–10].

Non-pharmaceutical interventions (NPIs) implemented due to COVID-19 pandemic have had a great impact on RSV transmission as previously reported in different European countries [11–12]. As a consequence, the majority of the European countries, observed atypical RSV epidemics that started later and affected older children [13]. An explanation for these observations is that the delayed epidemics increased the susceptible fraction of the population and infants were exposed to RSV at an older age [11]. In France, an increase in the proportion of hospitalised cases aged >3 months and up to 5 years during the 2020/2021 atypical RSV season was reported in the Rhône-Loire metropolitan area (part of the Auvergne-Rhône-Alpes region) [14] and in the Parisian area [15].

As indicated above, younger age at the time of infection is associated with greater clinical severity, longer hospital stays or ICU admission, which in turn can be associated with higher costs. So far, there are no published data on how the age shift in hospitalisations observed during this atypical RSV 2020/21 season affected direct hospitalisation costs. This may be of great interest, since the temporary protection conferred by passive immunisation may also lead to an increase in the age at first infection [16]. This has been the subject of mathematical modelling studies that evaluated the cost-effectiveness of passive immunisation using maternal vaccines and mAbs and reported a reduction in the number of hospitalised young infants who represent the highest costs [17–19]; inducing an age shift of hospitalised children towards older age groups [16,18]. However, there is no real-word evidence as these passive immunisation strategies have not been implemented yet on a wide scale (i.e. all infants at the beginning of the season).

The aim of the present study was to estimate the impact of age distribution, the clinical severity, and the incidence of RSVH on hospitalisation costs stratified by age group between pre-COVID-19 seasons and 2020/21 RSV season.

## 2. Methods

### 2.1. Study design and population

This observational cohort study included data from four cohorts of children born in the three main public hospitals of the metropolitan area of Lyon (part of the Auvergne-Rhône-Alpes region). Data were collected retrospectively from the Hospices Civils de Lyon (HCL) database (2013/2015, 2014/2016, 2015/2017 and 2019/2021). The present study included data previously reported by Kramer *et al.* for the 2014–2017 period and who included children < 12 months of age [8]; for the present study this was complemented by the collection of data for those aged 12–24 months. For 2013/2015, 2014/2016 and 2015/2017 cohorts, the birth period considered was between 1 June and 31 May, and for 2020/21 cohort between 1 September and 31 August, to take into account the observed 3-month delay in the 2020/21 seasonal epidemic [13]. RSV cases detected between 01/09/2014–31/05/2015, 01/09/2015–31/05/2016 and 01/09/2016–31/05/2017 were included in 2014/15, 2015/16 and 2016/17 RSV pre-COVID-19 seasons, respectively. RSV cases detected between 01/12/2020 to 31/08/2021 were included in the 2020/2021 atypical RSV season.

A RSV case was defined as a child hospitalised during the RSV season in the first two first years of life during the study period and confirmed by real-time reverse transcriptase (RT)-PCR. Characteristics of children hospitalised for RSV were extracted from the HCL database: age, sex, prematurity (defined as < 37 weeks of gestational age), parity (primiparous vs multiparous), and type of gestation (single or multiple).

### 2.2. Epidemiological indicators

The incidence rate of RSVH for each cohort was estimated by the number of RSVH per 1000 person-months for each RSV season. For the incidence rate calculation, the children at risk during the specific season (<2 years of age) of the corresponding cohort were used as denominator, i.e. for the 2014/15 RSV season those of the 2013/15 cohort.

### 2.3. Costs and length of stay

Costs are presented from the national health insurance perspective. Direct medical RSVH costs per stay and per patient charged by the hospital to the national health insurance were extracted from the French medical information system (*Programme de Médicalisation des Systémes d'Information*), along with the length of stay [6]. The costs were adjusted to 2021 euro value by applying the consumer price index in mainland France. Briefly, costs per stay and per patient are mainly determined by the Diagnosis Related Group (DRG), the severity grade, ICU admission, the presence of comorbidities, and the length of stay. RSVH costs were extracted individually from the three main public hospitals of the metropolitan area of Lyon. Detailed costs were not provided, and only the DRG, severity grade and the total costs charged for the stay were retrieved. Patients with outlier values showing a cost 4 SD above the mean or who underwent major surgery were removed from the costs and length of stay calculations.

