Clinical and viral factors associated with disease severity and subsequent wheezing in infants with respiratory syncytial virus infection

Running title: Factors associated with RSV severity

Joseph P McGinley[1,a], Gu-Lung Lin[1,a], Deniz Öner[2], Tanya Golubchik[3], Daniel O'Connor[1], Matthew D Snape[1], Olivier Gruselle[4], Annefleur C Langedijk[5], Joanne Wildenbeest[5], Peter Openshaw[6], Harish Nair[7], Jeroen Aerssens[2], Louis Bont[5,b], Federico Martinón-Torres[8,b], Simon B Drysdale[9,b], Andrew J Pollard[1,b], on behalf of the RESCEU Investigators

[1]Oxford Vaccine Group, Department of Paediatrics, University of Oxford, and the NIHR Oxford Biomedical Research Centre, Oxford, United Kingdom

[2]Translational Biomarkers, Infectious Diseases Therapeutic Area, Janssen Pharmaceutica NV, Beerse, Belgium

[3]Big Data Institute, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom

[4]GlaxoSmithKline, Wavre, Belgium

[5]Department of Paediatric Immunology and Infectious Diseases, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, Netherlands

[6]National Heart and Lung Institute, Imperial College London, London, United Kingdom

[7]Centre for Global Health, Usher Institute, Edinburgh Medical School, University of Edinburgh, Edinburgh, United Kingdom

[8]Translational Pediatrics and Infectious Diseases, Hospital Clínico Universitario de Santiago de Compostela, Santiago de Compostela, Spain

[9]Paediatric Infectious Diseases Research Group, Institute for Infection and Immunity, St George's, University of London, London, United Kingdom

[a]J. P. M. and G.-L. L. contributed equally to this work.

[b]L. B., F. M.-T., S. B. D. and A. J. P. contributed equally to this work.

25 Correspondence: J. P. McGinley, DPhil, Oxford Vaccine Group, Centre for Clinical Vaccinology and
26 Tropical Medicine, Churchill Hospital, Oxford OX3 7LE, United Kingdom
27 (joseph.mcginley@paediatrics.ox.ac.uk).

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Abstract

Respiratory syncytial virus (RSV) causes substantial morbidity and mortality in infants and young children worldwide. There is conflicting evidence on the association between RSV genotype, viral load, and disease severity. Here we evaluated host demographic and viral factors associated with RSV disease severity in 325 RSV-infected infants under 1 year of age from three European countries during 2017–2020. Younger infants had a higher clinical severity (ReSViNET) score and were more likely to require hospitalisation, intensive care, respiratory support, and/or mechanical ventilation than older infants (<3 months vs. 3 to <6 months and 3 to <6 months vs. ≥6 months). Older age (≥6 months vs. <3 months), higher viral load, and RSV-A were associated with a greater probability of fever. RSV viral load decreased by ~60% daily between 3 and 9 days after symptom onset. RSV-A and RSV-B caused similar disease severity and had similar viral dynamics. The rate of viral load change was similar in infants with different clinical outcomes, including the ReSViNET scores, presence of fever, and the requirement for intensive care or mechanical ventilation. Infants with a more severe RSV infection, demonstrated by having a higher ReSViNET score, fever, and requiring hospitalisation and intensive care, were more likely to have developed subsequent wheezing at 1 year of age. Taken together these findings highlight the substantial morbidity caused by RSV infection in young infants and provide strong evidence of an association with post-infectious wheezing. Preventive intervention with vaccines or monoclonal antibodies could substantially improve health in infancy and reduce RSV-associated pressures on health systems.

Key words: respiratory syncytial virus, disease severity, wheezing, subgroup, viral load

Introduction

Human respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infection (LRTI) in infants and young children. The annual RSV epidemic is responsible for an estimated 33 million episodes of LRTI, 3 million hospitalisations, and up to 75,000 in-hospital deaths globally in children

under 5 years of age [1]. Infants under 3 months of age, those born before 30 weeks' gestation, and those with cardiopulmonary disease are at higher risk of severe RSV infection than healthy term infants [2]. Despite the impact of the disease, there is no licensed vaccine or effective treatment for RSV disease, and the standard of care remains supportive management of respiratory compromise.

RSV is classified into two subgroups, A and B. Both subgroups co-circulate during annual epidemics with alternating patterns of subgroup dominance [3]. The majority of studies have shown that RSV-A causes more severe infection than RSV-B [4, 5], although a few studies have shown the opposite [6] or similar disease severity with both subgroups [7, 8]. Similarly, there is conflicting evidence on the association between RSV viral load and disease severity [9-12].

There is evidence of the association between RSV-associated LRTI in early childhood and the development of recurrent wheeze and asthma in later childhood up to early adulthood [13-16]. A double-blind, placebo-controlled, randomised trial showed that prophylaxis with palivizumab (an anti-RSV monoclonal antibody) in otherwise healthy preterm infants born at 33–35 weeks' gestation reduced the number of days of recurrent wheeze in the first year of life [17]. A follow-up study of the same cohort, however, did not find a significant difference in the incidence of asthma nor any changes in lung function at 6 years of age [18]. Another double-blind, placebo-controlled, randomised trial showed no effect of prophylaxis with motavizumab (another anti-RSV monoclonal antibody) in healthy term infants on rates of wheeze during the first 3 years of life [19]. Further studies are required to establish the causal link between RSV infection and subsequent wheeze and asthma, and the potential of preventative or therapeutic interventions [20].

In this study, we prospectively enrolled RSV-infected infants in the Netherlands, Spain, and the United Kingdom (UK) between 2017 and 2020. We sought to explore the host demographic and viral factors associated with the clinical characteristics of RSV infection and subsequent wheeze. In doing so, we could advance our understanding of RSV infection and help identify target populations where trials of therapeutic and preventative measures could be directed.

Methods

Study design and clinical data collection

Infants with primary RSV infection under 1 year of age were prospectively enrolled in a clinical study from communities and hospitals in the Netherlands, Spain, and the UK during the 2017–2020 RSV seasons (from October to April). This study is one of four clinical studies in the REspiratory Syncytial virus Consortium in EUrope (RESCEU) project and has been described in detail previously (ClinicalTrials.gov identifier: NCT03756766) [21]. Infants who were previously healthy and those with pre-existing medical conditions (including prematurity, defined as being born before 37 weeks' gestation) were eligible for inclusion in this study. The goal was to recruit 500 previously healthy infants and 50 infants with pre-existing medical conditions. Exclusion criteria included infants who had received antiviral medication to treat RSV infection (e.g., ribavirin), human immunoglobulin, or monoclonal antibodies (including palivizumab), infants who had been exposed to an RSV investigational vaccine or medication, and infants who had received steroids or montelukast within 7 days of enrolment in the study. These medications may affect the symptom presentation, so infants who had received any of them were excluded from this study. RSV infection was confirmed using point-of-care testing on the Alere™ i RSV assay (Abbott, Illinois, United States) in a community setting or by routine tests (e.g., rapid antigen detection or PCR) at a central laboratory in a hospital setting.

