Burden, Etiology, and Risk Factors of Respiratory Virus Infections Among Symptomatic Preterm Infants in the Tropics: A Retrospective Single-Center Cohort Study

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Background. The burden of respiratory viral infections (RVIs) among preterm infants in the first few years of life, especially those living in the tropics with year-long transmissions of respiratory viruses, remains unknown. We aimed to describe the clinical epidemiology and associated risk factors for RVIs among symptomatic preterm infants ≤32 weeks up to 2 years of life.

Methods. We performed a data linkage analysis of clinical and hospital laboratory databases for preterm infants born at KK Women's and Children's Hospital, Singapore, from 2005 to 2015. RVI episodes during initial admission and subsequent hospital readmissions were included.

Results. Of 1854 infants in the study, 270 (14.5%) infants were diagnosed with at least 1 RVI. A total of 285 (85.3%) episodes were diagnosed postdischarge, with the highest risk for RVIs being from 3 to 5 months of age. The incidence of RVI in this population was 116 per 1000 infant-years and respiratory syncytial virus was the main overall causative pathogen. Infants with RVIs were more likely to be born at ≤27 weeks' gestational age (odds ratio [OR], 1.7; 95% confidence interval [CI], 1.2–2.3), to have received postnatal steroids (OR, 1.5; 95% CI, 1.0–2.1), and to be diagnosed with bronchopulmonary dysplasia (OR, 1.7; 95% CI, 1.2–2.4).

Conclusions. The burden of RVIs is high in preterm infants in the tropics, affecting >1 of 10 infants born at ≤32 weeks' gestation before 2 years of age. Respiratory syncytial virus was the main causative pathogen identified. Risk factors for RVI included extremely low gestational age, receipt of postnatal steroids, and bronchopulmonary dysplasia.

Keywords. respiratory tract infections; viruses; respiratory syncytial virus infections; premature infant; incidence.

Respiratory viral infections (RVIs) among preterm infants can result in significant morbidity and contribute to mortality [1, 2]. Compared to term infants, preterm infants are reported to have more severe symptoms when affected by these infections [3–5], resulting in longer duration of hospital stays, longer hypoxia durations, and more intensive care unit readmissions [5–8]. RVIs have also been reported to lead to long-term respiratory morbidities, including asthma [9, 10]. Limited data exist on the burden of RVIs beyond the initial birth admission and the first few months of life. Importantly, there is a dearth of published data from the tropics, where the epidemiology of respiratory viruses such as influenza and respiratory syncytial virus (RSV) are different from temperate climes. Year-long transmission of these viruses would have a major impact on their incidence and burden among preterm infants in the region.

Most available studies have also focused on RSV-related disease burden in this population. Reports on other viruses such as parainfluenza virus (PIV), rhinovirus, and human metapneumovirus (HMPV) have not been widely reported [11–13]. Ongoing transmission of these viruses has been demonstrated during nonoutbreak situations in the neonatal intensive care unit (NICU) and postdischarge [6, 8, 14, 15]. In this article, we aim to characterize the burden, etiology, and risk factors of RVIs in symptomatic preterm infants in the tropics.

METHODS

Study Design and Setting

We performed a retrospective cohort study of preterm infants born at KK Women's and Children's Hospital (KKH), Singapore, over an 11-year period (2005–2015). All live-born very-low-birthweight (VLBW) infants born at 23–32 weeks' completed gestational age and admitted to the hospital's neonatal unit were included. Infants with major congenital anomalies, stillbirths, and labor-room deaths were excluded. Data were included for these infants up to 2 years of age.

KKH is an 830-bed referral hospital and is the largest tertiary-level perinatal center in Singapore, with 40 NICU beds and 60 special care nursery beds. KKH provides care for >11 500 pregnant women and 1200 preterm infants annually and is the only specialist women's and children's public hospital in Singapore.

The neonatal department cares for more than two-thirds of all infants born <1000 g in Singapore [16]. Around 180 infants ≤32 weeks' gestation (of which about 90 are ≤28 weeks) are admitted to KKH NICU annually. Isolation and cohorting is practiced for RVI-infected patients and potential contacts, with initiation of contact or droplet precautions as appropriate [17]. Children <16 years of age are barred from the units and all staff and visitors are advised against entering the units if they are unwell.

It is standard clinical practice for all patients admitted to KKH with a history of respiratory symptoms (eg, cough, coryza, breathing difficulties) to have a nasopharyngeal swab tested for respiratory viruses, initially via direct immunofluorescence. Subsequent samples may also be sent for multiplex polymerase chain reaction (PCR) testing if there is a strong suspicion for RVI despite negative immunofluorescence test.

Data Sources

The KKH VLBW clinical database [16] records perinatal, neonatal, and maternal information using a standardized data collection form for all live-born infants <1500 g in the hospital. The data are cross-checked for validity by an audit officer before submission into the electronic database. We extracted a line list of all positive RVIs from the hospital microbiology laboratory database from 1 January 2005 to 31 December 2015. Data linkage was performed between the KKH VLBW database and the laboratory extraction using unique national identification numbers (a number allocated to every baby born in Singapore).

