Increasing burden of viral bronchiolitis in the pediatric intensive care unit

Increasing burden of viral bronchiolitis in the pediatric intensive care unit; an observational study

Authors

Rosalie S. Linssen[1] MD, Anne C. Teirlinck[2] PhD, Michiel van Boven[2], Dominique Biarent[3] MD, Luca Stona[4], Angela Amigoni[5] MD, Rosanna I. Comoretto[6] PhD, Stephane Leteurtre[7,8] MD PhD, Amélie Bruandet[9] MD PhD, Gunnar K. Bentsen[10] MD PhD, Inger Marie Drage[11] MD, Xin Wang[12], Harry Campbell[12] MD, Job B.M. van Woensel[1] MD PhD, Louis Bont[13, 14] MD PhD, Reinout A. Bem[1] MD PhD.

Author Affiliations

1. Pediatric Intensive Care Unit, Emma Children's hospital, Amsterdam University Medical Centers, location AMC, Amsterdam, the Netherlands
2. Center for infectious Disease Control, National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands
3. Pediatric Intensive Care and Emergency Department, Hospitale Universitaire des Enfants Reine Fabiola, Université Libre de Bruxelles, Belgium
4. Fondazione Penta Child Health Research ONLUS, Padova, Italy
5. Pediatric Intensive Care Unit, Department of Woman's and Child's Health, University Hospital of Padova, Padova, Italy
6. Unit of Biostatistics, Epidemiology and Public Health, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padova, Padova, Italy
7. Univ. Lille, CHU Lille, ULR 2694 - METRICS: Évaluation des technologies de santé et des pratiques médicales, F-59000 Lille, France

8. Groupe Francophone de Réanimation et d'Urgences pédiatriques – GFRUP-. Paris, France
9. Medical Information Department, Lille University Hospital, Lille, France
10. Division of Emergencies and Critical Care, Oslo University Hospital – Rikshospitalet, Oslo, Norway
11. Division of Emergencies and Critical Care, Oslo University Hospital – Ullevaal, Oslo, Norway
12. Centre for Global Health, Usher Institute, University of Edinburgh, Edinburgh, United Kingdom
13. UMCU Laboratory of Translational Immunology, Wilhelmina Children's Hospital, University Medical Center of Utrecht, Utrecht, the Netherlands
14. Respiratory Syncytial Virus Network (ReSViNET) Foundation, Zeist, the Netherlands

Corresponding Author:

Rosalie S. Linssen MD, Pediatric Intensive Care Unit, Emma Children's Hospital, Amsterdam University Medical Centers, location AMC, PO Box 22660, 1100DD, Amsterdam, the Netherlands, E: r.s.linssen@amsterdamumc.nl, T: +31 20 56 62453

ORCID ID: 0000-0003-2568-216X

Word count: 1162

STATEMENTS PAGE

Author contributions:

Rosalie S. Linssen: designed the study, participated in data collection, data interpretation and report writing.

Anne C. Teirlinck: participated in study design, data collection, data interpretation, statistical analysis and report writing.

Michiel van Boven: participated in data interpretation, statistical analysis and report writing.

Dominique Biarent: participated in study design, data interpretation and report writing.

Luca Stona: participated in study design, data interpretation and report writing.

Angela Amigoni: participated in study design, data interpretation and report writing.

Rosanna Comoretto: participated in study design, data interpretation and report writing.

Stephane Leteurtre: participated in study design, data interpretation and report writing.

Amélie Bruandet: participated in study design, data interpretation and report writing.

Gunnar K. Bentsen: participated in study design, data interpretation and report writing.

Inger Marie Drage: participated in study design, data interpretation and report writing.

Xin Wang: participated in study design, data interpretation and report writing.

Harry Campbell: participated in study design, data interpretation and report writing.

Job B.M. van Woensel: participated in study design, data interpretation and report writing.

Louis Bont: participated in study design, data interpretation and report writing.

Reinout A. Bem: participated in study design, data interpretation and report writing.