A nasopharyngeal swab was collected from each participant within 96 hours of symptom onset or 48 hours of admission to the hospital. In addition, hospitalised participants had daily nasopharyngeal swabs collected, where possible, until hospital discharge. Swabs were immersed in M4RT® transport medium after collection, aliquoted, and frozen at –80℃ until use.

Demographic and clinical information was gathered through initial screening, medical record review, and a 14-day online diary completed from the time of enrolment by the parents. Clinical

severity was evaluated using the following criteria: (1) the ReSViNET score [22]; (2) presence of fever; and requirement for (3) hospitalisation, (4) intensive care (i.e., admission to a high dependency unit or an intensive care unit), (5) respiratory support, and/or (6) invasive mechanical ventilation. The ReSViNET score takes seven clinical parameters into account, including feeding intolerance, medical intervention, respiratory difficulty, respiratory frequency, apnoea, general condition, and fever. Total scores range from 0 to 20, with higher scores indicating more severe disease. Fever was defined as at least one episode of a rectal or tympanic temperature of 38℃ or above during the acute course of the infection.

Additional clinical information was gathered using parental questionnaires when the participants were 1 year of age. This included the occurrence of subsequent wheezing and other respiratory symptoms during the period between the RSV infection and the first birthday.

The study was conducted in accordance with the provisions of the Declaration of Helsinki and was approved by the relevant ethics committees at each site: the Medical Ethical Committee, University Medical Center Utrecht (no. 17/563) in the Netherlands; Comité de Ética de la Investigación de Santiago-Lugo (no. 2017/395) in Spain; and the Health Research Authority (no. 231136) and South Central and Hampshire A Research Ethics Committee (no. 17/SC/0522) in the UK. The parents or guardians of all participants provided written, informed consent.

Viral load measurement and typing

Viral load and RSV subgroup were determined by quantitative reverse transcription PCR (RT-qPCR). RT-qPCR was performed at GlaxoSmithKline (protocol proprietary). The primers of this duplex RT-qPCR assay targeted the N gene for both RSV-A and RSV-B. The limit of detection was 304 copies/mL for RSV-A and 475 copies/mL for RSV-B.

Samples with undetectable viral load were removed from analyses. To compare viral load data between participants, either initial or peak viral load was used. For participants with serial swabs

collected, initial viral load was defined as the viral load of the first collected sample with detectable viral load, and peak viral load was defined as the maximum viral load detected among all available samples. For participants who had only one viral load data point, it was used to represent both initial and peak viral load.

When there was not enough sample for RT-qPCR or the viral load was below the limit of detection, subgroup information was gathered from a previously described viral whole-genome sequencing study on the same cohort [23].

Statistical analyses

Pearson correlation analyses were used to evaluate the correlation between variables. Mann–Whitney U or Kruskal–Wallis tests were used to compare continuous variables between groups. Chi-square tests with Yates' correction were employed for contingency analyses, and Fisher's exact tests were used when the expected value for a cell was less than five. The rate of viral load change was determined by linear regression of viral load on the days after symptom onset, where samples with undetectable viral load were removed from the regression analysis.

When comparing clinical outcome variables between different groups of participants, multiple linear regression (for continuous outcome variables), multiple logistic regression (for dichotomous outcome variables), and proportional odds ordered logistic regression (for ordered outcome variables) were used to adjust for covariates (e.g., participant age, gestational age, sex, etc.). Likelihood ratio tests were used to evaluate the effect of age or country on the goodness of fit of models including other covariates. A post hoc adjustment for multiple comparisons with the Benjamini–Hochberg procedure was applied to determine false discovery rate–corrected Q values in all these comparisons of clinical outcomes between participants. Analysis of covariance (ANCOVA) tests were performed to compare the rates of viral load decline between different groups of participants.

All statistical analyses were performed using R (v4.1.1) [24]. A P value, or Q value in the case of multiple comparisons, of less than 0.05 was considered to indicate statistical significance.

Results

Study population

A total of 325 RSV-infected infants were enrolled from the Netherlands, Spain, and the UK during 2017–2020 (Table S1). Infants enrolled in the Netherlands were younger and had a higher proportion requiring intensive care and mechanical ventilation than those enrolled in the other two countries [median age (interquartile range, or IQR), 2.5 (1.4–5.7) vs. 3.5 (1.7–7.5) months; intensive care, 42% vs. 16%; mechanical ventilation, 44% vs. 12%; Table S2].

Excluding five infants without available age information, the median age of the 320 infants was 3.0 months (IQR, 1.5–6.6 months). Females accounted for 42% of the infants. Eight percent of the infants were born preterm; 31% of these preterm infants were born before 32 weeks' gestation, all of whom were enrolled in the UK. Of the 325 infants, 44 (14%) had comorbidities, including prematurity with or without bronchopulmonary dysplasia, ventricular septal defect, congenital hypothyroidism, wheeze, or other congenital abnormalities. The demographic characteristics of these infants are shown in Tables 1 and S2.

The associations between disease severity and demographic features (age, gestational age, sex, comorbidity) were evaluated using different clinical outcomes, including ReSViNET score, presence of fever, and the need for hospitalisation, intensive care, respiratory support, or mechanical ventilation, after adjusting for these demographic variables and RSV subgroup. These clinical outcomes were positively correlated with each other, except fever (Figure 1). While older infants had a lower ReSViNET score and were less likely to require hospitalisation, intensive care, respiratory support, and/or mechanical ventilation, they were more likely to have fever than younger infants (Table 1).

Preterm and term infants did not show any significant difference in these clinical outcomes. Similarly, male and female infants had similar disease severity in all tested clinical outcomes. Infants with any pre-existing medical condition had a higher ReSViNET score [mean ± standard deviation (SD), 12.0 ± 4.8 vs. 8.6 ± 4.5; Q = 0.044] and were more likely to require respiratory support [Odds Ratio (OR), 4.9; 95% confidence interval (CI), 1.5 to 19; Q = 0.049] than those without comorbidity.

Figure 1. Correlations between clinical outcome variables. Pearson correlation analyses were used to evaluate the correlations between these variables. Pearson correlation coefficients for these correlations are colour coded according to the legend. Significant correlations are marked with stars. All significant correlations had a P value of <0.001. PICU denotes paediatric intensive care unit. The ReSViNET score accounts for seven clinical variables: feeding intolerance, medical intervention, respiratory difficulty, respiratory frequency, apnoea, general condition, and fever.