### 2.4. Statistical analysis

Frequencies of RSV cases between the two periods according to different characteristics were compared by using the Chi-squared test or Fisher's exact test, and length of stay and costs expressed as median and interquartile range [IQR] were compared between age groups and periods using the Mann-Whitney *U* test. Bonferroni correction was applied for further pairwise comparisons. All tests were conducted using R software version 4.1.2. (R Development Core Team, 2022), and a *p*-value of 0.05 was defined as the cut-off for statistical significance.

### 2.5. Ethics statement

This observational study was approved by the Institutional Review Board of the Hospices Civils de Lyon (AGORA-502 IpCoVRS; CSE-HCL – IRB 00013204; date: 26/05/2021) and the data were anonymised before the research team had access to them. In accordance with national regulations, parents were informed about the study if their children's data were used. An information sheet was sent to parents by postal mail and they were given the opportunity

to refuse their children's participation in the study; these were excluded.

## 3. Results

The number of births included in the cohorts of the RSV seasons 2014/15–2016/17 ranged from 18,076 to 18317, and for the 2020/21 season cohort 17,561 births were included. The median age of hospitalised children was significantly lower in the 2014/17 RSV seasons (2.2 months, IQR [1.1–4.8]) compared to the 2020/21 season (3.3 months, IQR [1.7–8.0]; $p < 0.001$; Table 1).

There was significant decrease in the incidence rate per 1000 person-months among those aged < 3 months in 2020/2021 compared to the pre-COVID-19 period (from 4.6, 95 % CI [4.1; 5.2] to 3.1 95 % CI [2.4; 4.0]; $p = 0.003$), and a significant increase among those aged 3–24 months (from 0.48, 95 % CI [0.41; 0.56] to 0.66, 95 % CI [0.52–0.84]; $p = 0.02$; Table 2). Among those aged < 6 months a non-significant decrease in the incidence rate in 2020/2021 compared to the pre-COVID-19 period was observed (from 3.0, 95 % CI [2.7; 3.3] to 2.4 [1.9–2.9]; $p = 0.052$), and a significant increase among those aged 6–24 months (from 0.30, 95 % [0.24; 0.37] to 0.46, 95 % CI [0.33; 0.62]; $p = 0.03$; Suppl. Table 1).

In the pre-COVID-19 period, the median RSVH costs per child among those aged < 3 months (€2955, IQR [2343–5164]) was significantly higher than among those aged 3–24 months (€2907, IQR [901–3665]; $p < 0.001$), as was the case in the 2020/2021 season (€3363, IQR [2389–5420] vs. €2389, IQR [697–3363]; $p < 0.001$). There was also a significantly lower median length of stay, both in the pre-COVID-19 period, respectively 5 days (IQR [3–8]) vs. 4 days (IQR [1–7], $p = 0.007$), and in the 2020/2021 RSV season, respectively 5 days (IQR [3–8] to 3 days (IQR [1–6], $p < 0.001$). There was no significant difference between periods in the median total costs per child aged < 3 months ($p = 0.79$), and a significant decrease in the median total costs per child aged 3–24 months ($p = 0.004$), even though there were no differences in the median length of stay ($p > 0.05$; Table 3). The median RSVH costs for preterm infants was higher (€3479, IQR 2803–9240 for pre-COVID-19 period, and €4137, IQR 2438–5449, during COVID-19 period) compared to full-term infants in both periods (respectively, €2934, IQR 912–4312, $p < 0.001$; and €2537, IQR 844–3363, $p = 0.006$). More than 70 % of patients were coded in as bronchiolitis in children aged < 12 months during the pre- and COVID-19 periods (71.9 % and 83.5 % respectively) and, conversely, more than 70 % were coded as pathologies other than bronchiolitis in children aged 12–24 months (71.9 % and 89.5 % respectively).

