



State of the Science Review

Respiratory syncytial virus nosocomial outbreak in neonatal intensive care: A review of the incidence, management, and outcomes



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Background: The main objective was to determine the incidence, management, and outcomes of respiratory syncytial virus nosocomial infection (RSVNI) outbreaks in neonatal intensive care units.

Methods: A comprehensive search of RSVNI in 9 databases was conducted from January 1, 2000 to May 1, 2021, of which the Cochrane Library comprised the Cochrane central register of controlled trials and the Cochrane database of systematic reviews. Two hundred and twenty-eight articles were retrieved and 17 were retained. A descriptive analysis was performed, and frequencies are reported as mean, median, and range where pertinent.

Results: One hundred and seventeen infants were analyzed and comprised preterms (88.1%) and those with pre-existing co-morbidities. The estimated proportional incidence of RSVNI was 23.8% (177/744) infants. Outbreaks were principally managed by conventional protective measures, neonatal intensive care unit closure, and visitor restriction. Palivizumab was used to control RSVNI in 10 studies. RSVNI-related mortality was 8.5% (15/177) and 8.0% (7/87) among infants where infection control was solely employed.

Conclusion: RSVNI is associated with significant morbidity and mortality. The use of palivizumab should be a multidisciplinary decision, based on rapidly spreading infection. Prospective studies are essential to determine the cost-benefit of palivizumab versus standard prevention control for an RSVNI outbreak.

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Respiratory syncytial virus (RSV) is the most common viral cause of respiratory tract infection in children less than 2 years of age. The world-wide burden of illness is significant and is accompanied by substantial morbidity and mortality especially in least developed and low-income countries. Stein et al reported that the highest incidence of RSV lower respiratory tract infection was among children <6 months (20 per 1000 children/year) with a fatality rate that was greatest in children aged <1 year (6.6 per 1000).¹ Shi et al estimated in 2015, that among children aged <5 years there were 33.1 million acute episodes of RSV illness globally, which resulted in 3.2 million hospital admissions, and almost 60,000 in-hospital deaths.² The

overall RSV-related mortality was gauged at 118,000 deaths but varied annually.

RSV is transmitted via direct contact with nasopharyngeal secretions of infected individuals or auto-inoculation after touching contaminated surfaces.³ Furthermore, the virus can survive for several hours on different surfaces.^{3,4} Nosocomial transmission of RSV occurs either by aerosolized small droplets,⁵ or by self-inoculation from contaminated fomites. Medical personnel and allied healthcare support staff are often the primary source for transmission in hospital-based settings.^{6,7} During an epidemic, it is estimated that approximately 20–40 percent of infants admitted for other medical disorders may acquire nosocomial RSV infection, as well as 50 percent of healthcare providers.⁴ The definition of respiratory syncytial virus nosocomial infection (RSVNI) varies in the published literature. Most reports define RSVNI as an infection identified 5 or more days post hospital admission and confirmed by assay or culture,⁸ although more recently an outbreak is defined as two cases of acute hospital-related respiratory tract infection within 48 hours, with a common

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epidemiological link (eg, unit), of which at least one is laboratory confirmed.⁹ Infection unrelated to the hospital setting is defined as community-acquired RSV infection.¹⁰ RSVNI is one of the major causes of morbidity and mortality especially in children with underlying medical complexity such as bronchopulmonary dysplasia, congenital heart disease, airway anomalies and immunosuppression.^{11–14} It results in prolonged neonatal hospitalization globally, and a RSV-related nosocomial outbreak in the neonatal intensive care unit (NICU) imposes significant costs on respective healthcare services and communities at large.¹⁵ The main objective of our study was to determine the incidence, management and outcomes associated with an RSVNI outbreak as reported in the current literature. The secondary objective was to evaluate outcomes related to the use of palivizumab prophylaxis in the control of RSVNI in the NICU setting.

METHODS

Definitions

The definition of a full-term infant for this study was a neonate ≥ 37 weeks gestational age (wGA); early and late preterm, 29–36 weeks wGA and extreme preterm, ≤ 28 wGA.

