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Viral respiratory infections in very low birthweight infants at neonatal intensive care unit: prospective observational study

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ABSTRACT

Background and objective Very low birthweight (VLBW) infants are highly susceptible to respiratory infections. Information about prevalence of viral respiratory infections (VRIs) in neonatal intensive care unit (NICU) is scarce. Recent evidence suggests short-term and long-term impact of VRI in morbidity of VLBW infants. The goal of this study is to conduct a VRI surveillance in VLBW infants during NICU admission to address the prevalence, type of viruses and associated clinical features.

Methods Prospective observational cohort study on infants below 32 gestational weeks admitted to a tertiary NICU during a 2-year period. Respiratory virus detection (influenza, parainfluenza, rhinovirus (hRV), enterovirus, respiratory syncytial virus, metapneumovirus, coronavirus, bocavirus and adenovirus) was performed by real time multiplex PCR assays in nasopharyngeal aspirates (NPAs), within the first 72 hours after birth and weekly, until discharge. Additional samples were taken if clinically indicated.

Results 147 out of 224 eligible infants were enrolled. At least one positive NPA was found in 38% of the study cohort. Main viruses identified were hRV (58%) and adenovirus (31%). Among the 56 infants with positive NPA, 26 showed non-specific respiratory features in 58% (increased respiratory workload, tachypnoea, apnoea) or typical cold features in 38% (rhinorrhea, cough, fever), at least in one episode. Antibiotics were prescribed in 29% of cases. Positive infants showed higher rates of bronchopulmonary dysplasia (BPD), need for supplemental oxygen and mechanical ventilation, and had longer hospital stay. Cox regression analysis found BPD as an independent risk factor for viral infection (p<0.001) and symptomatic VRI (p<0.04).

Conclusions Systematic surveillance in VLBW infants reports VRI is frequent, particularly by hRV. Asymptomatic infection is highly prevalent which is critical in the face of establishing appropriate preventive strategies. Infants with BPD are especially vulnerable to such infections.

INTRODUCTION

Viral respiratory infections (VRIs) are very common in childhood representing between 65% to 80% of hospital admissions, during the first 2 years of life.[1 2] Many of these viruses

What is known about the subject?

► Viral respiratory infections (VRIs) are very common in childhood and are associated with severe morbidity, mainly in susceptible infants.
► VRI may potentially worsen the clinical course in infants, especially in the first year of life.
► Respiratory syncytial virus is the respiratory virus most frequently associated with the classical outbreaks in neonatal units and associated symptoms of cold in infants.

What this study adds?

► VRIs in VLBW infants during neonatal intensive care unit (NICU) admission is more frequent than previously recognised.
► Half of the episodes are asymptomatic, reinforcing the role of systematic surveillance.
► Human rhinovirus is the most prevalent respiratory virus in the preterm infant during NICU admission, causing rather mild clinical disease.
► Bronchopulmonary dysplasia increases the risk of VRI, indicating a greater susceptibility of these patients.

colonise the nasopharynx without symptoms[3 4] or may be associated with mild upper respiratory infections. In addition to the classical viruses such as respiratory syncytial virus (RSV), influenza and rhinovirus (hRV), other species like metapneumovirus (hMPV), coronavirus (CoV) or bocavirus (hBoV) are relevant agents causing VRI and associated morbidity, mainly in susceptible infants.[5–10]

Very low birthweight (VLBW) infants are highly vulnerable to respiratory infections. However, there is a real gap of knowledge about the role of VRI in the preterm infant during neonatal intensive care unit (NICU) admission.[11–17] First, the prevalence is unknown because in the clinical suspicion of

infection routine, virus search is not included, and this search is limited to RSV[18 19] ignoring the role of other viruses. VLBW infants usually do not develop classical signs of cold. Instead, they present with non-specific clinical features like apnoeas, need for increased respiratory support or feeding difficulties. In other words, clinical signs that mirror bacterial infection in these patients. This is the reason for the widespread use of antibiotics when facing these clinical courses which potentially lead to microbial resistance. On the other hand, failure to identify these VRIs carries the risk of transmission to other infants with the appearance of outbreaks.