Total RSVH costs decreased by €191,428 (41.6 %) among those aged < 3 months in the 2020/21 RSV season compared to the mean total costs per season pre-COVID-19. In children aged 3–24 months, there was no major impact between periods (€10,342 [5.4 %] reduction in 2020/21 RSV season). Independently of age, the total RSVH costs decreased by €201,770 (31.0 %) in the 2020/21 RSV season compared to the mean total costs per season pre-COVID-19 (Table 3).

**Table 1**
Characteristics of children < 2 years of age hospitalised during the pre-COVID-19 RSV seasons (2014/17) and the 2020/21 RSV season from the birth cohorts of the study.

| RSV season | 2014/2015 | 2015/2016 | 2016/2017 | Total 2014/2017 | 2020/2021 | *p*-value[c] |
|---|---|---|---|---|---|---|
| RSVH[a], n | 153 | 169 | 132 | 454 | 134 | |
| Total births, n | 18,077 | 18,076 | 18,317 | 54,471 | 17,561 | |
| Age (months), median [IQR] | 2.1 [1.1–5.3] | 2.1 [1.0–3.4] | 2.6 [1.4–5.3] | 2.2 [1.1–4.8] | 3.3 [1.7–8.0] | <0.001 |
| Sex, n ( %) | | | | | | |
| Female | 63 (41.2) | 78 (46.2) | 70 (53.0) | 211 (46.5) | 61 (45.2) | 0.87 |
| Male | 90 (58.8) | 91 (53.8) | 62 (47.0) | 243 (53.3) | 74 (54.8) | |
| Gestational age, n ( %) | | | | | | |
| <37 weeks | 25 (16.3) | 39 (23.1) | 26 (19.7) | 90 (19.8) | 27 (20.0) | 1.0 |
| ≥37 weeks | 128 (83.7) | 130 (76.9) | 106 (80.3) | 364 (80.2) | 108 (80.0) | |
| Parity[b], n ( %) | | | | | | |
| Primiparity | 22 (14.4) | 35 (28.7) | 30 (30.9) | 87 (26.1) | 25 (25.5) | 1.0 |
| Multiparity | 92 (60.1) | 87 (71.3) | 67 (69.1) | 246 (73.9) | 73 (74.5) | |
| Type of pregnancy, n ( %) | | | | | | |
| Simple gestation | 139 (90.8) | 146 (86.4) | 127 (96.2) | 412 (90.7) | 122 (90.4) | 1.0 |
| Multiple gestation | 14 (9.2) | 23 (13.6) | 5 (3.8) | 42 (9.3) | 13 (9.6) | |

[a] RSV-associated hospitalisations.
[b] 39 patients with no data available in 2014/15, 47 in 2015/16, 37 in 2016/17 and 35 in 2020/21.
[c] Comparison between RSV seasons pre-COVID-19 (Total 2014/2017) and the 2020/2021 RSV season, Chi-squared test.

**Table 2**
Incidence rate of RSV-hospitalisations stratified by age group between pre-COVID-19 period (2014/17 RSV seasons) and COVID-19 period (2020/21 RSV season).

| Age group | RSV seasons 2014/17[a] | RSV season 2020/21[b] | *p*-value |
|---|---|---|---|
| | Incidence rate per 1000 person-months [95 %CI] | Incidence rate per 1000 person-months [95 %CI] | |
| <3 months | 4.6 [4.1; 5.2] | 3.1 [2.4; 4.0] | 0.003 |
| ≥3-12 months | 0.72 [0.61; 0.86] | 0.93 [0.71; 1.2] | 0.14 |
| ≥12-24 months | 0.20 [0.14; 0.29] | 0.36 [0.23; 0.58] | 0.06 |
| ≥3-24 months | 0.48 [0.41; 0.56] | 0.66 [0.52–0.84] | 0.02 |
| Overall | 1.11 [1.0; 1.2] | 1.02 [0.86; 1.2] | 0.40 |