Search strategy

We conducted a comprehensive literature search across databases, including PubMed, Medline, Embase, Web of Science, CINAHL and the Cochrane Library. The Cochrane central register of controlled trials, the Cochrane Database of Systematic Reviews, and the database of abstracts of reviews of effectiveness (DARE) were searched for the topic of interest. All reports were checked for additional pertinent references and articles identified were compared, to verify matching and exclude duplication. The first author (RM) reviewed the abstracts of articles from the initial search. If descriptive information from the abstract was limited, the complete article was reviewed for appropriate inclusion criteria. Discrepancies were discussed with a second co-author (BP) and consensus reached. The following keywords: neonate, infant, NICU, RSV bronchiolitis, nosocomial infection, and outbreak; and MeSH terms: RSV OR respiratory syncytial virus, AND nosocomial infection, AND neonate OR infant AND neonatal intensive care unit OR NICU, were employed respectively for the search. The search was limited to published studies in the English language, human subjects, and studies published from January 1, 2000 up to May 1, 2021. We included all reports irrespective of study design that encompassed infants with RSVNI less than 6-months of age and those with all comorbidities such as congenital heart disease, chronic lung disease/bronchopulmonary dysplasia and dysmorphic syndromes. Articles that were not exclusively about infants with RSV infection were excluded.

Data evaluation

All included studies were subjected to a risk of bias assessment using the National Heart, Lung, and Blood Institute (NHLBI) Study Quality Assessment Tool.¹⁶ A quality rating (Good, Fair, Poor) was judged after answering several questions for each study design. The rating was conducted by two investigators and consensus on disagreement was reached through further discussion and approval by a third individual (RM).

Analysis

We conducted a descriptive analysis of the data, since accurate quantitative data assessment was limited by the study designs, the heterogeneity of the population under review and the absence of

documented effect estimates to facilitate a meta-analysis. Frequencies are reported for categorical data and mean, or median and range or interquartile range are outlined as measures of central tendency and dispersion respectively, for continuous data where reported.

RESULTS

A total of 228 articles were retrieved from the initial search. Figure 1 outlines the search strategy and summarizes data retrieval. A total of 17 articles were included in the final review; 2 were case series, 12 were observational reports, 1 was a prospective cohort design, 1 was a case-control study and 1 was a literature review. From the risk of bias assessment, 15 studies were rated as “good,” and 2 studies were rated “fair” by the quality assessment tool. Scores of 0–2, 3–5, and ≥ 6 were given quality ratings of “poor,” “fair,” and “good,” respectively (Table 1).¹⁶ The demographic characteristics of the infants included in the review are shown in Table 2.

A total of 177 infants were included in the analysis and comprised those who were healthy or with co-morbidities such as chronic lung disease, congenital heart or neurological disease, or other neonatal disorders, including the need for invasive mechanical ventilation before RSV infection (Table 2). There was a preponderance of male sex among the RSVNI infants with a ratio of 2:1 and the largest proportion were preterm infants (Table 3; $n = 156$; 88.1%). The mean duration of 12 RSVNI outbreaks, across 11 reports was 19.8 days (range: 5–40). The mean and median (range) length of hospital stay in 2 and 4 studies was (30.5–81.4) and (9–44) days respectively (Table 3). The estimated proportional incidence of RSVNI relative to the total number of infants in the NICU during an outbreak was 23.8% (177/744), where the denominator was reported, excluding the index case(s).

The signs and symptoms of RSVNI ranged from mild upper respiratory tract infection with cough, fever, and rhinorrhoea to more severe features involving the lower respiratory tract such as apnoea, tachypnoea, hypoxemia, cyanosis, basal lung crepitations and acute respiratory distress syndrome.¹⁷

Table 3 summarizes the patients' management and outcomes of RSVNI acquired in the NICU. The diagnosis of RSV was confirmed on naso-pharyngeal swabs or aspirate by Respi-Strip (immunochromatography test), immunoassay, or polymerase chain reaction (PCR). Conventional protective measures of hand hygiene, gloves, masks and gowns, isolation of infected cases, cohorting, NICU closure and visitor restriction were adopted in most of the studies ($n = 15$). Episodes of RSVNI were managed with nasal oxygen and both non-invasive and invasive mechanical and high frequency ventilation where required. Treatment modalities included ribavirin, caffeine, nebulized saline, steroids, surfactant, epinephrine, salbutamol, nitric oxide, intravenous immunoglobulin, extracorporeal membrane oxygenation and antibiotics. Palivizumab was used to control RSVNI in 10 studies after standard containment strategies had failed. The overall RSVNI-associated survival rate was 91.5% (162/177). The total RSV-related mortality among the cases was 8.5% (15/177) and 8.0% (7/87) among the patients where infection control was employed as the sole strategy for RSV outbreak containment ($n = 7$ studies).