All authors verified the data they contributed. All authors approved the final version of this manuscript.

Declarations of Interests: none

Financial disclosure: none

Role of the funding source: none

Funding: This work was supported by the Innovative Medicines Initiative 2 Joint Undertaking (to RESCEU, under grant agreement 116019). This Joint Undertaking receives support from the European Union's Horizon 2020 Research and Innovation Program and the European Federation of Pharmaceutical Industries and Associations.
Additional funding by Janivo Foundation, the Netherlands (grant number: not applicable) and the CJ Vaillant Foundation, the Netherlands (grant number: not applicable). R. Linssen received an Amsterdam UMC PhD Scholarship (grant number: not applicable).

Data sharing: data from specific national/site collaborators will only be shared upon reasonable request and in agreement with the data-providing site.

Patient consent: not applicable.

Ethical approval: Consent waivers were obtained from local medical ethical committees where appropriate.

ABSTRACT

Purpose: Viral bronchiolitis is a major cause of pediatric intensive care unit (PICU) admission. Insight in the trends of bronchiolitis-associated PICU admissions is limited, but imperative for future PICU resource and capacity planning.

Materials and Methods: We retrospectively studied trends in PICU admissions for bronchiolitis in six European sites, including three full national registries, between 2000 – 2019 and calculated population-based estimates per 100,000 children where appropriate. Information concerning risk factors for severe disease and use of invasive mechanical ventilation was also collected when available.

Results: In total, there were 15,606 PICU admissions for bronchiolitis. We observed an increase in the annual number, rate and estimates per 100,000 children of PICU admissions for bronchiolitis at all sites over the last two decades, while the proportion of patients at high risk for severe disease remained relatively stable.

Conclusions: The international increased burden of bronchiolitis for the PICU is concerning, and warrants further international attention and investigation.

Key Words: Pediatrics, bronchiolitis, critical care

BACKGROUND

Bronchiolitis, a common clinical entity of acute viral-induced lower respiratory tract disease in children below two years of age [1], poses one of the most important, current threats to global child health. In recent years, international efforts and WHO-commissioned global surveillance programs have established the overall burden of bronchiolitis, in particular caused by respiratory syncytial virus (RSV), revealing a steady position as a leading cause of hospitalization in young children for low, middle and high-income countries [2, 3]. Although bronchiolitis-associated mortality has been reduced to a minimum in high-income countries with access to critical care facilities, seasonal viral outbreaks put high pressure on pediatric intensive care units (PICUs). Importantly, recent studies from the US and Australia/New Zealand show an increase in the yearly number of PICU admissions for bronchiolitis during the last two decades [4, 5]. Insight in trends of bronchiolitis-associated PICU admissions is imperative in light of promising RSV vaccination programs [6], as well as future PICU resource and capacity planning. To this aim, we addressed the burden of severe bronchiolitis by retrospectively analyzing the trend in PICU admissions in six European countries during the period 2000 to 2019.

METHODS

National, quality-controlled registry data as well as single-center data were eligible for inclusion. Three national databases (France, FR, data ranging from 2011-2019; the Netherlands, NL, 2003-2018; Scotland, SCT, 2001-2016) and three single-center PICUs (Brussels, Belgium, BE, 2000-2019; Padua, Italy, IT, 2000-2019; Oslo, Norway, NW, 2000-2019) were included in the study. Waivers were obtained from local medical ethical committees where appropriate. We collected PICU admission numbers for bronchiolitis in children below two years of age (for international classification of diseases codes see Supplemental Table 1), and when available,

data concerning all PICU admissions (including other etiologies) in children below two years old, preterm birth (gestational age < 37 weeks), comorbidity (congenital heart disease, cystic fibrosis, bronchopulmonary disease and trisomy 21), and use of invasive mechanical ventilation (IMV, including high-frequency oscillation). Population estimates were extracted from Eurostat (https://ec.europa.eu/eurostat) and the National Records of Scotland (nrscotland.gov.uk; mid-year population estimates NHS) on March 9, 2021. We performed linear regression to assess for changes over time for continuous variables of interest and binary logistic regression for discrete variables where appropriate.