[a] 2014–2017 pre-COVID-19 RSV seasons from 1 September to 31 May, and birth cohorts 2013/15, 2014/16 and 2015/17 from 1 June to 31 May two years later.
[b] RSV 2020/21 season from 1 December 2020 to 31 August 2021 and birth cohort 2019/2021 from 1 September 2019 to 31 August 2021.

**Table 3**
Length of stay and RSV-hospitalisation costs stratified by age group between pre-COVID-19 period (2014/17 RSV seasons) and COVID-19 period (2020/21 RSV season).

| Age group | RSV seasons 2014/17[a] | | | RSV season 2020/21[b] | | | Difference in total costs, €, % |
|---|---|---|---|---|---|---|---|
| | Median length of stay per patient, days [IQR] | Median cost per patient, € [IQR] | Mean total costs per season[c], € | Median length of stay, days [IQR] | Median cost per patient, € [IQR] | Total costs, € | |
| <3 months | 5 [3–8] | 2955 [2343–5164] | 459,772 | 5 [3–8] | 3363 [2389–5420] | 268,344 | −191,428, −41.6 |
| ≥3-12 months | 4 [1–7] | 2907 [901–3479] | 136,337 | 3 [2–6] | 2405 [844–3363] | 142,517 | +6,180, +4.5 |
| ≥12-24 months | 3.5 [1–9] | 3041 [908–4216] | 53,729 | 2 [1–4] | 1042 [504–3258] | 37,207 | −16,522, −30.8 |
| ≥3-24 months | 4 [1–7] | 2907 [901–3665] | 190,066 | 3 [1–6] | 2389 [697–3363] | 179,724 | −10,342, −5.4 |
| Overall | 4 [2–8] | 2955 [1047–4529] | 649,838 | 4 [2–7] | 2537 [844–3544] | 448,068 | −201,770, −31.0 |

[a] 2014–2017 pre-COVID-19 RSV seasons from 1 September to 31 May, and birth cohorts 2013/15, 2014/16 and 2015/17 from 1 June to 31 May two years later; two patients with outlier values showing a cost 9 SD above the mean who underwent major surgery were removed from the costs and length of stay calculations.
[b] RSV 2020/21 season from 1 December 2020 to 31 August 2021 and birth cohort 2019/2021 from 1 September 2019 to 31 August 2021.
[c] Mean total costs for the 2014/15, 2015/16 and 2016/17 seasons.

## 4. Discussion

In the present study we observed a reduction in the overall incidence of RSVH and associated costs in children at higher risk for severe RSV infection (<3 months of age) in Lyon during the first RSV season after the COVID-19 pandemic compared to previous seasons. Despite the increased incidence in children aged 3–24 months, it did not have a significant impact on total hospitalisation costs. Therefore, this age shift in the incidence of RSVH was associated with a relative decrease in hospitalisation costs by more than a third, corresponding to more than €200,000.