DISCUSSION

Respiratory syncytial virus (RSV) outbreaks among vulnerable patients in hospital settings are a major concern and cause a considerable public health burden.¹⁸ RSV infections lead to 200,000 deaths per year and is the most common cause of viral-related hospitalization in middle-income and developed countries due to the rapid spread during community and hospital outbreaks. Preterm infants ≤ 35 wGA and those with pre-existing medical disorders are more susceptible to RSV because of either their underdeveloped immune system or already compromised health status.^{19–22} We reviewed a

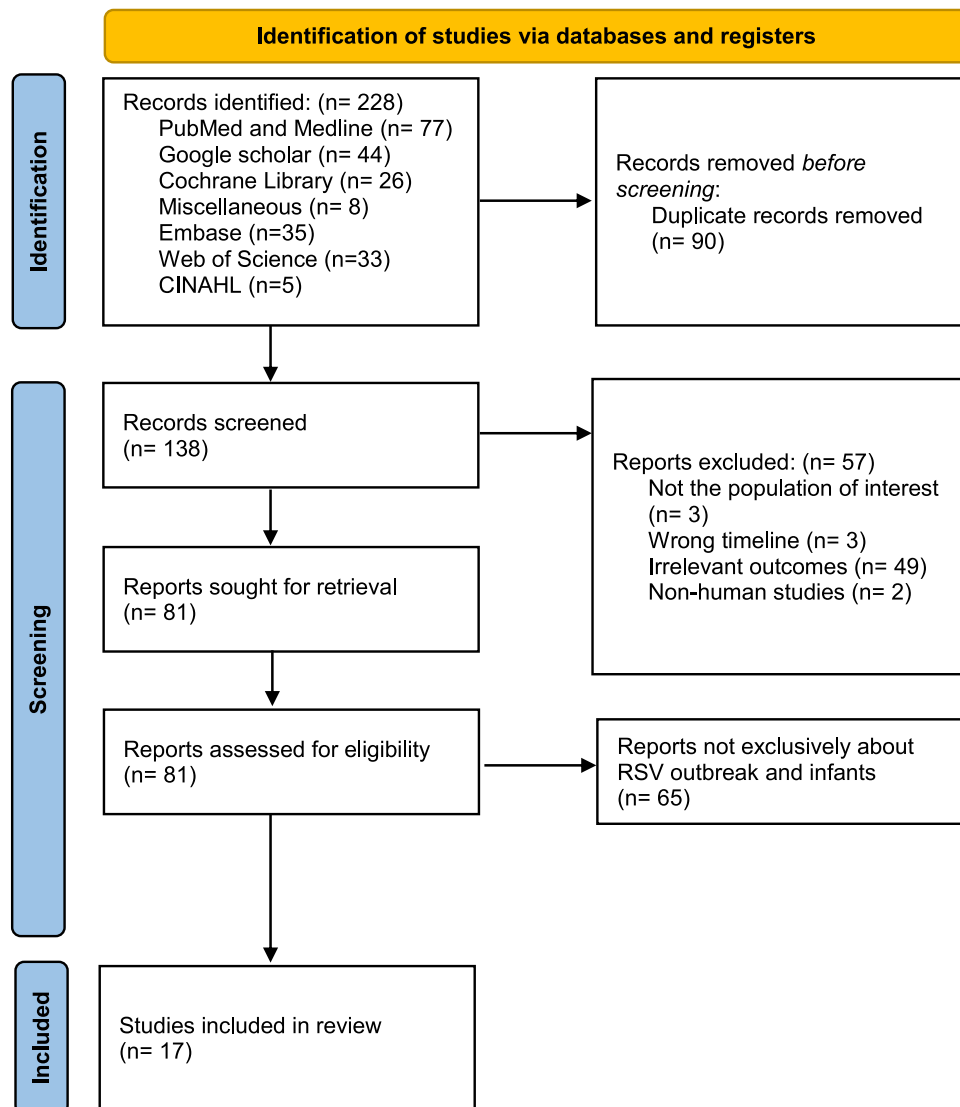


Fig 1. Flow diagram of assembled articles for analysis.