RESULTS

Between 2000 and 2019, there were 15,606 PICU admissions for bronchiolitis at the participating sites. Detailed information considering the PICUs and catchment population is presented in the Supplementary text and Supplementary Table 1A-1B. There was a significant increase in the number of PICU admissions for bronchiolitis in all sites over the study period (Fig 1A). This increasing trend was also observed in the relative contribution of bronchiolitis-related PICU admissions to the overall number of PICU admissions (Fig 1B), and in the population-based estimates per 100,000 children (Fig 1C) for the sites with available data. In the five sites (FR, NL, SCT, BE, IT) with data on patient characteristics, we did not observe a concomitant increase in the proportion of children at high risk for a severe course of bronchiolitis, including patients younger than 6 months of age, comorbidity or preterm birth (Fig 2 and Supplemental Fig 1). In the four sites (FR, NL, BE, IT) with data on respiratory support, the overall use of IMV appeared to decrease over time (FR: OR 0.86 95% CI 0.84 – 0.88, NL: OR 0.92 95% CI: 0.90 – 0.93, for a complete list see Supplemental Fig 2). However, we observed large differences in the proportion of children who received IMV,

with sites using IMV either in the majority (NL) or minority (FR, BE) of patients (Supplemental Text and Supplemental Fig 2).

DISCUSSION

In this study, we described the burden of severe viral bronchiolitis that requires PICU admission over the last two decades in six European countries using three full national registries and three single-center databases. We observed an increase in the annual number, rate and estimates per 100,000 children of PICU admissions for bronchiolitis in children below two years old in all the included sites.

The potential reasons (e.g. host-, virus- and environmental-related factors) for this rise in burden of bronchiolitis for the PICU remain unclear. In our retrospective analysis there was no evidence of any change in the proportion of high-risk patients traditionally associated with a severe course of bronchiolitis. Previous studies focusing on RSV-bronchiolitis exclusively, showed normal fluctuations – but no real increase in the RSV load among the general population and only a minimal increase in hospital admissions to the general wards, which thus cannot explain the increase in PICU admissions for bronchiolitis over time [7, 8]. Our study spanned a period of almost 20 years in which pediatric critical care practice, including at the sites in this study, has changed in terms of availability of non-invasive respiratory support (e.g. high flow nasal cannula, HFNC). Although we observed considerable variation in intubation rates between sites in this study (due to differences in health-care infrastructure and respiratory support strategies between sites), overall IMV rates appear to slightly decrease over the years. This moderate decline in the percentage of children receiving IMV may be related to the tremendous increased use of non-invasive respiratory support, such as HFNC, both in- and outside the PICU [5, 7, 9]. Paradoxically, absolute numbers of patients receiving

IMV appear to remain constant, and this indicates that the proportion of children in whom non-invasive respiratory support sufficed, functioned as the main driver for the overall increase in burden of bronchiolitis for PICUs. Similarly, previous studies have suggested the introduction of an important change in practice with lowering of PICU referral thresholds, specifically by widespread adoption of HFNC [5, 7, 9]. By showing a consistent increase in PICU admissions in various European countries, all with a different pediatric critical care infrastructure, our study further indicates that such observations do not stand alone, but likely reflect a larger (global) trend [5, 7, 9]. However, current retrospective registry-based analysis precludes from drawing any firm conclusions on the relationship between available respiratory support modalities and trends of PICU admissions.

Our data are derived from the pre-COVID-19 period, after which bronchiolitis incidence rates have dropped dramatically, but are currently developing [10]. A possible explanation for the dramatic drop in bronchiolitis cases may be the introduction of non-pharmaceutical interventions such as social distancing, that caused the infection rate of several respiratory viruses among the population to reach an all-time low. This may contribute to the emergence of a young population with low (herd) immunity for important common respiratory viruses such as RSV [11]. Caution is warranted in the upcoming years, as a highly unpredictable pattern in PICU admission rates for bronchiolitis may develop, potentially threatening critical health care capacity [10].