The reduction of the incidence of RSVH in infants < 3 months of age strongly impacted the total hospitalisation costs, since this group usually requires longer stays, more ICU admissions and mechanical ventilation [7–8]. The mean cost of RSVH in infants aged < 3 months were similar to those estimated by Demont *et al.* in France between 2010 and 2018 [6], and slightly below the mean cost estimated in a meta-analysis of 41 countries in Europe, North America, and Australia [20]. However, we also observed a significant increase in the proportion of RSV patients hospitalised aged 3–24 months in the 2020/2021 season, as previously described in the same region of France [13]. The median costs decreased in older age groups in both periods due to shorter length of stay and lower clinical severity, as they are less prone to severe RSV complications [21]. However, it was not possible to explore whether this was related to more frequent ICU admission as, although this contributes to the calculation of costs, we were unable to identify the proportion of costs associated with ICU admission. We also observed a larger difference between the median costs in both periods, perhaps related to the smaller sample size during the COVID-19 period and differences in the coding of different clinical presentations according to age. The increase in the incidence of RSVH in children aged 3–24 months did not have a major impact on the total costs in the present study. Nevertheless, we did observe a major increase in DRG coded as pathologies other than bronchiolitis in children aged 12–24 months. Similarly, a Danish nationwide cohort study found an increase in hospital admissions among children 24–59 months of age with atypical RSV-complications other than classic bronchiolitis during the 2021–21 RSV season, of which clinicians need to be aware of and strength the surveillance in these age groups for correct identification and treatment [22].

Passive immunoprophylaxis is expected to lead to a greater reduction in the incidence of RSVH compared to NPIs in infants < 3 months of age. The age shift observed in the present study partially aligns with a modelling study that estimated that nirsevimab may reduce the number of LRTI caused by RSV between 49.7 % and 51.9 % among infants aged < 6 months and cause a modest increase of LRTI in children aged 12–24 months during their second season [16]. Similarly, van Boven *et al.* predicted that maternal vaccination would reduce the incidence of infection in infants in the first year of life but would lead to a slight increase in those aged 1–4 years [23]. This age shift of RSVH towards older children is of concern, but, as observed herein, it is unlikely that it would have a major impact on costs. However, these older and potentially milder cases may be absorbed by primary care and not captured by surveillance system. In this regard, enhanced surveillance in older children and systematic RSV laboratory confirmation should be encouraged to avoid any reporting bias.

One of the major strengths of the present study is that it included laboratory confirmed cases and covered the second largest metropolitan area in France, which can be a good approximation for the rest of the country. One limitation of the study could be that that the RSV seasons prior to the COVID-19 period, between 2017 and 2020, were not assessed. However, this would not affect the results and conclusions of the study, as the objective was to compare a period before and after the implementation of the NPIs due to COVID-19. In this sense, there was also a similar age shift between the 2018/19–2019/20 and 2020/21 RSV seasons as described elsewhere [14]. In addition, the RSV subtype might also be associated with less severe clinical disease during the RSV 2020/21 season, however, the predominant subtype in Lyon during the 2020/21 RSV season was RSV-A (90 % of isolates) [14], which has been associated with greater severity [24]. Healthcare-seeking behaviour might have changed due to the COVID-19 pandemic, but we believe that this would not have affected the study population that included children < 2 years of age who required hospitalisation. Furthermore, it is important to mention that we cannot exclude an increase in outpatient costs, linked to an increase in the frequency of milder disease, as we only evaluated direct costs of hospitalisation.

In conclusion, this observational study highlights how a 1.5-fold increase in the median age of RSVH with a decrease in incidence in the youngest infants had a significant impact on the reduction of total seasonal hospitalisation costs. Hence, future passive immunisation strategies that aim to reduce the incidence in young infants, and indirectly may lead to an increase in the incidence of RSVH in older age groups as observed in the present study, would also reduce the overall RSVH costs in children aged < 2 years. However,

stakeholders should be aware of this potential increase of RSV cases in older age groups with a wider range of clinical presentations to avoid any bias in estimating the cost-effectiveness of passive immunisation strategies.

## 5. Contribution and authorship

A.R., B.L. and J.-S.C. conceived and design the study; A.R., S.P., D. P., Y.G., E.J., A.-F.M.-D., S.C.-T., A.D. and J.-S.C. acquired and interpreted the data; A.R. and J.S.C. wrote the first draft of the manuscript. S.P., D.P., Y.G., E.J., B.L., A.-F.M.-D., S.C.-T. and A.D. critically reviewed the manuscript. All authors approved the final version of the manuscript. All authors attest they meet the ICMJE criteria for authorship.