total of 177 infants with RSV NI, reported in 17 different studies and the assembled cohort were predominantly preterm with a greater proportion being male (66.4%) sex.^{10,15,17,22-36}

Risk factors for RSV-related nosocomial transmission

The risk factors implicated in the nosocomial spread of RSV are similar to those that enhance the acquisition of RSV infection within the community. Prematurity is a known risk factor for more severe RSV infection and is associated with prolonged hospitalization. Infants <30 wGA have a 3-fold higher hospitalization rate and longer lengths of hospital stay than term infants and require more health-care and NICU admissions and have worse outcomes including increased need for supplemental oxygen and non-invasive ventilation.^{19,37-42} The risk increases with lower birth weight and gestational age and in the presence of socioeconomic and environmental factors such as smoking, household crowding and day care.^{12,19,40,42,43}

Two studies of children with RSVNI, found higher rates of preterm birth (≤ 34 wGA, 20% vs 6.8%), ICU admission (20% vs 5.7%), mechanical ventilation (16.7% vs 3.0%), longer mean length of hospital stay

(28.1 vs 4.9 days), severe underlying disease (73% vs 15%) and higher mortality (3.3% vs 0.2%) compared to the community-associated RSV group.^{44,45} In our study infants who specifically acquired RSVNI during an NICU outbreak also experienced prolonged lengths of hospital stay, increased rates of invasive and non-invasive mechanical ventilation, need for extracorporeal membrane oxygenation, high hospital costs and RSV-related mortality.^{10,15,24-28}

Among the assembled RSVNI cases, prematurity featured prominently,^{10,17,24-28,30,33-36} compared to those infants who had acquired RSV within the community, and the patients had one or more pre-existing medical conditions; congenital heart disease, bronchopulmonary dysplasia/chronic lung disease, neurological impairment, congenital anomalies and need for respiratory support prior to the onset of infection.^{10,23,26,28} It is well established that children with comorbidities and medical complexity are at substantial risk for RSV infection, complications during illness and mortality,^{11-14,20-22,27,28,31,46,47} and RSVNI likely imposes an additional burden on disease severity. However, Moreno et al²³ found no correlation between the risk of RSVNI and underlying medical disorders. Although two-thirds of RSVNI occurred in the male sex (66.4%) the finding was inconsistent across the included studies.

Table 1
Risk of bias assessment of the included studies (n = 17)

Author (year)	Was the study question or objective clearly stated?	Was the study population clearly and fully described, including a case definition?	Were the cases consecutive?	Were the subjects comparable?	Was the intervention clearly described?	Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Was the length of follow-up adequate?	Were the statistical methods well-described?	Were the results well-described?	Overall rating
Rose E. (2021) ³⁶	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
Vain N. (2020) ³⁵	No	No	Yes	Yes	No	No	No	No	Yes	Fair
Comas-Garcia A. (2020) ¹⁵	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
de Souza L. (2019) ³⁶	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Hammoud M. (2016) ²⁵	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
Parejo J. (2016) ²³	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Alan S. (2016) ¹⁶	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
Alan S. (2013) ²⁹	Yes	No	Yes	Yes	Yes	Yes	NR	Yes	Yes	Good
de A Silva C. (2012) ¹⁷	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
O'Connell K. (2011) ³⁴	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
Dizdar E. (2010) ²⁷	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
Kurtz H. (2008) ²⁴	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
Halasa N. (2005) ²⁸	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Abadeso C. (2004) ³²	Yes	No	Yes	Yes	Yes	Yes	NR	Yes	Yes	Good
Heerens A. (2002) ³¹	Yes	No	Yes	N/A	Yes	CD	NR	No	Yes	Fair
Kilani R. (2002) ³⁰	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
Cox R. (2001) ³³	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good

CD, cannot determine; N/A, not available; NR, not reported.

Rating¹⁶

Good: Has the least risk of bias, and results are considered valid (Score ≥ 6).

Fair: Susceptible to some bias deemed insufficient to invalidate results (Score: 3–5).

Poor: Indicates significant risk of bias (Score: 0–2).

