Brief Report

Hospital-acquired viral respiratory tract infections in the neonatal unit: a comparison with other inpatient groups

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Short title: Burden of neonatal hospital-acquired viral respiratory infections

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Abstract

Background: Hospital-acquired viral respiratory tract infections (VRTIs) cause significant morbidity and mortality in neonatal patients. This includes escalation of respiratory support, increased length of hospital stay and need for home oxygen, as well as higher healthcare costs. To date, no studies have compared population rates of VRTIs across age groups.

Aim: Quantify the rates of hospital-acquired VRTIs in our neonatal population compared with other inpatient age groups in Nottinghamshire, UK.

Methods: We compared all hospital inpatient PCR positive viral respiratory samples between 2007 and 2013 and calculated age stratified rates based on population estimates.

Results: From a population of 4,707,217 we identified a previously unrecognised burden of VRTI in neonatal patients, only second to the 0-1 year old group. Although only accounting for 1.3% of the population, half of the infections were in infants <1 year old and NICU patients. Human rhinovirus was the most dominant virus across the inpatient group, particularly in neonatal patients. Despite a two- to three-fold increase in the rate of positive samples in all groups during the colder months (1.1/1000 October to March vs. 0.4/1000 April to September), rates in the NICU did not change throughout the year at 4.3/1000. Pandemic H1N1 influenza rates were 20 times higher in neonatal patients and infants <1 year old.

Conclusion: Good epidemiological and interventional data are needed to help inform visiting and infection control policies to reduce transmission of hospital-acquired viral infections to this vulnerable population, particularly during pandemic seasons.

Introduction

Hospital-acquired viral respiratory tract infections (VRTIs) on the neonatal intensive care unit (NICU) are associated with the need for escalation of respiratory support, increased length of hospital stay, increased bronchopulmonary dysplasia and almost double the requirement for home oxygen[1,2]. In addition, there are significant NICU resource implications for healthcare providers with additional associated costs of almost £28,000 per infant with a VRTI[1].

Treatment for the majority of VRTIs is supportive. As such, they are not routinely tested for unless there is a specific clinical concern. Previous studies have found viral nasal carriage in 52% of asymptomatic infants[3] and 8% of infants had a VRTI when screened in parallel as part of late-onset sepsis workup[2].

On the NICU, VRTIs are hospital-acquired and so are most likely to originate from staff or visitors. In the UK, infection control and visiting policies relating to VRTIs vary widely[4]. The inpatient burden of hospital-acquired VRTIs in the NICU, compared with that of the local population in hospital with a VRTI, has not previously been established. In the context of the associated morbidity and mortality in this vulnerable population, especially during pandemics, it is important to quantify this risk. We aimed to quantify the burden of VRTIs on the NICU compared with other inpatient age groups in the same geographical area.

Methods

We performed a cross-sectional cohort study on all positive viral respiratory samples, analysed by polymerase chain reaction (PCR), from inpatients admitted to two large tertiary hospitals in Nottingham between 2007 and 2013. Patients were stratified into groups according to age: NICU inpatients admitted for >4 hours, 0-1 years (infants, not on NICU), 1-4 years (pre-school children), 5-15 years (school-age children), 16-59 years and those ≥60 years old.

NICU rates were calculated as number of positive PCRs per 1000 neonatal admissions to the two tertiary units during the study period. Rates for all other age groups were calculated as the number of positive PCRs in hospital inpatients per 1000 residents using local age-specific population estimates for Nottinghamshire in the respective years from the Office of National Statistics[5].

The seasonal patterns were split into the UK's non-peak (April to September) and peak (October to March) viral infection periods. During the peak months of 2009/2010, 2010/2011 and 2011/2012, we instigated a restricted visiting policy with only parents/carers allowed to visit their baby in response to the H1N1 pandemic[6]. Rates were therefore calculated with and without restrictions.