## Funding

The authors state that there was no funding for this study.

## Data availability

Data will be made available on request.

## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: J.S.C participated as an expert to Pfizer scientific advisory board and in PROMISE General Assembly. J.S.C. did not receive funding for these activities.

## Acknowledgements

We thank the paediatric department and laboratory technical staff for obtaining the virological data, as well as Philip Robinson (Hospices Civils de Lyon) for manuscript preparation.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.05.021.

## References

[1] Li Y, Wang X, Blau DM, Caballero MT, Feikin DR, Gill CJ, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. Lancet 2022;399:2047–64. https://doi.org/10.1016/S0140-6736(22)00478-0.

[2] Navarro Alonso JA, Bont LJ, Bozzola E, Herting E, Lega F, Mader S, et al. RSV: perspectives to strengthen the need for protection in all infants. Emerg Themes Epidemiol 2021;18:15. https://doi.org/10.1186/s12982-021-00104-5.

[3] Fryzek JP, Martone WJ, Groothuis JR. Trends in chronologic age and infant respiratory syncytial virus hospitalization: an 8-year cohort study. Adv Ther 2011;28:195–201. Erratum in: Adv Ther. 2011; 28:1126. doi: 10.1007/s12325-010-0106-6.

[4] Jepsen MT, Trebbien R, Emborg HD, Krause TG, Schønning K, Voldstedlund M, et al. Incidence and seasonality of respiratory syncytial virus hospitalisations in young children in Denmark, 2010 to 2015. Euro Surveill 2018;23:17–00163. https://doi.org/10.2807/1560-7917.ES.2018.23.3.17-00163.

[5] Vicente D, Montes M, Cilla G, Perez-Yarza EG, Perez-Trallero E. Hospitalization for respiratory syncytial virus in the paediatric population in Spain. Epidemiol Infect 2003;131:867–72. https://doi.org/10.1017/s0950268803008926.

[6] Demont C, Petrica N, Bardoulat I, Duret S, Watier L, Chosidow A, et al. Economic and disease burden of RSV-associated hospitalizations in young children in France, from 2010 through 2018. BMC Infect Dis 2021;21:730. https://doi.org/10.1186/s12879-021-06399-8.

[7] McLaurin KK, Farr AM, Wade SW, Diakun DR, Stewart DL. Respiratory syncytial virus hospitalization outcomes and costs of full-term and preterm infants. J Perinatol 2016;36:990–6. https://doi.org/10.1038/jp.2016.113.

[8] Kramer R, Duclos A, Lina B, Casalegno JS. Cost and burden of RSV related hospitalisation from 2012 to 2017 in the first year of life in Lyon, France. Vaccine 2018;36:6591–3. https://doi.org/10.1016/j.vaccine.2018.09.029.

[9] Ohuma EO, Okiro EA, Ochola R, Sande CJ, Cane PA, Medley GF, et al. The natural history of respiratory syncytial virus in a birth cohort: the influence of age and previous infection on reinfection and disease. Am J Epidemiol 2012;176:794–802. https://doi.org/10.1093/aje/kws257.

[10] Koltai M, Krauer F, Hodgson D, van Leeuwen E, Treskova-Schwarzbach M, Jit M, et al. Determinants of RSV epidemiology following suppression through pandemic contact restrictions. Epidemics 2022;40:. https://doi.org/10.1016/j.epidem.2022.100614100614.

[11] Li Y, Wang X, Cong B, Deng S, Feikin DR, Nair H. Understanding the potential drivers for respiratory syncytial virus rebound during the coronavirus disease 2019 pandemic. J Infect Dis 2022;225:957–64. https://doi.org/10.1093/infdis/jiab606.

[12] Bozzola E, Barni S, Villani A. Respiratory syncytial virus pediatric hospitalization in the COVID-19 era. Int J Environ Res Public Health 2022;19:15455. https://doi.org/10.3390/ijerph192315455.