RSV detection during an NICU outbreak

Early detection of RSV infection is an essential step to prevent and expediently manage an outbreak. There are several diagnostic tests to rapidly identify RSV infection during an outbreak, which vary in their sensitivity, specificity, and turnaround time.⁴⁸ Some methods such as direct immunofluorescence assays can be conducted rapidly but require laboratory expertise and have poor sensitivity like point-of-care tests that utilize antigen detection. Newer, rapid antigen detection tests are more useful and have a higher sensitivity in infants aged 0–5 months (84%) compared to children aged 24–35 months.⁴⁹ Real-time reverse transcriptase-polymerase chain reaction (RT-PCR) has a high sensitivity (overall 95%) and the turnaround time is within hours, that facilitate rapid detection of RSVNI during an outbreak.³⁴ Both RT-PCR and antigen detection tests are currently employed for the diagnosis of RSV infection in infants either individually or as part of a broad viral panel. New, molecular point-of-care diagnostic tests are quicker and more sensitive than rapid RSV antigen tests, faster and less complex than most available RT-PCR tests and have high sensitivity and specificity (>98%), similar to RT-PCR.^{48–50} Given the rapid spread of RSVNI in the NICU, quick detection is highly essential to institute isolation measures, heighten preventive strategies to facilitate containment, and reduce potential morbidity among high-risk infants.^{34,51}

Outcomes and mortality

Infants with RSVNI experienced prolonged illness. Alan et al¹⁰ reported RSVNI hospital stays of median 22.5 days, (range: 5–180; n = 24) days versus 8 (range: 2–45; n = 226) days in community acquired RSV. Comas Garcia et al¹⁵ documented in a case-control study (n = 24 in each cohort) that the duration of hospital stay was 8.5 days longer in infants with RSVNI (median 44 days; interquartile range [IQR], 39–64.5) compared to those without RSV infection (median 35.5 days; IQR, 26.5–52.5). Similarly, Moreno et al²³ noted mean hospital stays in RSVNI versus non-infected infants of 30.5 (IQR, 17.25–54.25) and 8.5 days (IQR, 4.25–21) respectively, while de Souza et al²⁶ reported mean hospital stays in RSVNI (n = 12) compared to community acquired RSV (n = 32) of (mean 81.4, range: 21–150 vs 11.3, range: 3–49) days.

Several studies reported the need for prolonged mechanical ventilation and associated morbidity in neonates with RSVNI, especially in preterm infants of lower birth weight and gestational age. In two studies with a comparison arm, the proportion of RSVNI infants requiring mechanical ventilation was significantly higher compared to either control subjects (54.2% vs 0.4%; $P < .001$)¹⁵ or a group with community acquired RSV (33.3% vs 8.4% CA [$P < .001$]).¹⁰ Short- and long-term complications following RSVNI include subglottic stenosis,⁵² chronic lung disease with oxygen dependency,^{25,33} pulmonary hypertension, seizures, and cerebral palsy.³³

The mortality associated with RSVNI is substantial. In a report by Langley et al two decades ago, among 1,516 children hospitalized with RSV, 91 (6%) had nosocomial infection.¹⁴ Four children with RSVNI (4.4%) died within 2 weeks of infection, compared with 6 (0.42%) with community-acquired RSV (relative risk: 10.4, 95% confidence interval: 3.0, 36.4). In the German surveillance study of RSVNI, the total mortality was also higher in the nosocomial group versus community-acquired RSV (7.8% vs 0.5%; $P < .001$) respectively, but the attributable mortality was similar.¹² Thorburn et al reported on RSVNI acquired in a paediatric intensive care setting in Liverpool, UK from 1999 to 2002. The RSVNI-specific mortality rate was 13.3% (2/15).¹³ The overall NICU-related mortality rate for RSV associated with an outbreak in our review was 8.5% (15/177) and ranged from 0% to 33.3%. Among infected patients where isolation, cohorting and infection control was employed as the sole strategy for RSV outbreak

Table 2

Demographic characteristics of infants with RSV nosocomial infection enrolled in the study