Results

The total local population was 4,707,217 during the study period with 6,924 individual PCR positive respiratory samples on inpatients during this time. Overall rates were highest

amongst infants 0-1yrs (61.0/1000) followed by the NICU population (17.1/1000, Table 1). Half of the positive PCR samples were from those <1 year of age but these accounted for only 1.3% of the population. Human Rhinovirus (HRV) was the most common virus in all groups other than those in the 0-1 age group, in whom Respiratory Syncytial Virus (RSV) was more common. In the NICU, HRV was particularly prevalent with a rate 2.5 times higher than all the other viruses combined. Although small numbers, H1N1 (pandemic influenza) rates were up to 20 times higher in the NICU and 0-1 year population compared to other groups.

Seasonality data (figure 1) showed that despite a two- to three-fold increase in the rate of positive samples in all groups during the peak months (1.1/1000 October to March vs. 0.4/1000 April to September), NICU rates remained similar throughout the year at 4.3/1000. Overall NICU VRTI rates during the peak months were 2.6/1000 with normal visiting, dropping to 1.4/1000 with restrictions. HRV rates were particularly affected by this policy dropping from 1.68/1000 to 0.38/1000 with restrictions.

Discussion

These are the first data to quantify the inpatient population rates of VRTIs and identify a previously unreported high rate in the NICU including during a pandemic influenza period. Early life is a period of first exposure to many viruses and this reflects the prevalence in this population with half of the cases in the under 1 year group.

The high rate in the NICU raises questions about the source of transmission of these viruses when the babies have never left hospital. These are hospital-acquired infections and must

come from visitors or staff unlike the other age groups where most are community-acquired. There is a lack of good quality evidence to inform NICU policies regarding viral transmission prevention measures, screening protocols, and infection control and isolation procedures following identification of cases[7]. This has been observed with wide variations in UK NICU policies[4]. During the pandemic influenza seasons, our hospitals trust like others implemented a policy of restricting visiting to parents only, reducing the incidence of VRTI by 39%[6]. However, pandemic influenza remained a small but significant risk, with five babies positive for H1N1 during the study period. Moreover, the rate on the NICU was similar to that of the community-exposed 0-1 year group being up to 20 times higher than other groups although we must be cautious about this rate in view of the small numbers.

In our study, HRV accounts for three quarters of infections and is the dominant pathogen in all age groups apart from the 0-1 year. Although HRV causes mild symptoms in older children and adults, in ex-preterm infants it may cause more severe respiratory illness[8]. Preterm infants often have significant oxygen requirements which could exacerbate lung inflammation during HRV infection[9]. These factors could account for some of the observations that NICU graduates with a VRTI spend longer in hospital and leave with significantly worse respiratory disease. This could increase their risk of later childhood and adulthood chronic respiratory disease.

Our study is limited by small numbers in two UK centres with testing dependent on the individual clinician. Our overall VRTI rates focus only on inpatients and so the community burden may be different, however, we aimed to look at those most severely affected and so require hospital treatment. Whilst the NICU cases are hospital-acquired infections we do not

have details on where the other patient groups acquired their infection i.e. in the community or hospital. Validation of these rates are required from similar centres.

Our data highlight the significant burden of inpatient VRTIs in the NICU. The dominance of HRV across the lifespan, particularly in the NICU, is a worry as studies have focused on RSV prophylaxis which is more prevalent in the early childhood group. Good epidemiological and interventional data are needed to help inform visiting and infection control policies to reduce transmission of viral infections to this population, particularly during pandemic seasons. The UK's National Institute of Health Research's pandemic influenza preparedness portfolio[10] is poised to study the next pandemic as it happens and so provide more timely and useful data. Although small numbers, the high rate of infections and significant morbidity in the NICU warrants neonatal inclusion in this important work as well as further studies to reduce the spread and burden in this high-risk population.