In conclusion, there is an increasing burden of viral bronchiolitis for PICUs in Europe over the last two decades, possibly related to increased utilization of non-invasive respiratory support modalities. This warrants attention and further detailed investigation by international

collaboration by the pediatric critical care community in prospective studies, as an incentive to inform health care policymakers and future preventive (immunization) strategies.

Acknowledgements: PICE study group members and the PICURe (Pediatric Intensive Care Unit Registry) members.

FIGURE CAPTIONS

Figure 1. Trends in PICU admissions for bronchiolitis (2000-2019)

1A, Annual number of PICU admissions for bronchiolitis in children 0 – 2 years old. Admission numbers for France (FR) and the Netherlands (NL) are x10. Linear regression for PICU admissions over time for the individual sites showed an increase in PICU admissions for bronchiolitis at all sites: FR (β 60.82, SE 16.95, p = 0.009), NL (β 11.88, SE 3.157, p = 0.002), Scotland (SCT) (β 3.294, SE 0.492, p < 0.0001), Belgium (BE) (β 3.689 SE 0.391 p < 0.0001), Italy (IT) (β 1.066, SE 0.213, p < 0.0001); Norway (NW) (β 2.289, SE 0.329, p < 0.0001). The unstandardized beta coefficients (β) represent the degree of change (increase) in PICU admissions over time.

1B, Annual number of PICU admissions for bronchiolitis in children 0-2 years old shown as the percentage (%) of all children 0-2 years old admitted to the PICU (data from BE, FR, NL and IT). ***1C***, Annual national PICU admissions for bronchiolitis in children 0-2 years old per 100,000 children 0-2 years old in the country (data from FR, NL and SCT).

Figure 2. Trends in patient characteristics (age, comorbidity and preterm birth) among the children admitted to the PICU for bronchiolitis (2000-2019)

Trends in time for the percentages (%) of young age, comorbidity and preterm birth among the admitted children to a PICU for bronchiolitis. For each variable, we summed the data for the sites having data available for that specific variable for that specific year. If no data was available for the variable for interest for a site or specific year, data provided by that site was excluded for that year (as such, used denominators vary between years). Data on the number of children younger than six months were shared by FR, NL, SCT, BR, IT. Data on comorbidity, premature birth and IMV were shared by FR, NL, BR, IT. Comorbidity is

considered the presence of congenital heart disease, cystic fibrosis, bronchopulmonary disease or trisomy 21. Specific trends per site are presented in Supplemental Fig 1.