Author (Year)	Country	Study type	Number of subjects, n	Male/Female	Comorbidities
Rose E. (2021) ³⁶	USA	Observational	6	N/A	PT, CLD, Other [§]
Vain N. (2020) ³⁵	Argentina	Retrospective	9	N/A	-
Comas-Garcia A. (2020) ¹⁵	Mexico	Case-control	24	21/3	RDS, Other [§]
de Souza L. (2019) ²⁶	Brazil	Retrospective	11	N/A	All cases had undescribed comorbidities
Hammoud M. (2016) ²⁵	Kuwait	Case series	12	7/5	PT
Parejo J. (2016) ²³	Spain	Observational	19	9/10	CLD, PD, RS, Other [§]
Alan S. (2016) ¹⁰	Turkey	Prospective cohort	24	16/8	PT, CLD, CHD, RS, Other [§]
Alan S. (2013) ²⁹	Turkey	Retrospective	4 (2 outbreaks)	N/A	PT
de A Silva C. (2012) ¹⁷	Brazil	Observational	10	N/A	PT, CLD, RDS, Pulmonary hypertension, Other [§]
O'Connell K. (2011) ³⁴	Ireland	Observational	3	N/A	MRSA colonization
Dizdar E. (2010) ²⁷	Turkey	Case series	15 [*]	10/5	RDS, RS, Other [§]
Kurz H. (2008) ²⁴	Austria	Review	0 [†]	1/0	
Halasa N. (2005) ²⁸	USA	Retrospective	8	3/5	CLD, Other [§]
Abadesso C. (2004) ³²	Portugal	Retrospective	7	N/A	PT
Heerens A. (2002) ³¹	USA	Retrospective	11	N/A	PT, CHD, CLD, RS, Other [§]
Kilani R. (2002) ³⁰	Saudi Arabia	Retrospective	8	6/2	PT, RDS, CLD, MRSA, Other [§]
Cox R. (2001) ³³	UK	Observational	6 [‡]	5/1	PT, CLD, RS, Other [§]
Total (n = 17)			177	77/39	

NOTE. Number of subjects excludes the index case where reported.

CHD, congenital heart disease; CLD, chronic lung disease; MRSA, methicillin-resistant staphylococcus aureus; NA, not available; PD, patent ductus arteriosus; PT, prematurity; RDS, respiratory distress syndrome; RS, respiratory support before infection; RSV, respiratory syncytial virus.

^{*}11 cases were detected on the same day by screening.[†]RSV infection only in the index case-not included.[‡]Index case died.[§]Other comorbidities include: Acute renal failure, anemia, asphyxia, congenital alveolar proteinosis, congenital diaphragmatic hernia, congenital respiratory tract anomaly, dysmorphic syndrome, feto-fetal transfusion syndrome, gastrointestinal malformation, gastroschisis, hyperbilirubinemia, ileostomy, intrauterine growth restriction, intraventricular hemorrhage, jejunal atresia, malformations, necrotizing enterocolitis, neurological disease, omphalocele, other nosocomial infection, perforated volvulus, periventricular leukomalacia, persistent fetal circulation, pneumonia, sepsis, surgical procedure.

containment, without the use of palivizumab in uninfected subjects, the mortality was 8.0% (7/87).

Costs for the control of RSVNI

In two studies, the overall hospital costs for the management of RSVNI were 41.9% higher than a control group and ranged from USD 1.1 to 1.3 million.^{15,28} Macartney et al estimated the cost-effectiveness of infection control as an intervention in the prevention of RSVNI by comparing hospital costs of 30 randomly selected nosocomial cases admitted to the Children's Hospital of Philadelphia from 1988 to 1996, versus a matched cohort of inpatient uninfected controls.⁵³ The investigators established that the cost per case of nosocomial infection prevented was USD\$1563 while the hospital cost per RSVNI case was \$9419 which yielded a cost-benefit ratio of 1:6. The authors recommended further economic analyses to support their findings.

RSVNI control and prevention

The pivotal strategies for the control of RSVNI are well delineated by Groothuis et al and other investigators, focus on rapid viral identification, institution of thorough hand hygiene, stringent use of gowns, gloves, face masks and eye protection, cohorting of infected infants with designated nursing staff and limiting visitors especially young siblings to the NICU during an outbreak.^{8,35,54} Although, it is logical to adopt these measures to contain the spread of RSV within NICUs, solid evidence in support of the preventive interventions is still lacking. In a recent Cochrane review, the pooled results of randomized trials did not demonstrate a clear reduction in respiratory viral infection with the use of medical/surgical masks during seasonal influenza (Risk ratio [RR] 0.99, 95% confidence interval [CI] 0.82-1).⁵⁵ However, hand hygiene accounted for a 16% relative reduction in acute respiratory illness (RR 0.84, 95% CI 0.82-0.86; 7 trials; 44,129 participants; moderate-certainty evidence). Early studies that

depended on culture proven RSV and traditional antigen detection tests were operator dependent and may have led to delayed cohorting of NICU patients and spread of infection during an outbreak.^{28,33,52,56} New, molecular RT-PCR tests for RSV either conducted singly (Alere i RSV test) or as part of a multiplex panel (bio-Merieux BioFire FilmArray) provide results in 13-45 minutes which is of essence to rapidly control outbreaks.^{17,24,34,48-51}