Gestational age is defined as the best estimate of completed weeks based on obstetric history, clinical examination, and prenatal ultrasound. Bronchopulmonary dysplasia (BPD) is defined as oxygen requirement or respiratory support for a chronic pulmonary disorder at 36 weeks' postmenstrual age [18]. An infant is small for gestational age (SGA) if the birth weight is <10th percentile according to Fenton growth charts [19]. Histologic chorioamnionitis is the presence of inflammatory cells in the chorioamniotic membrane, umbilical cord, and/or the placental disc [20]. Postnatal steroid usage is the provision of inhaled, oral, and/or parenteral steroids for treatment of chronic lung disease.

Laboratory Testing

Viral infections were detected using 1 of 2 standard laboratory methods—direct fluorescent antibody (DFA) and/or multiplex real-time PCR assay. The 8 viruses detected by DFA (D[3] Double Duet DFA Respiratory Virus Screening and ID Kit; Diagnostic Hybrids, Athens, Ohio) include influenza A, influenza B, RSV, adenovirus, PIV-1, PIV-2, PIV-3, and HMPV. Per the manufacturer's documentation, the positive percentage agreement of virus detection by this test with a predicate test was 100% (95% confidence interval [CI], 98.5%–100%) and the negative agreement was 99.3% (95% CI, 98.1%–99.7%). From 2009 onward, a commercial multiplex PCR kit (Seeplex RV15 ACE detection kit; Seegene, Seoul, Korea) was introduced in the department,

where the following additional viruses were detectable: PIV-4, coronavirus 229E, coronavirus OC43, bocavirus, rhinovirus, and enterovirus (Supplementary Table 1). Positive results of the same organisms from repeat or multiple testing during the same admission were counted as 1 episode. A separate RVI episode was counted for any subsequent admissions with a different virus, at least 7 days from the previous episode [7].

Statistical Analysis

We compared the variables of interest between infants with and without RVIs using χ^2 test for proportions and Mann-Whitney U test, as appropriate. Analysis was performed for the whole study population and also for subgroups of different respiratory viruses. Comparisons were also made of clinical characteristics and RVI distribution between predischarge (postdelivery and prior to initial discharge) and postdischarge periods.

Gestational age and age-specific RVI incidence rates were calculated for laboratory-confirmed RVI episodes per 1000 infant-years for the gestational age categories ≤26 weeks, 27–29 weeks, and 30–32 weeks, and the chronologic age categories <3 months, 3 to <6 months, 6 months to <1 year, and 1–2 years. Infant-years were counted as the time from birth until 2 years of age or until RVI or death. The duration of observation was adjusted as appropriate for infants born in 2014 and 2015 to include time up to end of the study period (31 December 2015). For calculation of RSV incidence, infants who received palivizumab (n = 43) were excluded from the analysis.

Multivariable logistic regression analysis was performed with the following predetermined clinically relevant variables: gender, SGA status, gestational age 23–27 weeks, vaginal delivery, Apgar score ≤5, receipt of antenatal steroids, receipt of surfactant, receipt of postnatal steroids, presence of placental histologic chorioamnionitis, and presence of BPD. Odds ratios (ORs) and adjusted odds ratios (aORs) were expressed with 95% CIs. A level of significance of α < .05 using a 2-tailed comparison was used in this study. Statistical analyses were performed using IBM SPSS Statistics version 23.0 (IBM Corporation, Armonk, New York).

Ethics Approval

Ethics approval was obtained from the SingHealth Centralised Institutional Review Board.

RESULTS

Study Population

A total of 1903 VLBW infants ≤32 weeks' gestation were born in KKH from 2005 to 2015. After exclusion of 49 stillbirths/labor room deaths, 1854 live-born infants admitted to NICU were included in the study. Of these infants, 270 (14.5%) were diagnosed with an RVI within the first 2 years of life (Table 1), where 1.7% and 12. 8% were positive pre- and postdischarge, respectively. Forty-seven (2.5%) infants had >1 episode of RVI, resulting in a total of 334 RVI events during the study period.