REFERENCES

1. Meissner HC. Viral Bronchiolitis in Children. N Engl J Med. 2016;374(1):62-72.
2. Shi T, McAllister DA, O'Brien KL, Simoes EAF, Madhi SA, Gessner BD, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet. 2017;390(10098):946-58.
3. Li Y, Johnson EK, Shi T, Campbell H, Chaves SS, Commaille-Chapus C, et al. National burden estimates of hospitalisations for acute lower respiratory infections due to respiratory syncytial virus in young children in 2019 among 58 countries: a modelling study. Lancet Respir Med. 2021;9(2):175-85.
4. Fujiogi M, Goto T, Yasunaga H, Fujishiro J, Mansbach JM, Camargo CA Jr., et al. Trends in Bronchiolitis Hospitalizations in the United States: 2000-2016. Pediatrics. 2019;144(6).
5. Schlapbach LJ, Straney L, Gelbart B, Alexander J, Franklin D, Beca J, et al. Burden of disease and change in practice in critically ill infants with bronchiolitis. Eur Respir J. 2017;49(6).
6. Griffin MP, Yuan Y, Takas T, Domachowske JB, Madhi SA, Manzoni P, et al. Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants. N Engl J Med. 2020;383(5):415-25.
7. Linssen RS, Bem RA, Kapitein B, Oude Rengerink K, Otten MH, den Hollander B. Burden of Respiratory Syncytial Virus bronchiolitis on the Dutch pediatric intensive care units. Eur J Pediatr. 2021; in press. doi: 10.1007/s00431-021-04079-y.
8. Reeves RM, van Wijhe M, Tong S, Lehtonen T, Stona L, Teirlinck AC, et al. Respiratory Syncytial Virus-Associated Hospital Admissions in Children Younger Than 5 Years in 7 European Countries Using Routinely Collected Datasets. J Infect Dis. 2020;222(Supplement_7):S599-S605.
9. Kalburgi S, Halley T. High-Flow Nasal Cannula Use Outside of the ICU Setting. Pediatrics. 2020;146(5).
10. Foley DA, Yeoh DK, Minney-Smith CA, Martin AC, Mace AO, Sikazwe CT, et al. The Interseasonal Resurgence of Respiratory Syncytial Virus in Australian Children Following the Reduction of Coronavirus Disease 2019-Related Public Health Measures. Clin Infect Dis.2021; ciaa1906. doi:10.1093/cid/ciaa1906.
11. Kinyanjui TM, House TA, Kiti MC, Cane PA, Nokes DJ, Medley GF. Vaccine Induced Herd Immunity for Control of Respiratory Syncytial Virus Disease in a Low-Income Country Setting. PLoS One. 2015;10(9):e0138018.

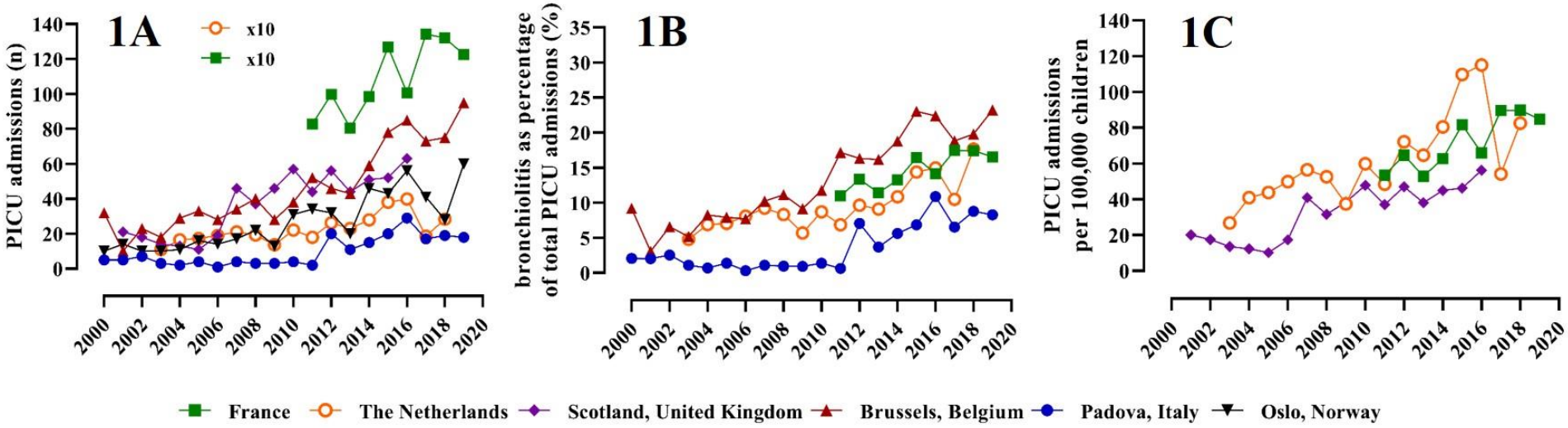

Figure 1. Trends in PICU admissions for bronchiolitis (2000-2019)

1A, Annual number of PICU admissions for bronchiolitis in children 0 – 2 years old. Admission numbers for France (FR) and the Netherlands (NL) are x10. Linear regression for PICU admissions over time for the individual sites showed an increase in PICU admissions for bronchiolitis at all sites: FR (β 60.82, SE 16.95, $p = 0.009$), NL (β 11.88, SE 3.157, $p = 0.002$), Scotland (SCT) (β 3.294, SE 0.492, $p < 0.0001$), Belgium (BE) (β 3.689 SE 0.391 $p < 0.0001$), Italy (IT) (β 1.066, SE 0.213, $p < 0.0001$); Norway (NW) (β 2.289, SE 0.329, $p < 0.0001$). The unstandardized beta coefficients (β) represent the degree of change (increase) in PICU admissions over time.