Second, VRI may potentially worsen the clinical course in a given infant. VRIs associate inflammatory mechanism that, together with the effect of mechanical ventilation and oxygen therapy-derived lung damage, could be determinants in the progression towards chronic lung disease.[20 21] In fact, Gagneur[11] reported increased respiratory support and oxygen supply for longer periods in neonates and older infants with CoV respiratory infections. Bennett[13] found a 52% prevalence of VRI among infants below 33 weeks of gestation. Hospital stay, mechanical ventilation and duration of oxygen therapy were longer, and the prevalence of bronchopulmonary dysplasia (BPD) was higher in positive infants. González-Carrasco,[14] in a cohort of preterm and term newborns, found a 22% prevalence of VRI, the infants below 32 weeks being particularly vulnerable.

Finally, the relevance of the asymptomatic carriers might be crucial.[3 4] Spreading time of respiratory viruses could last for several weeks, specially in infants.[22 23]

Our purpose is to report about a systematic VRI surveillance study in VLBW infants during NICU admission, with a focus on the prevalence, the type of viruses associated with VRI, the clinical features heralding viral infection and the impact of VRI on morbidity.

METHODS
Study population
A prospective observational cohort study was conducted at the Department of Neonatology at La Paz University Hospital (Madrid, Spain), between April 2016 and March 2018. Our NICU covers 5500 births annually with approximately 130 admissions below 1500 g.

Infants below 32 weeks of gestation admitted to the NICU within the first 72 hours from birth and had signed informed parental consent were enrolled in the study. Exclusion criteria were admission beyond 72 hours of life, death within the first week, severe congenital malformations or declined parental consent.

Informed consent was obtained from parents. Each infant's information was treated anonymously.

Patient and public involvement
Patients were not invited to comment on the study design, and were not consulted to develop patient-relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Study procedures
Nasopharyngeal aspirates (NPAs) were collected within the first 72 hours after birth and then weekly, until discharge. Additional NPAs were collected in the case of respiratory features (cough, increased respiratory workload, rhinopharyngeal secretions, fever, increased episodes of desaturation, bradycardia or apnoea with or without need for additional respiratory support) or unspecific clinical worsening that motivated antibiotic prescription. A new episode was considered in case of positive NPA after at least two previous negative samples and a minimum of 21 days after the last positive one, or when positive NPA to a different virus specie was detected. Clinical data were extracted from clinical records and prospectively registered. Epidemiological survey was undertaken in positive NPAs to rule out nosocomial outbreak (rooming-in with other positive cases). BPD was defined as treatment with oxygen >21% for at least 28 days and severity was categorised at 36 weeks of postmenstrual age or discharge.[24]

Microbiological assay
NPAs were analysed at the Influenza and Respiratory Viruses Laboratory at the National Centre for Microbiology (Madrid, Spain). Samples were processed within 24 hours after collection. On reception, three aliquots were prepared and stored at −80°C. Both, the reception and the NPA sample processing areas, are separated from those defined as working areas.

RNA and DNA from 200 μl aliquots of NPA were extracted using the QIAamp MinElute Virus Spin Kit in an automated extractor (QIAcube, Qiagen, Valencia, Spain).

Respiratory virus detection was performed by four independent real time multiplex PCR (RT-PCR) assays. First assay detected influenza A, B and C viruses; a second assay was used to detect parainfluenza viruses 1 to 4, hRV and enteroviruses; a third assay detected RSV types A and B, hMPV, hBoV and adenoviruses. These assays used the SuperScript III Platinum One-Step Quantitative RT-PCR System (Invitrogen). Human CoV was investigated using a generic RT-PCR that was able to detect both alpha and beta CoV. Primers and Taqman probes that were used had already been reported by the study investigators.[25]

Data analysis
Continuous variables were described using mean (SD), minimum and maximum, or median (IQR). Categorical variables were described using absolute and relative frequencies.