RSV subgroup and viral load

Of the 292 infants for whom RSV subgroup information was available, 151 (52%) were infected with RSV-A, 140 (48%) with RSV-B, and 1 was coinfected with RSV-A and RSV-B. The subgroup information of 14 infants was gathered from sequencing results due to lack of RT-qPCR data. RSV-B was the predominant circulating subgroup during the 2017–18 RSV season, accounting for 67% (38/57) of the isolates, whereas RSV-A dominated the 2019–20 season, accounting for 64% (79/123) of the infections. During the 2018–19 season, RSV-A and RSV-B were co-circulating with similar prevalence. The incidences of the two subgroups in each country and season are shown in Table 2. RSV-A-infected and RSV-B-infected infants had similar demographic and clinical features in our dataset, except infants infected with RSV-A were more likely to have fever than those infected with

RSV-B (OR, 1.8; 95% CI, 1.1 to 3.2; P = 0.029) (Table 3). However, this difference was not significant after correction for multiple comparisons.

Nasopharyngeal viral load data were available for 278 infants. Among them, 77 had multiple days of viral load data during hospitalisation (mean ± SD, 3.6 ± 2.0 days). Combining all 483 viral load data points from the 278 infants, samples collected within 7 days of symptom onset had mean ± SD viral load of 6.4 ± 1.5 $\log_{10}$ copies/mL. This figure decreased to 4.6 ± 1.5 $\log_{10}$ copies/mL for samples collected between 8 and 14 days of symptom onset. No sample collected after 16 days of symptom onset had detectable viral load.

Samples generating the initial and peak viral loads were collected 3.9 ± 1.7 and 4.1 ± 1.8 days (mean ± SD) after symptom onset, respectively. RSV-A and RSV-B samples had similar peak viral load (Figure 2 and Table 3). After adjusting for age, gestational age, sex, comorbidity, RSV subgroup, and days between symptom onset and sample collection, infants with a febrile RSV infection had a higher peak viral load than those with an afebrile RSV infection (7.1 ± 1.2 vs. 6.6 ± 1.4 $\log_{10}$ copies/mL, P = 0.042) (Table 4). However, this difference became insignificant after correction for multiple comparisons (Table 4) or excluding infants with only one swab collected (Table S3). Figure S1 shows the probability of fever increasing with age, viral load, and RSV-A infection. Peak viral load did not correlate with the ReSViNET score, the need for hospitalisation, intensive care, respiratory support, and/or mechanical ventilation after adjusting for the same covariates (Table 4, and Table S3 Similar results were seen when using initial viral load in the above-mentioned comparisons (data not shown).

RSV viral dynamics were analysed using serial viral load data from 77 hospitalised infants. Overall, viral load decreased by 59% daily (95% CI, 48% to 67%) between 3 and 9 days after symptom onset (Figure S2). Infants in different age groups or severity groups had similar rates of decrease in viral load. In addition, infants infected with RSV-A and RSV-B had similar rates of viral clearance (Table S4).

Figure 2. Distributions of peak viral loads for RSV-A and RSV-B. Samples generating the peak viral loads were collected 4.0 ± 1.8 and 4.1 ± 1.8 days (mean ± SD) after symptom onset for RSV-A and RSV-B, respectively. A Mann–Whitney U test was used to evaluate the significance of the difference in peak viral load between the two subgroups. The centre line of each box denotes the median; box limits, the first and third quartiles; whiskers, the highest and lowest values within 1.5 times the interquartile range from the box limits; and outlying points, outliers. The P value is shown above the boxplot.

Respiratory sequelae at 1 year of age

Among the 325 infants, 165 (51%) had 1-year follow-up data on respiratory sequelae. Association analysis of clinical features and sequelae (wheezing episodes since infection) was performed using this cohort (Table 5). The median age at the time of the RSV infection of infants who subsequently developed wheezing in this study was 3.7 months (IQR, 1.3-6.2 months), while infants who did not subsequently develop wheezing had a median age of 4.3 months (IQR, 1.5-7.3 months) when infected. Hospitalisation showed the greatest influence on the development of subsequent wheezing ($Q = 2.8\times10^{-4}$) after adjusting for age, gestational age, sex, comorbidity, and viral subgroup, while high ReSViNET scores, fever, and requirement of intensive care were also significantly associated with wheezing development (Q = 0.007, 0.014, and 0.014, respectively) (Table 5).

Discussion

In this study, we found that chronological age was significantly associated with severe RSV disease. Younger infants were more likely to require hospitalisation, intensive care, respiratory support, and/or mechanical ventilation, while older infants were more likely to have fever. While both RSV subgroups

had similar viral dynamics, RSV-A and high viral load were associated with a higher probability of fever than RSV-B and low viral load. Infants who had a high ReSViNET score, fever, or required hospitalisation or intensive care were more likely to develop subsequent wheezing at 1-year follow-up.

We demonstrated a positive relationship between the probability of fever and infant age. Elevated levels of interferon (IFN)-α and IFN-γ have been known to cause fever, based on results of IFN trials [25]. Studies have also shown that decreased levels of type I IFN (particularly IFN-α1) and IFN-γ in peripheral blood and the nasopharynx are associated with more severe RSV disease in children under 2 years of age [12, 26]. In addition, one study showed that RSV induced lower levels of IFN-α in infants than in children 12 months to <5 years old [27], suggesting that younger infants may have lower levels of IFN than older infants at acute RSV infection. Altogether, IFN levels may explain why younger infants have more severe disease but a lower incidence of fever than older ones. Blood, stool, urine, and respiratory microbiome swabs were collected in this study to investigate the immunological factors determining disease severity. Results of these analyses will be published separately.

RSV-A was more likely to cause a febrile infection than RSV-B in our cohort, while other clinical outcomes were not significantly different between the two subgroups. Previous studies have shown conflicting results on the association between RSV subgroup and disease severity [4-8], but none have included fever as an outcome variable. From our previous sequencing study [23], we have shown that all of the RSV strains isolated in this study were genotype ON1 (RSV-A) and BA (RSV-B), which are the current dominating strains worldwide [28-30].

In our dataset, viral load positively correlated with the probability of fever, but not with other clinical outcome measures. Studies enrolling previously healthy RSV-infected children under 2 years of age had contrasting results. One showed that viral load positively correlated with the duration of hospitalisation and the requirement for intensive care and mechanical ventilation [9], while the other showed that a higher initial viral load was associated with milder disease in terms of the need for

hospitalisation and intensive care [31]. These studies did not evaluate the association between viral load and the possibility of fever [9, 31]. Furthermore, we did not find the rate of viral clearance associated with any of the tested clinical variables. However, delayed viral clearance has been shown in children requiring a longer duration of hospitalisation and those requiring intensive care [9, 31].