All the reports on RSVNI in the NICU setting documented the use of standard preventive measures as the first step in the control of an outbreak which is rational and aligns with the published literature.^{8,14,22,23,34,36,57-60} In our review, 7 out of the 17 studies implemented infection control measures as the sole intervention.^{10,15,30-32,35,36} In a prospective study, van de Pol et al reviewed RSV transmission in a paediatric intensive care unit.⁵¹ Through careful surveillance, the investigators determined that non-infected patients were exposed for 683 days to RSV-shedding patients, and none acquired RSV which supports the use of routine control measures to effectively control transmission. Palivizumab, a monoclonal antibody with efficacy and safety against RSV infection is well-established in randomized trials,^{61,62} but it is not recommended for RSV outbreaks because of the lack of evidence.⁶³ Ten studies reported the adoption of strict prevention strategies during RSVNI outbreaks in the NICU, but RSV spread could not be halted. Multidisciplinary consultation led to the use of palivizumab either in subgroups of patients,²⁸ or all infants' resident in the NICU, which effectively terminated RSV transmission, without incumbent mortality.^{17,24-29,32-34} Ashkenazy-Hoffnung et al indicate that RSVNI disease is serious and even low nosocomial rates contribute significantly to poor outcomes.⁴⁴ Each additional day of hospital stay accounts for greater risk of acquiring RSVNI (odds ratio, 1.02 per day) but the correlation between prolonged hospitalization and nosocomial infection remains to be determined. The authors reported that prophylaxis may not be effective in RSVNI since one-third of cases with RSVNI occurred in infants who did not qualify for prophylaxis by current

Table 3
Management and outcome of RSV outbreaks across the included studies (n = 17)

Author/Year	Number of subjects, n	Denominator in NICU (n)	Length of stay, days	Duration of outbreak (days) and management	Outbreak resolution, Yes/No	Death, n (%)
Rose E. (2021) ³⁶	6 PT	N/A	9 (range: 3–125)	(11); Infection control reinforcement (ICR), respiratory support (RS), antibiotics	Yes	No death
Vain N. (2020) ³⁵	9 PT	18	N/A	(14); RS	Yes	1 (11.1)
Comas-Garcia A. (2020) ¹⁵	24 PT	24	44 (IQR: 39–64.5)	Outbreak duration N/A; ICR, RS, antibiotics	Yes	1 (4.2)
de Souza L. (2019) ²⁶	11 PT	36	81.4 (21–150)	(13); ICR, RS, PVZ prophylaxis	Yes	1 (9.1)
Hammoud M. (2016) ²⁵	12 PT	90	16 (IQR: 12–36)	(24); ICR, RS, PVZ prophylaxis	Yes	No death
Parejo J. (2016) ²³	19; 16 PT, 3 Term	48	30.5 (IQR: 17.3–54.3)	(35); ICR, RS, PVZ prophylaxis	Yes	2 (10.5)
Alan S. (2016) ¹⁰	24; 13 PT, 11 Term	250	22.5 (5–180)	7 outbreaks (October 2013–March 2014); ICR, RS, salbutamol, systemic steroids, nebulized saline	Yes	1 (4.2)
Alan S. (2013) ²⁹	1PT; 3 PT [‡]	30	N/A	Outbreaks: 12 d, 19 d [‡] ; ICR, PVZ prophylaxis;	Yes	No death
de A Silva C. (2012) ¹⁷	10 PT	18	N/A	(5); ICR, RS, PVZ prophylaxis	Yes	No death
O'Connell K. (2011) ³⁴	3 PT	24	N/A	(8); ICR, PVZ prophylaxis	Yes	No death
Dizdar E. (2010) ²⁷	15 PT*	50	N/A	Outbreak duration N/A; ICR, RS, ribavirin, salbutamol, caffeine, steroids, nitric oxide, antibiotics, PVZ prophylaxis	Yes	5 (33.3)
Kurz H. (2008) ²⁴	1PT [‡]	11	10	Outbreak duration N/A; ICR, RS, PVZ prophylaxis	Yes	No death
Halasa N. (2005) ²⁸	8 PT	56	N/A	(20); ICR, RS, ECMO, PVZ prophylaxis	Yes	No death
Abadesso C. (2003) ³²	7; 4PT, 3 Term	52	N/A	Outbreak duration N/A; ICR, RS, PVZ after second outbreak	Yes	1 (14.3)
Heerens A. (2002) ³¹	11; 7 PT, 4 Term	N/A	N/A	Outbreak duration N/A; RS, PVZ after second outbreak. In the third outbreak, two infants on PVZ acquired nosocomial RSV	Yes	2 (18.2)
Kilani R. (2002) ³⁰	8 PT	20	N/A	(40); ICR, RS, ribavirin, steroids, surfactant, epinephrine, nitric oxide, IVIG	Yes	1 (12.5)
Cox R. (2001) ³³	6 PT	17	N/A	(36); ICR, RS, palivizumab prophylaxis	Yes	No death [§]
Total	177 (156 PT)	744				15 (8.5)