1B, Annual number of PICU admissions for bronchiolitis in children 0-2 years old shown as the percentage (%) of all children 0-2 years old admitted to the PICU (data from BE, FR, NL and IT). ***1C***, Annual national PICU admissions for bronchiolitis in children 0-2 years old per 100,000 children 0-2 years old in the country (data from FR, NL and SCT).

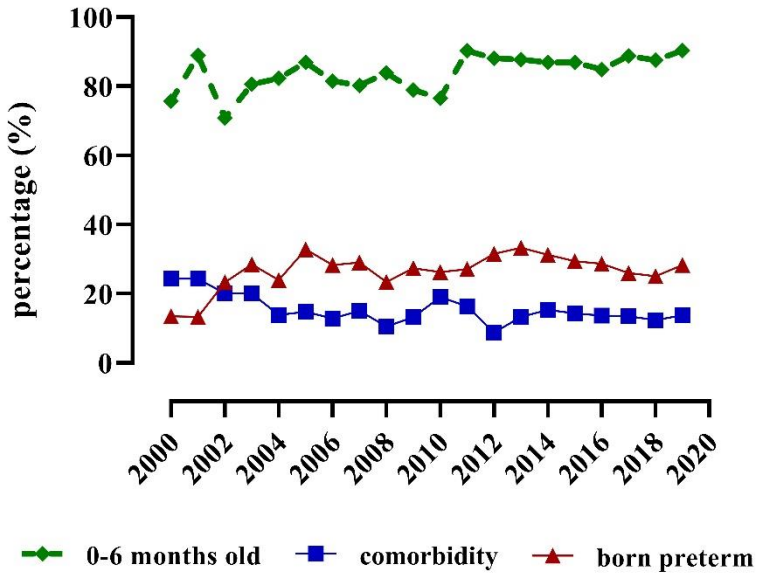

Figure 2. Trends in patient characteristics (age, comorbidity and preterm birth) among the children admitted to the PICU for bronchiolitis (2000-2019)

Trends in time for the percentages (%) of young age, comorbidity and preterm birth among the admitted children to a PICU for bronchiolitis. For each variable, we summed the data for the sites having data available for that specific variable for that specific year. If no data was available for the variable for interest for a site or specific year, data provided by that site was excluded for that year (as such, used denominators vary between years). Data on the number of children younger than six months were shared by FR, NL, SCT, BR, IT. Data on comorbidity, premature birth and IMV were shared by FR, NL, BR, IT. Comorbidity is considered the presence of congenital heart disease, cystic fibrosis, bronchopulmonary disease or trisomy 21. Specific trends per site are presented in Supplemental Fig 1.

Increasing burden of viral bronchiolitis in the pediatric intensive care unit; an observational study

Authors

Rosalie S. Linssen[1] MD, Anne C. Teirlinck[2] PhD, Michiel van Boven[2], Dominique Biarent[3] MD, Luca Stona[4], Angela Amigoni[5] MD, Rosanna I. Comoretto[6] PhD, Stephane Leteurtre[7,8] MD PhD, Amélie Bruandet[9] MD PhD, Gunnar K. Bentsen[10] MD PhD, Inger Marie Drage[11] MD, Xin Wang[12], Harry Campbell[12] MD, Job B.M. van Woensel[1] MD PhD, Louis Bont[13, 14] MD PhD, Reinout A. Bem[1] MD PhD.