Association between qualitative variables were analysed using the χ^2 test or Fisher's exact test. For the comparison between qualitative and quantitative data the Students's t test as parametrical test and the Mann-Whitney U test
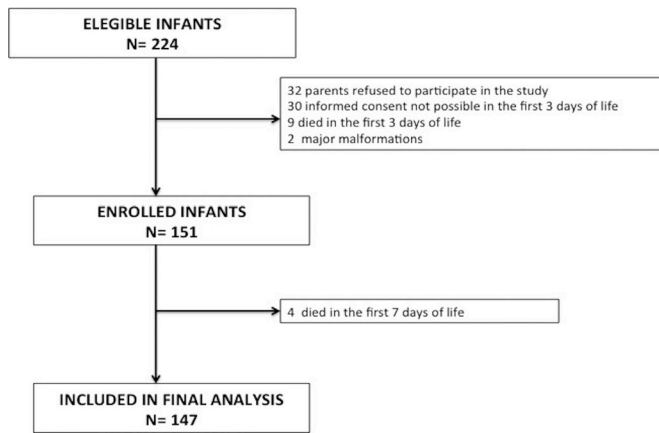
Figure 1 : Flow diagram of study participants

as non-parametrical test were used. A two-sided value of p<0.05 was considered statistically significant.

Cox regression analysis was used to estimate the association between the independent variables (birth weight, gestational age, supplemental oxygen duration, days to reach full enteral nutrition, length of hospitalisation, BPD) and the dependent variables (negative and positive infants, symptomatic and asymptomatic infection, or type of virus). All analyses were performed using the statistical

programme SAS V.9.3 (SAS Institute, Cary, North Carolina, USA).

RESULTS

During the study period, 224 infants below 32 weeks of gestation were eligible for the study. A total of 151 infants met inclusion criteria. Four infants who died within the first 7 days after birth were excluded (figure 1). The mean gestational age and birth weight of the remaining 147 that form the study population were 28 (2.1) weeks and 1099 (319) grams, respectively. Forty five per cent of the study infants were male.

At least one positive NPA was found in 56 infants (38% of study cohort). Seven babies suffered more than one VRI episode. Demographics and other relevant clinical data of infants who became positive and negative are displayed in table 1.

The variety of viruses that were identified is displayed (figure 2), the most frequently isolated types being hRV (58%) and adenovirus (31%). Mean shedding time was 13 days (range 2–48 days), without significant differences between the most frequently isolated viruses (hRV 14 (2–43) days; adenovirus 10 (3–30) days). Positive NPA occurred in clusters during the autumn and winter

Table 1 Demographic and relevant clinical data of the study population according to the results of nasopharyngeal aspirates

	Whole cohort			Positive patients		
	Negative n=91	Positive n=56	P value	Symptomatic n=26	Asymptomatic n=30	P value
GA (week), mean (SD), (min, max)	28.8 (2) (24 to 32)	28.1 (2.2) (24.1 to 32)	**0.08**	27.8 (2.2) (24 to 31)	28.4 (2.2) (24 to 32)	0.28
BW (g), mean (SD), (min, max)	1145(347) (498–2130)	1027(256), (603–1650)	0.02	1005 (219) (712 to 1450)	1045 (288) (603 to 1650)	0.357
Male, n (%)	38 (42)	28(50)	0.39	*19 (73)*	*9 (30)*	***0.003***
Non-specific respiratory signs, n(%)	29 (32)	15 (27)	0.58	–	–	–
Typical cold features, n (%)	4 (4)	10 (18)	***0.009***	–	–	–
Other, n(%)	13 (14)	1 (2)	***0.018***	–	–	–
BPD, n (%)	*34 (38)*	*38 (68)*	***0.001***	*22(82)*	*16(55)*	***0.035***
Suppl. oxygen (days), median (IQR)	*21 (3–42)*	*54 (10–71)*	***0.001***	*63 (36–81)*	*43 (6–64)*	***0.08***
MV (invasive or non-invasive) (days), Median (IQR)	4 (2–17)	13.5 (3–31)	0.005	27 (3–34)	7 (3–26)	0.32
0xygen at discharge,n (%)	7 (8)	5 (9)	1	4 (16)	1 (3)	*
Days to reach full enteral nutrition, median (IQR)	*10 (7–15)*	*11 (9–21)*	***0.02***	*13 (9–22)*	*11 (7–20)*	***0.45***
Length of stay (days), median (IQR),	*57 (39–76)*	*73 (52–86)*	***0.02***	*76 (53–87)*	*67 (49–87)*	0.28