It is worth noting that studies on the association between RSV disease severity and viral factors (subgroup and viral load) have yielded conflicting results [4-12, 31]. The inconsistency is likely due to differences in study populations, definitions of disease severity, and/or genotypes of the infecting viruses. Our study is robust insofar as it included infants with a wide range of disease severities and from 3 different countries, albeit limited to Europe. We also included infants who were previously healthy and those who had comorbidities. Furthermore, we used several clinical outcome measures to account for the variability in disease presentation. Individual variation in patient characteristics (particularly immunological characteristics) is a potential cause of the difficulties in robustly assessing the relationship between viral load and disease severity. It may be possible to control for immunological variation using a biomarker that measures immunological predisposition towards more severe RSV disease to produce a more accurate assessment.

In our dataset, having more severe disease, demonstrated by high ReSViNET scores, fever, and requiring hospitalisation or intensive care, was associated with subsequent wheezing. The fact that multiple clinical variables correlated with wheezing suggests a complex origin for wheezing. Further follow up of these children up to 3 years of age is ongoing and will reveal if wheezing is transient or persistent throughout early childhood. Prospective controlled trials including interventions, such as vaccines or monoclonal antibodies, may be required to definitively characterise the relationship between RSV disease and respiratory sequelae.

Our study represents one of the most comprehensive datasets evaluating the associations between host demographic and viral factors and RSV disease severity and sequelae. Our findings deepen our understanding of the risk factors for severe RSV disease and subsequent wheezing, and identify the

target populations for therapeutic and preventative measures, particularly antivirals, vaccines, and monoclonal antibodies, in late-stage clinical trials.

RESCEU investigators

Harish Nair, Harry Campbell, Steve Cunningham, Debby Bogaert (University of Edinburgh); Philippe Beutels (Universiteit Antwerpen); Louis Bont, Joanne Wildenbeest, Annefleur C Langedijk (University Medical Centre Utrecht); Andrew Pollard, Christopher Butler, Matthew Snape, Simon Drysdale, Gu-Lung Lin, Daniel O'Connor, Elizabeth Clutterbuck, Joseph McGinley (University of Oxford); Peter Openshaw, Ryan Thwaites, Dexter Wiseman (Imperial College London); Federico Martinón-Torres, Alberto Gómez-Carballa, Carmen Rodríguez-Tenreiro, Irene Rivero-Calle, Ana Dacosta-Urbieta (Servicio Galego de Saude); Terho Heikkinen (University of Turku and Turku University Hospital); Adam Meijer (National Institute for Public Health and the Environment); Thea K Fischer (Statens Serum Institut); Maarten van den Berge (University of Groningen); Carlo Giaquinto (PENTA Foundation); Michael Abram (AstraZeneca); Tin Tin Myint (Pfizer); Olivier Gruselle, Bishoy Rizkalla (GlaxoSmithKline); Charlotte Vernhes, Scott Gallichan (Sanofi Pasteur); Jeroen Aerssens, Deniz Öner (Janssen); Veena Kumar (Novavax); Eva Molero (Team-It Research).

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Author contributions

J. P. M., G.-L. L., and D. Ö. conceived and designed the work. J. P. M., G.-L. L, D. Ö., M. D. S., A. C. L., J. W., P. O., H. N., J. A., L. B., F. M.-T., S. B. D., and A. J. P. conducted and supervised the clinical studies. O. G. arranged the RT-qPCR assays. J. P. M., G.-L. L., D. Ö., S. B. D., and A. J. P. analysed and interpreted the data. J. P. M. and G.-L. L. drafted the manuscript, and T. G., D. O'C., S. B. D., and A. J. P. substantively revised it. All authors have approved the submitted version and agreed to submit the manuscript.

Competing interests

D. Ö. and J. A. are employees of Janssen Pharmaceutica NV. O. G. is an employee of the GSK group of companies. H. N. has received funding from Sanofi and Pfizer and has received honoraria from Sanofi, Abbvie, Janssen, ReViral, and Novavax. F. M.-T. has received honoraria from GSK, Pfizer Inc, Sanofi Pasteur, MSD, Seqirus, and Janssen for taking part in advisory boards and expert meetings and for acting as a speaker in congresses outside the scope of the submitted work. F. M.-T. has also acted as principal investigator in randomized controlled trials of the above-mentioned companies as well as Ablynx, Regeneron, Roche, Abbott, Novavax, and MedImmune, with honoraria paid to his institution. F. M.-T. receives support for his research activities from the Instituto de Salud Carlos III (Proyecto de Investigación en Salud, Acción Estratégica en Salud): Fondo de Investigación Sanitaria (FIS;PI1601569/PI1901090) del plan nacional de I+D+I and 'fondos FEDER'. S. B. D has been an investigator for clinical trials of vaccines and antimicrobials for pharmaceutical companies including AstraZeneca, Merck, and Janssen, and sits on an RSV advisory board for Sanofi Pasteur. A. J. P. is a National Institute for Health Research (NIHR) Senior Investigator with funding from the British Research Council. All other authors report no potential conflicts. The views expressed in this article are those of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the organizations with which the authors are employed/affiliated.

353 Table 1. Characteristics of the RSV-infected infants, stratified by age group (N = 320).[a]

	<3 months (N = 160)	3 to <6 months (N = 63)	≥6 months (N = 97)	P value	Q value
Demographic features					
Gestational age					
Median (IQR)—weeks	39.0 (38.0–40.1)	39.6 (38.1–40.3)	39.9 (38.8–40.7)	0.012	
Distribution				0.990	
<32 weeks	4/160 (3)	1/62 (2)	3/96 (3)		
32 to <37 weeks	9/160 (6)	3/62 (5)	6/96 (6)		
≥37 weeks	147/160 (92)	58/62 (94)	87/96 (91)		
Female sex	57 (36)	25 (40)	50 (52)	0.041	
Weight—total no.	158	59	94		
Mean ± SD—kg	4.5 ± 1.0	6.7 ± 0.9	8.4 ± 1.3	2.7×10^{-49}	
Comorbidity	21 (13)	6 (10)	17 (18)	0.338	
Virological features					
Subgroup A	73/147 (50)	35/61 (57)	41/78 (53)	0.597[b]	
Peak viral load—total no.	137	56	77		
Mean ± SD—$\log_{10}$ copies/mL	6.6 ± 1.4	6.8 ± 1.3	7.1 ± 1.3	0.109[c]	
Clinical features[d]					
ReSViNET score					
Mean ± SD	10.3 ± 4.6	8.9 ± 4.7	7.0 ± 4.2	2.1×10^{-8}	4.8×10^{-8}