ICR, infection control reinforcement; IQR, interquartile range; IVIG, intravenous immunoglobulin; N/A, not available; NICU, neonatal intensive care unit; PT, preterm; PVZ, palivizumab; RS, respiratory support; RSV, respiratory syncytial virus.

*11 RSV cases identified simultaneously on testing.

[‡]RSV infection identified only in the index case-not counted.

[§]First outbreak 12 d, second outbreak 19 d.

[§]Except for the index case.

guidelines.⁶³ However, Dizdar et al reported that palivizumab protected overt clinical RSV infection in 94.6% of the 37 cases during an outbreak.²⁷ Saadah et al predicted the effectiveness of palivizumab in a RSVNI outbreak utilizing a hypothetical neural network model.⁶⁴ The authors concluded that palivizumab may be effective in a subset of extremely low birth weight male infants with significant congenital heart disease. In our study it was difficult to ascertain an estimate of the effect of palivizumab because it was employed at various time points during the outbreak or in a select group of patients who qualified for prophylaxis based on approved institutional or country-specific guidelines. The current data from two-third of the studies reflect that cohorting and preventive measures combined with immunization of all infants, irrespective of criteria may contain RSV spread, and the strategy has gained momentum in the recent era, despite the lack of solid evidence and absence of cost-benefit analyses. This may

imply that healthcare providers in the real-world experience err on the side of the potential benefit provided by prophylaxis versus the risk of mortality and possible legal implications that overshadow the outbreak scenario.

Several limitations of this review should be addressed. First, the studies were mainly retrospective case reports and case series which comprise weak evidence in the hierarchy of clinical trials. Second, potential biases may have confounded data interpretation. These include ascertainment, detection, selection and reporting biases of the cases through varying definitions of RSVNI and RSV diagnostic tests employed over time and incomplete descriptions of infants included in the cohorts. Underreporting of RSVNI-related outbreaks in the literature, likely compromised our ability to ascertain the true incidence. Third, a cause-effect relationship of palivizumab on RSVNI could not be established because the inception of prophylaxis

occurred at different time intervals during the outbreaks. Fourth, the risk of bias tool may have resulted in more favourable reporting of the quality of the respective studies since minimum rather than rigorous requirements were met in each category. Last, although the overall assembled RSVNI population comprised 177 subjects, the sample sizes were relatively small in some reports to establish firm conclusions.

CONCLUSION

Viral epidemics do occur regularly in NICUs, but regular surveillance is not routinely performed. RSVNI is associated with significant morbidity and mortality when compared to RSV acquired within the community. Rapid identification of RSV is highly essential during an outbreak using RT-PCR and molecular assays with a rapid turnaround time. Preventive measures remain the cornerstone for the control of an RSV-related epidemic in the NICU and should be implemented promptly following the identification of the index case. The use of palivizumab should be determined via inter-disciplinary decision making and directed by the infectious disease service and targeted either to infants within the setting who qualify for prophylaxis, or all incumbents based on the rapidity of disease spread. Further prospective studies or cluster randomized control studies are necessary to clearly determine the cost-benefit of palivizumab during an RSV outbreak in the NICU versus solitary preventive measures.

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