[13] van Summeren J, Meijer A, Aspelund G, Casalegno JS, Erna G, Hoang U, et al. Low levels of respiratory syncytial virus activity in Europe during the 2020/21 season: what can we expect in the coming summer and autumn/winter? Euro Surveill 2021:26. https://doi.org/10.2807/1560-7917.ES.2021.26.29.2100639.

[14] Casalegno JS, Ploin D, Cantais A, Masson E, Bard E, Valette M, et al. Characteristics of the delayed respiratory syncytial virus epidemic, 2020/2021, Rhône Loire, France. Euro Surveill 2021:26. https://doi.org/10.2807/1560-7917.ES.2021.26.29.2100630.

[15] Fourgeaud J, Toubiana J, Chappuy H, Delacourt C, Moulin F, Parize P, et al. Impact of public health measures on the post-COVID-19 respiratory syncytial virus epidemics in France. Eur J Clin Microbiol Infect Dis 2021;40:2389–95. https://doi.org/10.1007/s10096-021-04323-1.

[16] Voirin N, Virlogeux V, Demont C, Kieffer A. Potential impact of nirsevimab on RSV transmission and medically attended lower respiratory tract illness caused by RSV: a disease transmission model. Infect Dis Ther 2022;11:277–92. https://doi.org/10.1007/s40121-021-00566-9.

[17] Cromer D, van Hoek AJ, Newall AT, Pollard AJ, Jit M. Burden of paediatric respiratory syncytial virus disease and potential effect of different immunisation strategies: a modelling and cost-effectiveness analysis for England. Lancet Public Health 2017;2:e367–74. doi: 10.1016/S2468-2667(17)30103-2.

[18] Li X, Hodgson D, Flaig J, Kieffer A, Herring WL, Beyhaghi H, et al. Cost-effectiveness of respiratory syncytial virus preventive interventions in children: a model comparison study. Value Health 2022;25:S1098–3015. https://doi.org/10.1016/j.jval.2022.11.014.

[19] Kieffer A, Beuvelet M, Sardesai A, Musci R, Milev S, Roiz J, et al. Expected impact of universal immunization with nirsevimab against RSV-related outcomes and costs among all US infants in their first RSV season: a static model. J Infect Dis 2022;226:S282–92. doi:10.1093/infdis/jiac216.

[20] Zhang S, Akmar LZ, Bailey F, Rath BA, Alchikh M, Schweiger B, et al. Cost of respiratory syncytial virus-associated acute lower respiratory infection management in young children at the regional and global level: a systematic review and meta-analysis. J Infect Dis 2020;222:S680–7. doi: 10.1093/infdis/jiz683.

[21] Saravanos GL, Sheel M, Homaira N, Dey A, Brown E, Wang H, et al. Respiratory syncytial virus-associated hospitalisations in Australia, 2006–2015. Med J Aust 2019;210:447–53. https://doi.org/10.5694/mja2.50159.

[22] Nygaard U, Hartling UB, Nielsen J, Vestergaard LS, Dungu KHS, Nielsen JPA, et al. 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. Lancet Child Adolesc Health 2023;S2352–4642(22):00371–6. https://doi.org/10.1016/S2352-4642(22)00371-6. Epub ahead of print.

[23] van Boven M, Teirlinck AC, Meijer A, Hooiveld M, van Dorp CH, Reeves RM, et al. Estimating transmission parameters for respiratory syncytial virus and predicting the impact of maternal and pediatric vaccination. J Infect Dis 2020;222:S688–94. doi: 10.1093/infdis/jiaa424.

[24] Vandini S, Biagi C, Lanari M. Respiratory syncytial virus: the influence of serotype and genotype variability on clinical course of infection. Int J Mol Sci 2017;18:1717. https://doi.org/10.3390/ijms18081717.