Distribution				1.2×10^{-6}	1.6×10^{-6}
0–7	49/155 (32)	26/61 (43)	51/90 (57)		
8–13	62/155 (40)	23/61 (38)	31/90 (34)		
14–20	44/155 (28)	12/61 (20)	8/90 (9)		
Fever	34/156 (22)	21/61 (34)	44/90 (49)	5.2×10^{-4}	5.2×10^{-4}
Hospitalisation	141/158 (89)	45/62 (73)	47/93 (51)	1.2×10^{-9}	4.3×10^{-9}
PICU admission	61/158 (39)	13/62 (21)	12/93 (13)	4.5×10^{-6}	5.3×10^{-6}
Respiratory support	126/148 (85)	37/55 (67)	34/81 (42)	6.5×10^{-13}	4.5×10^{-12}
Mechanical ventilation	55/148 (37)	10/55 (18)	5/81 (6)	5.6×10^{-7}	9.8×10^{-7}

[a] Five infants without available age information were excluded from this table. IQR denotes interquartile range; SD, standard deviation; and PICU, paediatric intensive care unit. Unless otherwise specified, data are shown as no. (%) or no./total no. (%) if there are missing data. Percentages may not total 100 due to rounding.

[b] Multiple logistic regression was used to adjust for sampling season. A likelihood-ratio test was used to assess the effect of age on the goodness of fit of the models.

[c] Multiple linear regression was used to adjust for days between symptom onset and sample collection. A likelihood-ratio test was used to assess the effect of age on the goodness of fit of the models.

[d] Multiple linear regression, ordered logistic regression, and multiple logistic regression were used to adjust for gestational age, sex, comorbidity, and viral subgroup when comparing different clinical features between the age groups. Likelihood-ratio tests were used to assess the effect of age on the goodness of fit of the models. Infants 3 to <6 months old had a similar rate of fever to that of infants <3 months old and infants ≥6 months old. Infants <3 months old and infants 3 to <6 months old had a similar distribution of the ReSViNET score. All other pairwise comparisons of the clinical features between the three age groups were significantly different.

Table 2. Incidences of the two RSV subgroups in each country and each season.

	RSV-A (N = 151)	RSV-B (N = 140)	Mixed (N = 1)	Unknown[a] (N = 33)
2017–18	19	38	0	0
Netherlands	15	36	0	0
Spain	0	0	0	0
United Kingdom	4	2	0	0
2018–19	53	58	1	11
Netherlands	13	23	0	4
Spain	6	4	0	6
United Kingdom	34	31	1	1
2019–20	79	44	0	22
Netherlands	28	17	0	1
Spain	14	5	0	0
United Kingdom	37	22	0	21

[a] Samples from 25 participants were not tested by quantitative reverse transcription PCR. Samples from eight participants were tested, but viral load was under the limit of detection.

381 Table 3. Characteristics of the RSV-infected infants by RSV subgroup.[a]

	RSV-A (N = 151)	RSV-B (N = 140)	P value	Q value
Demographic features				
Age				
Median (IQR)—months	3.1 (1.5–6.4)	2.8 (1.5–6.1)	0.689	
Distribution—no./total no. (%)			0.595	
<3 months	73/149 (49)	74/137 (54)		
3 to <6 months	35/149 (23)	26/137 (19)		
≥6 months	41/149 (28)	37/137 (27)		
Gestational age				
Median (IQR)—weeks	39.4 (37.9–40.3)	39.3 (38.3–40.1)	0.715	
Distribution—no./total no. (%)			0.436	
<32 weeks	3/150 (2)	5/140 (4)		
32 to <37 weeks	11/150 (7)	6/140 (4)		
≥37 weeks	136/150 (91)	129/140 (92)		
Female sex—no. (%)	61 (40)	64 (46)	0.426	
Weight—total no.	151	132		
Mean ± SD—kg	6.1 ± 1.9	6.0 ± 2.0	0.836	
Comorbidity—no. (%)	17 (11)	21 (15)	0.440	
Virological feature				
Peak viral load—total no.	139	136		
Mean ± SD—$\log_{10}$ copies/mL	6.9 ± 1.3	6.7 ± 1.4	0.183[b]	

Clinical features[c]				
ReSViNET score				
Mean ± SD	8.8 ± 4.3	9.1 ± 5.0	0.730	0.851
Distribution—no./total no. (%)			0.918	0.918
0–7	63/149 (42)	57/137 (42)		
8–13	60/149 (40)	49/137 (36)		
14–20	26/149 (17)	31/137 (23)		
Fever—no./total no. (%)	54/150 (36)	34/137 (25)	0.029	0.203
Hospitalisation—no. (%)	114 (75)	99 (71)	0.151	0.352
PICU admission—no. (%)	34 (23)	44 (31)	0.114	0.352
Respiratory support—no./total no. (%)	93/133 (70)	88/127 (69)	0.366	0.512
Mechanical ventilation—no./total no. (%)	31/133 (23)	38/127 (30)	0.325	0.512

[a] IQR denotes interquartile range; SD, standard deviation; PICU, paediatric intensive care unit. Percentages may not total 100 due to rounding.

[b] Multiple linear regression was used to adjust for days between symptom onset and sample collection.

[c] Multiple linear regression, ordered logistic regression, and multiple logistic regression were used to adjust for age, gestational age, sex, and comorbidity when comparing different clinical features between the subgroups.

Table 4. Associations between clinical variables and peak viral load in RSV-infected infants (N = 275).[a]

	Number of infants	Peak viral load (Mean ± SD)	Days since symptom onset	P value	Q value
ReSViNET score				0.246	0.493
0–7	115	6.7 ± 1.4	3.7 ± 1.5		
8–13	101	6.8 ± 1.3	4.3 ± 1.9		
14–20	54	6.8 ± 1.3	4.5 ± 1.9		
Fever				0.042	0.251
No	190	6.6 ± 1.4	4.1 ± 1.8		
Yes	81	7.1 ± 1.2	4.1 ± 1.8		
Hospitalisation				0.456	0.547
No	75	6.8 ± 1.5	3.3 ± 1.3		
Yes	200	6.8 ± 1.3	4.3 ± 1.8		
PICU admission				0.331	0.496
No	200	6.8 ± 1.4	4.0 ± 1.8		
Yes	75	6.8 ± 1.3	4.3 ± 1.9		
Respiratory support				0.717	0.717
No	74	7.0 ± 1.4	3.5 ± 1.4		
Yes	172	6.7 ± 1.3	4.4 ± 1.9		
Mechanical ventilation				0.133	0.400
No	180	6.8 ± 1.4	4.1 ± 1.8		
Yes	66	6.9 ± 1.3	4.3 ± 1.9		

[a] SD denotes standard deviation and PICU denotes paediatric intensive care unit. Ordered logistic regression or multiple logistic regression was used to adjust for age, gestational age, sex, comorbidity,

RSV subgroup, and days between symptom onset and sample collection when comparing viral load between infants with different clinical features.