Students's t test, Mann-Whitney U test, Fisher's exact test
*p value could not be obtained due to lack of cases
BPD, bronchopulmonary dysplasia; BW, birth weight; Typical cold features, rhinorrea, cough, fever; GA, gestational age; MV, mechanical ventilation; Non-specific respiratory signs, increased respiratory workload, tachypnoea, apnoea; symptomatic, al least one episode.;
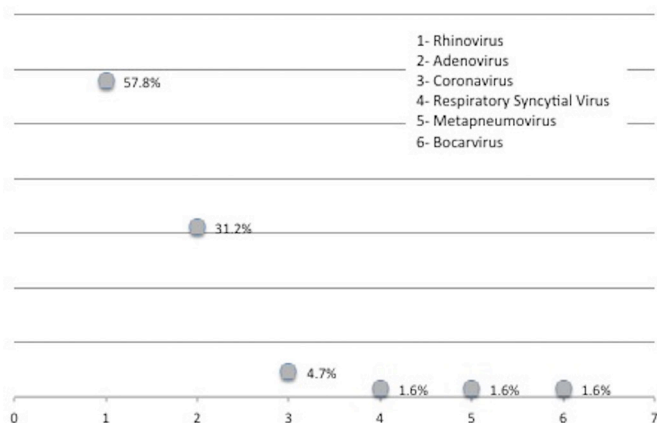
Figure 2 . Viral respiratory infections etiology

seasons. Only one case of positive NPA was found to be eventually related to nosocomial infection (cot-side infant also positive, and related in time).

Among the 56 infants with positive NPA, 26 had at least a symptomatic episode (table 1). Clinical features presented at the time of NPA collection were: non-specific respiratory clinical signs (increased respiratory workload, tachypnoea, apnoea) in 58% of cases, typical cold features (rhinorrhoea, cough, fever) in 38% and other signs in 4%. Twenty-nine per cent of infants received antibiotics due to clinical suspicion of bacterial sepsis (unspecific clinical condition worsening). As a consequence of clinical deterioration, 12 infants had increased oxygen supply and 4 required mechanical ventilation (two infants invasive ventilation). Postnatal age at first positive NPA ranged between 3 days and 111 days, median 43 days (IQR 28–53).

Among the total VRI episodes (n=64), 38 were caused by hRV and 26 by non-hRV species. Type of virus did not influence the clinical course of the patients who became positive. Asymptomatic infection (hRV 20 (53%); non-hRV 13 (50%); p=1), increased apnoea rates (hRV 6 (16%); non-hRV 9 (37%); p=0.07) or need for mechanical ventilation (hRV 1 (3%); non-hRV 3 (12%); p (insufficient cases)) were comparable among hRV and non-hRV episodes.