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References:

1. Zinna S, Lakshmanan A, Tan S, McClaughry R, Clarkson M, Soo S, et al. Outcomes of Nosocomial Viral Respiratory Infections in High-Risk Neonates. Pediatrics. 2016;138(5).

2. Ronchi A, Michelow IC, Chapin KC, Bliss JM, Pugni L, Mosca F, et al. Viral respiratory tract infections in the neonatal intensive care unit: the VIRIoN-I study. J Pediatr. 2014 Oct;165(4):690–6.

3. Bennett NJ, Tabarani CM, Bartholoma NM, Wang D, Huang D, Riddell SW, 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 Nov;161(5):814–8.

4. Tan S, Clarkson M, Sharkey D. Variation in Visiting and Isolation Policies in Neonatal Units: A U.K. Nationwide Survey. The Pediatric Infectious Disease Journal. 2018 Jan;37(1):e20.

5. Population estimates for the UK, England and Wales, Scotland and Northern Ireland - Office for National Statistics [Internet]. [cited 2019 Nov 19]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2017

6. Szatkowski L, McClaughry R, Clarkson M, Sharkey D. Restricted visiting reduces nosocomial viral respiratory tract infections in high-risk neonates. Eur Respir J. 2019 Mar;53(3).

7. French CE, McKenzie BC, Coope C, Rajanaidu S, Paranthaman K, Pebody R, et al. Risk of nosocomial respiratory syncytial virus infection and effectiveness of control measures to prevent transmission events: a systematic review. Influenza Other Respir Viruses. 2016 Jul;10(4):268–90.

8. Costa LF, Queiróz DAO, Lopes da Silveira H, Bernardino Neto M, de Paula NT, Oliveira TFMS, et al. Human rhinovirus and disease severity in children. Pediatrics. 2014 Feb;133(2):e312-321.

9. Cui TX, Maheshwer B, Hong JY, Goldsmith AM, Bentley JK, Popova AP. Hyperoxic Exposure of Immature Mice Increases the Inflammatory Response to Subsequent Rhinovirus Infection: Association with Danger Signals. J Immunol. 2016 01;196(11):4692–705.

10. Simpson CR, Beever D, Challen K, Angelis DD, Fragaszy E, Goodacre S, et al. The UK's pandemic influenza research portfolio: a model for future research on emerging infections. The Lancet Infectious Diseases. 2019 Aug 1;19(8):e295–300.

Table 1: Rate of positive viral respiratory tract samples per thousand people according to age category

	Population Age Category							
Virus	**NICU** n=6,556	**0-1yrs** n=53,519	**1-4yrs** n=212,135	**5-15yrs** n=588,149	**16-59yrs** n=2,688,207	**≥60yrs** n=1,158,651	**Rate** n=4,707,217	**Total positive**
Adenovirus	0.31	3.01	0.69	0.07	0.02	0.01	**0.09**	414
Influenza	0.31	2.13	0.54	0.12	0.05	0.09	**0.11**	528
H1N1 Influenza	0.76	0.77	0.19	0.04	0.04	0.02	**0.05**	242
Parainfluenza	1.83	4.43	0.63	0.07	0.03	0.08	**0.13**	601
Rhinovirus	12.20	21.51	2.59	0.30	0.11	0.15	**0.51**	2,423
RSV	1.07	27.02	1.97	0.09	0.04	0.08	**0.45**	2,107
Others	0.61	4.52	0.85	0.07	0.03	0.06	**0.13**	609
Rate	**17.08**	**60.99**	**7.45**	**0.75**	**0.31**	**0.49**	**1.47**	**-**
Total positive	**112**	**3,376**	**1,581**	**442**	**842**	**571**	**6,924**	**6,924**

(Others= Cytomegalovirus, Coronavirus, Epstein-Barr virus, Herpes simplex virus and Murine pneumonia virus)

Figure 1: Age stratified rates of positive viral respiratory tract samples per thousand people (log scale) during non-peak (April to September) and peak (October to March) months.