Table 5. Characteristics of the RSV-infected infants by respiratory sequelae at 1 year of age (N = 165).[a]

	Non-wheezer (N = 84)	Wheezer (N = 81)	P value	Q value
Demographic features				
Age				
Median (IQR)—months	4.3 (1.5–7.3)	3.7 (1.3–6.2)	0.948	
Distribution—no./total no. (%)			0.876	
<3 months	33/83 (40)	44/77 (57)		
3 to <6 months	20/83 (24)	13/77 (17)		
≥6 months	30/83 (36)	20/77 (26)		
Gestational age				
Median (IQR)—weeks	39.0 (38.0–40.0)	39.0 (38.0–40.0)	0.571	
Distribution—no./total no. (%)			0.704	
<32 weeks	0	0		
32 to <37 weeks	4/83 (5)	5/81 (6)		
≥37 weeks	79/83 (95)	76/81 (94)		
Female sex—no. (%)	42 (50)	37 (46)	0.689	
Weight				
Mean ± SD—kg	6.1 ± 1.8	6.0 ± 1.8	0.911	
Comorbidity—no. (%)	5 (6)	7 (9)	0.714	
Virological features				
Subgroup A—no. (%)	45 (54)	40 (49)	0.451	
Peak viral load—total no.[b]	77	67		
Mean ± SD—$\log_{10}$ copies/mL	7.9 ± 0.5	8.1 ± 0.6	0.228	

Clinical features[c]				
ReSViNET score				
Mean ± SD	7.1 ± 5.0	9.3 ± 4.5	0.002	0.007
Distribution—no./total no. (%)			0.016	0.024
0–7	43/81 (53)	25/81 (31)		
8–13	22/81 (27)	34/81 (42)		
14–20	16/81 (20)	22/81 (27)		
Fever—no./total no. (%)	18/81 (22)	33/81 (41)	0.017	0.024
Hospitalisation—no. (%)	47 (56)	59 (73)	3.9×10^{-5}	2.8×10^{-4}
PICU admission—no. (%)	19 (23)	29 (36)	0.011	0.024
Respiratory support—no. (%)	41 (49)	51 (63)	0.212	0.212
Mechanical ventilation—no. (%)	14 (17)	25 (31)	0.084	0.098

[a] IQR denotes interquartile range; SD, standard deviation; PICU, paediatric intensive care unit.

[b] Multiple linear regression was used to adjust for days between symptom onset and sample collection.

[c] Multiple linear regression, ordered logistic regression, and multiple logistic regression were used to adjust for age, gestational age, sex, comorbidity, and viral subgroup when comparing different clinical features between the RSV-infected infants without and with subsequent wheezing.

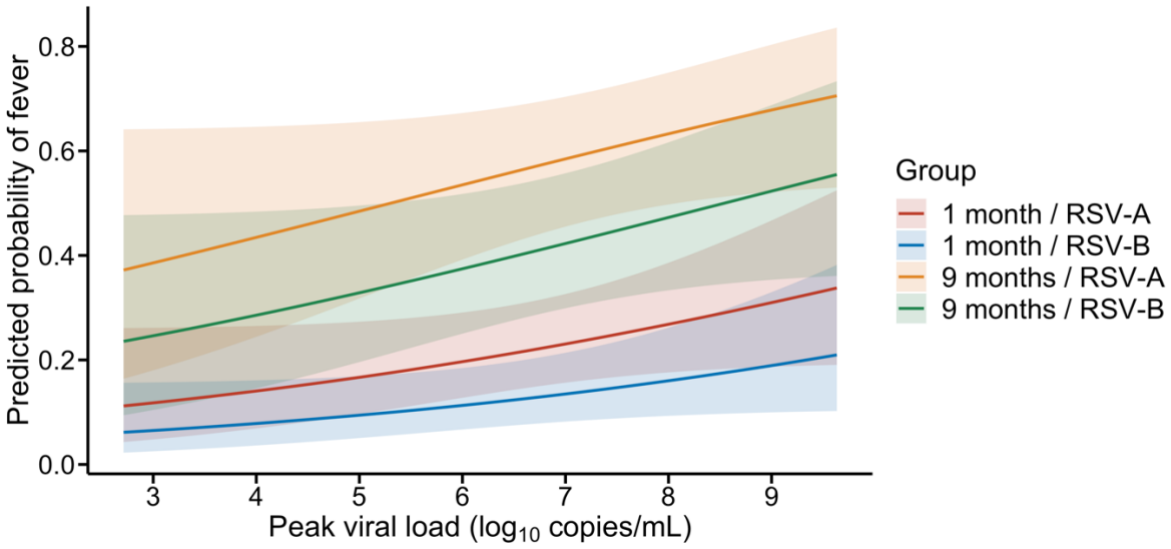

Figure S1. Predicted probability of fever for different ages, peak RSV viral loads, and subgroups. The probability of fever was predicted based on a multiple logistic regression model with age (two groups), RSV subgroup, and viral load as explanatory (independent) variables. Each age group had 100 RSV-A and 100 RSV-B simulated data points, distributed evenly between 2.7 $\log_{10}$ and 9.6 $\log_{10}$ copies/mL, the lowest and the highest viral load in our dataset, respectively. Shaded area around each line represents the 95% confidence interval.

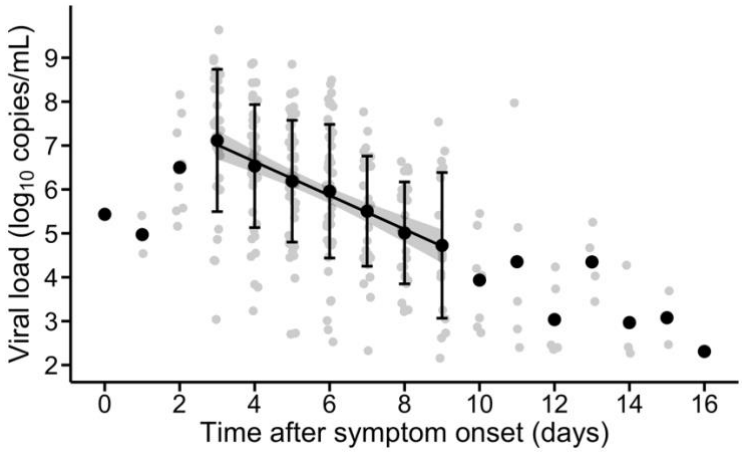

Figure S2. Viral dynamics in serial samples of the hospitalised infants (N = 77). Samples with undetectable viral load were excluded from this analysis. Each grey dot is a single sample (N = 281). Black dots and error bars denote the mean value and standard deviation of data at each time point,

respectively. The line across different days is the regression line ($R^2 = 0.184$, $P = 2.2\times10^{-12}$), and the shaded area around this line represents the 95% confidence interval. The error bars and linear regression were only performed on days with at least 10 samples, which were between day 3 and day 9.