VRI was more frequent among infants with BPD (58%) than in infants without BPD (24%) (p=0.001). Cox regression analysis found BPD as an independent risk factor for viral infection (OR 4.12, 95% CI 2.12 to 8.41, p<0.001) and symptomatic infection (OR 3.4, 95% CI 1.03 to 11.05, p<0.04). Kaplan-Meier curves did not
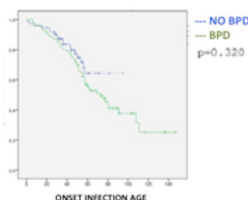

Figure 3 Kaplan-Meier curves between bronchopulmonary dysplasia (BPD) and onset infection age

show differences between patients with and without BPD in relation to age at onset of VRI (figure 3). Male sex increased significantly the risk of symptomatic infection (OR 3, 95% CI 1.4 to 6.7, p<0.003). Neither birth weight nor gestational age influenced the risk of viral infection or symptomatic infection.

DISCUSSION

Nosocomial VRIs in the NICU were believed to be anecdotal. This study found that 38% of infants born below 32 weeks of gestation have at least one positive NPA sample during their NICU admission. Nearly 50% of these colonised infants show a variety of clinical signs at the time the NPA is taken.

Systematic VRI surveillance is not an established routine in NICU. During the last decade several reports describe a variable prevalence of VRI in this setting, ranging from 8% to 52%.[11–16] In our series, the type of virus that was more frequently isolated was hRV, followed by adenovirus. In spite of the general thought that RSV is the virus most frequently associated with classical respiratory features in the premature infant, studies like ours, in which specific surveillance has been done, have shown a higher prevalence of non-RSV-related aetiology.[11–17] Steiner[22] found hRV infection in 15% of VLBW infants who showed typical clinical signs of viral respiratory tract infection. Our findings support that clinical features related to upper respiratory tract viral infection are diverse and more importantly, that a significant number of positive infants are free of clinical signs. In addition, VRI may associate non-specific clinical signs that could be interpreted as prematurity-related events or bacterial infection. Therefore, this study supports that the current nosocomial VRI in neonatal facilities is more common than what has been previously recognised and may associate significant disease burden, particularly in the more vulnerable preterm infant.

Shedding of respiratory viruses is long, ranging from 1 week to 6 weeks.[13 22] Transmission of respiratory viruses is described as high, either by direct contact or the aerosol route. There is transfer of virus from surfaces to hands during routine activities.[26] Therefore, a high index of suspicion and systematic surveillance is needed to avoid epidemic outbreaks in neonatal units. In our study population, 54% of positive infants were asymptomatic and among the babies who showed any abnormal clinical sign, less than 40% presented with the classical features of cold. Other studies also remark that atypical, non-upper respiratory tract viral infection signs, such as increased number of desaturation episodes, apnoea, tachypnoea or respiratory stalemate,[11–13] are more frequently shown in the positive preterm infants.

It is noteworthy that almost a third of infants had the first presumption diagnosis of bacterial sepsis so that antibiotics were prescribed. Failure to think about these VRIs has the immediate consequence of unnecessary antibiotic use and prolonged antibiotic treatment duration.

Gagneur[11] described up to 85% antibiotic prescription in infants with documented VRI compared with those who were not infected. In addition, duration of antibiotic treatment was also significantly longer. Recent studies which searched for a viral aetiology in infants with clinical suspicion of late-onset bacterial sepsis have shown a prevalence of positive viral tests close to 10%.[27 28]

VRIs associated with higher rates of morbidity. Infants with VRI had more need of supplementary oxygen, reached full enteral nutrition later and, consequently, had longer length of hospital stay, features already described.[11–14] It is relevant to note that BPD was shown as an independent risk factor for viral infection in the Cox regression analysis, after adjusting by gestational age and birth weight. Infants with BPD had a fourfold increased risk of VRI, indicating a greater susceptibility to infection in these patients. This finding has only been previously described by Bennett.[13] BPD is closely associated with antenatal inflammation, oxygen toxicity and ventilator-induced trauma. Babies with BPD also have a longer hospital stay and more antibiotic prescription, potentially affecting the establishment-promoting microbiota on respiratory mucosa.[20] High levels of proinflammatory cytokines which modulate human airway epithelial responses to VRI have been shown in infants with BPD.[21] All these factors may alter the immune system that, in addition to the genetic predisposition, could explain the increased susceptibility to VRIs in infants with BPD.[20 21]