Author Affiliations

1. Pediatric Intensive Care Unit, Emma Children's hospital, Amsterdam University Medical Centers, location AMC, Amsterdam, the Netherlands
2. Center for infectious Disease Control, National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands
3. Pediatric Intensive Care and Emergency Department, Hospitale Universitaire des Enfants Reine Fabiola, Université Libre de Bruxelles, Belgium
4. Fondazione Penta Child Health Research ONLUS, Padova, Italy
5. Pediatric Intensive Care Unit, Department of Woman's and Child's Health, University Hospital of Padova, Padova, Italy
6. Unit of Biostatistics, Epidemiology and Public Health, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padova, Padova, Italy
7. Univ. Lille, CHU Lille, ULR 2694 - METRICS: Évaluation des technologies de santé et des pratiques médicales, F-59000 Lille, France

8. Groupe Francophone de Réanimation et d'Urgences pédiatriques – GFRUP-. Paris, France
9. Medical Information Department, Lille University Hospital, Lille, France
10. Division of Emergencies and Critical Care, Oslo University Hospital – Rikshospitalet, Oslo, Norway
11. Division of Emergencies and Critical Care, Oslo University Hospital – Ullevaal, Oslo, Norway
12. Centre for Global Health, Usher Institute, University of Edinburgh, Edinburgh, United Kingdom
13. UMCU Laboratory of Translational Immunology, Wilhelmina Children's Hospital, University Medical Center of Utrecht, Utrecht, the Netherlands
14. Respiratory Syncytial Virus Network (ReSViNET) Foundation, Zeist, the Netherlands

Corresponding Author:

Rosalie S. Linssen MD, Pediatric Intensive Care Unit, Emma Children's Hospital, Amsterdam University Medical Centers, location AMC, PO Box 22660, 1100DD, Amsterdam, the Netherlands, E: r.s.linssen@amsterdamumc.nl, T: +31 20 56 62453

ORCID ID: 0000-0003-2568-216X

Word count: 1162

STATEMENTS PAGE

Author contributions:

Rosalie S. Linssen: designed the study, participated in data collection, data interpretation and report writing.

Anne C. Teirlinck: participated in study design, data collection, data interpretation, statistical analysis and report writing.

Michiel van Boven: participated in data interpretation, statistical analysis and report writing.

Dominique Biarent: participated in study design, data interpretation and report writing.

Luca Stona: participated in study design, data interpretation and report writing.

Angela Amigoni: participated in study design, data interpretation and report writing.

Rosanna Comoretto: participated in study design, data interpretation and report writing.

Stephane Leteurtre: participated in study design, data interpretation and report writing.

Amélie Bruandet: participated in study design, data interpretation and report writing.

Gunnar K. Bentsen: participated in study design, data interpretation and report writing.

Inger Marie Drage: participated in study design, data interpretation and report writing.

Xin Wang: participated in study design, data interpretation and report writing.

Harry Campbell: participated in study design, data interpretation and report writing.

Job B.M. van Woensel: participated in study design, data interpretation and report writing.

Louis Bont: participated in study design, data interpretation and report writing.

Reinout A. Bem: participated in study design, data interpretation and report writing.

All authors verified the data they contributed. All authors approved the final version of this manuscript.

Declarations of Interests: none

Financial disclosure: none

Role of the funding source: none

Funding: This work was supported by the Innovative Medicines Initiative 2 Joint Undertaking (to RESCEU, under grant agreement 116019). This Joint Undertaking receives support from the European Union's Horizon 2020 Research and Innovation Program and the European Federation of Pharmaceutical Industries and Associations.
Additional funding by Janivo Foundation, the Netherlands (grant number: not applicable) and the CJ Vaillant Foundation, the Netherlands (grant number: not applicable). R. Linssen received an Amsterdam UMC PhD Scholarship (grant number: not applicable).

Data sharing: data from specific national/site collaborators will only be shared upon reasonable request and in agreement with the data-providing site.

Patient consent: not applicable.

Ethical approval: Consent waivers were obtained from local medical ethical committees where appropriate.