Table S1. Number of RSV-infected infants in each country and each season.

	Netherlands	Spain	United Kingdom	Total
2017–18	51	0	6	57
2018–19	40	16	67	123
2019–20	46	19	80	145
Total	137	35	153	325

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Table S2. Characteristics of the RSV-infected infants, stratified by country (N = 325).[a]

	Netherlands (N = 137)	Spain (N = 35)	UK (N = 153)	P value	Q value
Demographic features					
Age					
Median (IQR)—months	2.5 (1.4–5.7)	2.9 (1.9–7.3)	3.8 (1.7–7.5)	0.047	
Distribution				0.085	
<3 months	74/132 (56)	20/35 (57)	66/153 (43)		
3 to <6 months	26/132 (20)	3/35 (9)	34/153 (22)		
≥6 months	32/132 (24)	12/35 (34)	53/153 (35)		
Gestational age					
Median (IQR)—weeks	39.6 (38.3–40.3)	39.7 (38.6–40.3)	39.1 (38.0–40.3)	0.494	
Distribution				0.012	
<32 weeks	0/136 (0)	0/35 (0)	8/152 (5)		
32 to <37 weeks	5/136 (4)	4/35 (11)	9/152 (6)		
≥37 weeks	131/136 (96)	31/35 (89)	135/152 (89)		
Female sex	55 (40)	16 (46)	65 (42)	0.817	
Weight—total no.	133	34	149		
Mean ± SD—kg	5.9 ± 1.9	5.8 ± 1.6	6.3 ± 2.2	0.175	
Comorbidity	13 (9)	7 (20)	24 (16)	0.138	
Virological features					
Subgroup A	56/132 (58)	20/29 (69)	75/130 (58)	0.118[b]	
Peak viral load—total no.	127	21	127		

Mean ± SD—log_{10} copies/mL	6.6 ± 1.4	6.7 ± 1.2	7.0 ± 1.3	0.012[c]	
Clinical features[d]					
ReSViNET score					
Mean ± SD	8.9 ± 5.2	8.8 ± 3.4	9.1 ± 4.6	0.613	0.613
Distribution				0.570	0.613
0–7	60/135 (44)	10/28 (36)	60/148 (41)		
8–13	42/135 (31)	16/28 (57)	59/148 (40)		
14–20	33/135 (24)	2/28 (7)	29/148 (20)		
Fever	35/135 (26)	18/29 (62)	47/148 (32)	7.2×10^{-4}	1.7×10^{-3}
Hospitalisation	89/136 (65)	24/29 (83)	121/153 (79)	0.034	0.060
PICU admission	57/136 (42)	3/29 (10)	26/153 (17)	3.9×10^{-9}	2.7×10^{-8}
Respiratory support	85/112 (76)	19/29 (66)	94/144 (65)	0.123	0.172
Mechanical ventilation	49/112 (44)	4/29 (14)	17/144 (12)	1.4×10^{-8}	4.8×10^{-8}

[a] IQR denotes interquartile range; SD, standard deviation; and PICU, paediatric intensive care unit. Unless otherwise specified, data are shown as no. (%) or no./total no. (%) if there are missing data. Percentages may not total 100 due to rounding.

[b] Multiple logistic regression was used to adjust for sampling season. A likelihood-ratio test was used to assess the effect of country on the goodness of fit of the models.

[c] Multiple linear regression was used to adjust for days between symptom onset and sample collection. A likelihood-ratio test was used to assess the effect of country on the goodness of fit of the models.

[d] Multiple linear regression, ordered logistic regression, and multiple logistic regression were used to adjust for age, gestational age, sex, comorbidity, and viral subgroup when comparing different clinical

features between the countries. Likelihood-ratio tests were used to assess the effect of country on the goodness of fit of the models.

Table S3. Associations between clinical variables and peak viral load in RSV-infected infants who had multiple swabs collected (N = 77).[a]

	Number of infants	Peak viral load (Mean ± SD)	Days since symptom onset	P value	Q value
ReSViNET score				0.201	0.251
0–7	16	7.0 ± 1.4	4.3 ± 1.3		
8–13	41	7.1 ± 1.2	4.6 ± 1.9		
14–20	18	7.4 ± 1.2	5.2 ± 1.8		
Fever				0.115	0.251
No	51	6.9 ± 1.2	4.7 ± 1.9		
Yes	25	7.5 ± 1.1	4.6 ± 1.4		
PICU admission				0.191	0.251
No	57	7.0 ± 1.2	4.7 ± 1.8		
Yes	19	7.4 ± 1.0	4.6 ± 1.6		
Respiratory support				0.317	0.317
No	9	7.7 ± 1.4	4.1 ± 1.1		
Yes	66	7.0 ± 1.2	4.8 ± 1.8		
Mechanical ventilation				0.061	0.251
No	56	7.0 ± 1.2	4.7 ± 1.7		
Yes	19	7.4 ± 1.1	4.7 ± 1.9		

[a] SD denotes standard deviation and PICU denotes paediatric intensive care unit. Ordered logistic regression or multiple logistic regression was used to adjust for age, gestational age, sex, comorbidity, RSV subgroup, and days between symptom onset and sample collection when comparing viral load between infants with different clinical features.

Table S4. Associations between clinical variables and daily viral load change in hospitalised infants (N = 77).[a]

	Daily change	95% CI	P value	Q value
Age			0.416	0.832
<3 months	46%	31–69%		
≥6 months	36%	23–57%		
Subgroup			0.828	0.859
RSV-A	40%	29–55%		
RSV-B	42%	29–60%		
ReSViNET score			0.769	0.859
0–7	53%	18–155%		
8–13	39%	21–72%		
14–20	56%	23–138%		
Fever			0.087	0.518
No	49%	35–70%		
Yes	30%	19–47%		
PICU admission			0.859	0.859
No	38%	28–50%		
Yes	39%	26–60%		
Mechanical ventilation			0.173	0.518
No	35%	26–46%		
Yes	49%	32–74%		

[a] Only 14 infants were 3 to <6 months old and only nine infants did not require respiratory support, so there were not enough data to compare the viral load changes in infants 3 to <6 months old and between

infants with and without respiratory support. CI denotes confidence interval and PICU denotes paediatric intensive care unit.