Regarding the clinical expression of VRIs associated to the aetiological agent, our results did not show any difference. We have not found in the literature clearly established data on the clinical features related to hRV infection in the premature infant during NICU admission. So far, the different disease expression of viral infection according to type of agent in this vulnerable population deserves further investigation.

The main limitation of our study is the relatively small sample size. Although this is one of the largest series of premature infants prospectively studied for VRI, the study is not able to reach statistical significance in several aspects. For instance, although hRV was the most frequently identified virus, eventual differences in the clinical outcomes of infected infants according to the type of virus could not be sorted out. Likewise, we could not fully characterise the clinical course associated to the various viruses that were found to cause infection. However, the strengths of this work include an uniform population of preterm infants, the systematic prospective study of all types of respiratory viruses, a large number of samples, and a close and prospective data recording during NICU admission.

In summary, systematic surveillance has allowed us to increase our knowledge about VRI in our clinical setting, in which hRV is the most prevalent. VRIs are frequent and commonly asymptomatic. Given the high contagiousness and easy transfer from contaminated surfaces, strict adherence to hand hygiene measures is essential for staff and families. Identification of an index case should move us to establish appropriate measures to prevent outbreaks. This surveillance should focus on infants with respiratory features, and infants with more subtle clinical signs, such as worsening of baseline respiratory condition or suspected late-onset bacterial sepsis. The potential negative impact on the infant's outcome is of concern. Special awareness should be kept in infants with BPD, as a particular susceptibility to these infections has been found in this study.

Further studies are needed to characterise viral-type specific clinical features as well as the eventual variable susceptibility in the preterm population. The evolution of infants who suffered VRI early in life should also be addressed in appropriate study designs.

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REFERENCES

1 Szabo SM, Gooch KL, Korol EE, et al. Respiratory distress syndrome at birth is a risk factor for hospitalization for lower respiratory tract infections in infancy. *Pediatr Infect Dis J* 2012;31:1245–51.

2 Calvo C, Pozo F, García-García ML, et al. Detection of new respiratory viruses in hospitalized infants with bronchiolitis: a three-year prospective study. *Acta Paediatr* 2010;99:883–7.

3 Nokso-Koivisto J, Kinnari TJ, Lindahl P, et al. Human picornavirus and coronavirus RNA in nasopharynx of children without concurrent respiratory symptoms. *J Med Virol* 2002;66:417–20.

4 García-García ML, Calvo C, Pozo F, et al. Human bocavirus detection in nasopharyngeal aspirates of children without clinical symptoms of respiratory infection. *Pediatr Infect Dis J* 2008;27:358–60.

5 Pozo F, García-García ML, Calvo C, et al. High incidence of human bocavirus infection in children in Spain. *J Clin Virol* 2007;40:224–8.

6 García-García ML, Calvo C, Rey C, et al. Human metapnuemovirus infections in hospitalized children and comparison with other respiratory viruses. 2005-2014 prospective study. *PLoS One* 2017;12:e0173504.

7 Coiras MT, Pérez-Breña P, García ML, et al. Simultaneous detection of influenza A, B, and C viruses, respiratory syncytial virus, and

adenoviruses in clinical samples by multiplex reverse transcription nested-PCR assay. *J Med Virol* 2003;69:132–44.

8 Coiras MT, Aguilar JC, García ML, *et al*. Simultaneous detection of fourteen respiratory viruses in clinical specimens by two multiplex reverse transcription nested-PCR assays. *J Med Virol* 2004;72:484–95.