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References

1. Shi T, McAllister DA, O'Brien KL, 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**; 390:946-58.

2. Hall CB, Weinberg GA, Blumkin AK, et al. Respiratory syncytial virus-associated hospitalizations among children less than 24 months of age. Pediatrics **2013**; 132:e341-8.

3. Cane PA. Molecular epidemiology of respiratory syncytial virus. Rev Med Virol **2001**; 11:103-16.

4. Walsh EE, McConnochie KM, Long CE, Hall CB. Severity of respiratory syncytial virus infection is related to virus strain. J Infect Dis **1997**; 175:814-20.

5. Jafri HS, Wu X, Makari D, Henrickson KJ. Distribution of respiratory syncytial virus subtypes A and B among infants presenting to the emergency department with lower respiratory tract infection or apnea. Pediatr Infect Dis J **2013**; 32:335-40.

6. Hornsleth A, Klug B, Nir M, et al. Severity of respiratory syncytial virus disease related to type and genotype of virus and to cytokine values in nasopharyngeal secretions. Pediatr Infect Dis J **1998**; 17:1114-21.

7. Esposito S, Piralla A, Zampiero A, et al. Characteristics and their clinical relevance of respiratory syncytial virus types and genotypes circulating in northern Italy in five consecutive winter seasons. PLoS One **2015**; 10:e0129369.

8. Martinello RA, Chen MD, Weibel C, Kahn JS. Correlation between respiratory syncytial virus genotype and severity of illness. J Infect Dis **2002**; 186:839-42.

9. El Saleeby CM, Bush AJ, Harrison LM, Aitken JA, Devincenzo JP. Respiratory syncytial virus load, viral dynamics, and disease severity in previously healthy naturally infected children. J Infect Dis **2011**; 204:996-1002.

10. Houben ML, Coenjaerts FE, Rossen JW, et al. Disease severity and viral load are correlated in infants with primary respiratory syncytial virus infection in the community. J Med Virol **2010**; 82:1266-71.

11. Hasegawa K, Jartti T, Mansbach JM, et al. Respiratory syncytial virus genomic load and disease severity among children hospitalized with bronchiolitis: multicenter cohort studies in the United States and Finland. J Infect Dis **2015**; 211:1550-9.

12. Thwaites RS, Coates M, Ito K, et al. Reduced nasal viral load and IFN responses in infants with respiratory syncytial virus bronchiolitis and respiratory failure. Am J Respir Crit Care Med **2018**; 198:1074-84.

13. Stein RT, Sherrill D, Morgan WJ, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. Lancet **1999**; 354:541-5.

14. Sigurs N, Aljassim F, Kjellman B, et al. Asthma and allergy patterns over 18 years after severe RSV bronchiolitis in the first year of life. Thorax **2010**; 65:1045-52.

15. Carbonell-Estrany X, Perez-Yarza EG, Garcia LS, Guzman Cabanas JM, Boria EV, Atienza BB. Long-term burden and respiratory effects of respiratory syncytial virus hospitalization in preterm infants-the SPRING study. PLoS One **2015**; 10:e0125422.

16. Wang X, Li Y, Nair H, Campbell H. Time-varying association between severe respiratory syncytial virus infections and subsequent severe asthma and wheeze and influences of age at the infection. J Infect Dis **2021**.

17. Blanken MO, Rovers MM, Molenaar JM, et al. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. N Engl J Med **2013**; 368:1791-9.

18. Scheltema NM, Nibbelke EE, Pouw J, et al. Respiratory syncytial virus prevention and asthma in healthy preterm infants: a randomised controlled trial. Lancet Respir Med **2018**; 6:257-64.

19. O'Brien KL, Chandran A, Weatherholtz R, et al. Efficacy of motavizumab for the prevention of respiratory syncytial virus disease in healthy Native American infants: a phase 3 randomised double-blind placebo-controlled trial. Lancet Infect Dis **2015**; 15:1398-408.

20. Brunwasser SM, Snyder BM, Driscoll AJ, et al. Assessing the strength of evidence for a causal effect of respiratory syncytial virus lower respiratory tract infections on subsequent wheezing illness: a systematic review and meta-analysis. Lancet Respir Med **2020**; 8:795-806.

21. Jefferies K, Drysdale SB, Robinson H, et al. Presumed risk factors and biomarkers for severe respiratory syncytial virus disease and related sequelae: protocol for an observational multicenter, case-control study from the respiratory syncytial virus consortium in Europe (RESCEU). J Infect Dis **2020**; 222:S658-S65.

22. Justicia-Grande AJ, Pardo-Seco J, Cebey-Lopez M, et al. Development and validation of a new clinical scale for infants with acute respiratory infection: the ReSVinet scale. PLoS One **2016**; 11:e0157665.

23. Lin GL, Drysdale SB, Snape MD, et al. Distinct patterns of within-host virus populations between two subgroups of human respiratory syncytial virus. Nat Commun **2021**; 12:5125.

24. R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, **2018**.

25. Dinarello CA, Cannon JG, Wolff SM. New concepts on the pathogenesis of fever. Rev Infect Dis **1988**; 10:168-89.

26. Aberle JH, Aberle SW, Dworzak MN, et al. Reduced interferon-gamma expression in peripheral blood mononuclear cells of infants with severe respiratory syncytial virus disease. Am J Respir Crit Care Med **1999**; 160:1263-8.

27. Marr N, Wang TI, Kam SH, et al. Attenuation of respiratory syncytial virus-induced and RIG-I-dependent type I IFN responses in human neonates and very young children. J Immunol **2014**; 192:948-57.

564 28. Zou L, Yi L, Wu J, et al. Evolution and transmission of respiratory syncytial group A (RSV-A)
565 viruses in Guangdong, China 2008-2015. Front Microbiol **2016**; 7:1263.
566 29. Cui G, Zhu R, Deng J, et al. Rapid replacement of prevailing genotype of human respiratory
567 syncytial virus by genotype ON1 in Beijing, 2012-2014. Infect Genet Evol **2015**; 33:163-8.
568 30. Song J, Wang H, Shi J, et al. Emergence of BA9 genotype of human respiratory syncytial virus
569 subgroup B in China from 2006 to 2014. Sci Rep **2017**; 7:16765.
570 31. Garcia-Maurino C, Moore-Clingenpeel M, Thomas J, et al. Viral load dynamics and clinical
571 disease severity in infants with respiratory syncytial virus infection. J Infect Dis **2019**; 219:1207-15.
572