9 López-Huertas MR, Casas I, Acosta-Herrera B, *et al*. Two RT-PCR based assays to detect human metapneumovirus in nasopharyngeal aspirates. *J Virol Methods* 2005;129:1–7.

10 Calvo C, García-García ML, Blanco C, *et al*. Human bocavirus infection in a neonatal intensive care unit. *J Infect* 2008;57:269–71.

11 Gagneur A, Sizun J, Vallet S, *et al*. Coronavirus-related nosocomial viral respiratory infections in a neonatal and paediatric intensive care unit: a prospective study. *J Hosp Infect* 2002;51:59–64.

12 van Piggelen RO, van Loon AM, Krediet TG, *et al*. Human rhinovirus causes severe infection in preterm infants. *Pediatr Infect Dis J* 2010;29:364–5.

13 Bennett NJ, Tabarani CM, Bartholoma NM, *et al*. Unrecognized viral respiratory tract infections in premature infants during their birth hospitalization: a prospective surveillance study in two neonatal intensive care units. *J Pediatr* 2012;161:814–8.

14 Gonzalez-Carrasco E, Calvo C, García-García ML, *et al*. Infecciones respiratorias virales en La unidad de cuidados intensivos neonatales. *Anales de Pediatría* 2015;82:242–6.

15 Zinna S, Lakshmanan A, Tan S, *et al*. Outcomes of nosocomial viral respiratory infections in high-risk neonates. *Pediatrics* 2016;138:e201151576.

16 Ronchi A, Michelow IC, Chapin KC, *et al*. Viral respiratory tract infections in the neonatal intensive care unit: the VIRIoN-I study. *J Pediatr* 2014;165:690–6.

17 Kujari A-M, Waris M, Lehtonen L, *et al*. Respiratory viral infections are not uncommon in neonatal intensive care units. *Acta Paediatr* 2014;103:e225–8.

18 Diniz EMdeA, Vieira RA, Ceccon MEJ, *et al*. Incidence of respiratory viruses in preterm infants submitted to mechanical ventilation. *Rev Inst Med Trop Sao Paulo* 2005;47:37–44.

19 Thwaites R, Piercy J. Nosocomial respiratory syncytial virus infection in neonatal units in the United Kingdom. *Acta Paediatr Suppl* 2004;93:23–5.

20 Pryhuber GS. Postnatal infections and immunology affecting chronic lung disease of prematurity. *Clin Perinatol* 2015;42:697–718.

21 Pérez GF, Pancham K, Huseni S, *et al*. Rhinovirus-Induced airway cytokines and respiratory morbidity in severely premature children. *Pediatr Allergy Immunol* 2015;26:145–52.

22 Steiner M, Strassl R, Straub J, *et al*. Nosocomial rhinovirus infection in preterm infants. *Pediatr Infect Dis J* 2012;31:1302–4.

23 Ruuskanen O, Waris M, Ramilo O. New aspects on human rhinovirus infections. *Pediatr Infect Dis J* 2013;32:553–5.

24 Jobe AH, Bankalari E. NICHD/NIH workshop summary: bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001;163:1723–9.

25 García-García ML, Calvo C, Ruiz S, *et al*. Role of viral coinfections in asthma development. *PLoS One* 2017;12:e1089083.

26 Winther B, McCue K, Ashe K, *et al*. Rhinovirus contamination of surfaces in homes of adults with natural colds: transfer of virus to fingertips during normal daily activities. *J Med Virol* 2011;83:906–9.

27 Kidszun A, Klein L, Winter J, *et al*. Viral infections in neonates with suspected late-onset bacterial Sepsis-A prospective cohort study. *Am J Perinatol* 2017;34:1–7.

28 Cerone JB, Santos RP, Tristram D, *et al*. Incidence of respiratory viral infection in infants with respiratory symptoms evaluated for late-onset sepsis. *J Perinatol* 2017;37:922–6.