Table 1. Clinical Characteristics and Comparisons of Preterm Infants With and Without Respiratory Viral Infections

Characteristics	All Infants (N = 1854)	Respiratory Virus Infected (n = 270)	Non-Respiratory Virus Infected (n = 1584)	Univariate OR (95% CI)	P Value
23–27 wk gestational age	699 (37.7)	150 (55.6)	549 (34.6)	2.4 (1.8–3.1)	<.001
Median maternal age, y (IQR)	32 (28–35)	32 (28–36)	32 (28–35)		.4
Median birthweight, g (IQR)	1080 (827–1304)	970 (800–1210)	1100 (830–1300)		<.001
Small for gestational age	209 (11.3)	25 (9.3)	184 (11.6)	0.8 (.5–1.2)	.3
Male sex	960 (51.8)	157 (58.1)	803 (50.7)	1.4 (1.0–1.8)	.02
Histologic chorioamnionitis	630 (34.0)	117 (43.3)	513 (32.5)	1.6 (1.2–2.1)	<.001
5-min Apgar score ≤5	148 (8.0)	29 (10.9)	125 (8.0)	1.4 (.9–2.2)	.1
Vaginal delivery	646 (34.8)	107 (39.6)	539 (34.0)	1.3 (1.0–1.7)	.09
Antenatal steroids	1652 (89.1)	239 (88.8)	1413 (89.5)	0.9 (.6–1.4)	.8
Surfactant	1051 (56.7)	175 (64.8)	876 (55.5)	1.5 (1.1–1.9)	.004
Postnatal steroids	382 (20.6)	94 (34.8)	288 (18.3)	2.4 (1.8–3.1)	<.001
Median duration of oxygen therapy, d (IQR)	2 (1–29)	13.0 (1–61)	1.0 (1–19)		<.001
Median duration of assisted ventilation, d (IQR)	15 (3–47)	43.0 (11–68)	12.0 (3–41)		<.001
Bronchopulmonary dyplasia	372 (20.1)	96 (35.6)	276 (17.5)	2.6 (2.0–3.4)	<.001

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CI, confidence interval; IQR, interquartile range, OR, odds ratio.

Causative Viral Pathogens

RSV (56.8%), PIV (22.2%), influenza (6.0%), and HMPV (6.0%) were the most common viral cause of respiratory infections in this cohort, accounting for 91% of all respiratory viruses detected (Table 2). For infants who developed RVIs predischarge, a significant proportion were due to PIV (36.7%) followed by RSV (30.6%). However, postdischarge, the main causative pathogen of community-acquired laboratory-confirmed RVI was RSV (61.4%). Approximately 7.5% (136/1811) of the cohort was readmitted for at least 1 episode of RSV. The rates of influenza infection were low and similar pre- and postdischarge. No viral coinfections were detected in this study.

Gestational Age and Age-Specific RVI Incidence

The overall incidence of RVI was estimated to be 116 per 1000 infant-years for our cohort. Infants born at ≤26 weeks' gestation

Table 2. Distribution of Viral Respiratory Infections

Respiratory Virus	Predischarge (n = 49)	Postdischarge (n = 285)	Frequency (n = 334)
Respiratory syncytial virus	15 (30.6)	175 (61.4)[a]	190 (56.8)
Parainfluenza	18 (36.7)	56 (19.6)[a]	74 (22.2)
Parainfluenza 1	0	10 (3.5)	10 (3.0)
Parainfluenza 2	1 (2.0)	2 (0.7)	3 (0.9)
Parainfluenza 3	16 (32.7)	44 (15.4)[a]	60 (18.0)
Parainfluenza 4	1 (2.0)	0	1 (0.3)
Influenza	3 (6.1)	17 (6.0)	20 (6.0)
Human metapneumovirus	3 (6.1)	17 (6.0)	20 (6.0)
Rhinovirus	5 (10.2)	7 (2.5)	12 (3.6)
Adenovirus	2 (4.1)	8 (2.8)	10 (3.0)
Bocavirus	1 (2.0)	3 (1.1)	4 (1.2)
Enterovirus	2 (4.1)	1 (0.3)	3 (0.9)
Coronavirus	0	1 (0.3)	1 (0.3)

Data are presented as No. (%) unless otherwise indicated.

[a] P < .05.

had the highest incidence of any RVI (214 per 1000 infant-years); the incidence for 27–29 weeks and 30–32 weeks was 128 and 54 per 1000 infant-years, respectively. Predischarge, the incidence of any RVI was similar for the 2 groups <30 weeks' gestation (Figure 1). Incidence of RSV was highest in those ≤26 weeks (65 per 1000 infant-years) and PIV incidence was highest in those 27–29 weeks (37 per 1000 infant-years). Postdischarge, infants ≤26 weeks had the highest incidence of any RVI, RSV, and PIV.

The median chronologic age of infection for all RVIs was 8.9 months (interquartile range, 9.9). Overall incidence of any RVI was highest in the 3 to <6 months age period (200 per 1000 infant-years). Predischarge, there were 11 RSV infections, of which 10 occurred in infants <6 months. Similarly, there were 18 PIV infections, of which 16 occurred in infants <6 months. Postdischarge, infants were at highest risk of RVI hospitalization when 3 to <6 months old (153.2 per 1000 infant-years) (Figure 2). The peak incidence for RSV hospitalization was 3 to <6 months old (93.1 per 1000 infant-years) followed closely by <3 months old (75.9 per 1000 infant-years) and 6 months to <1 year (60.1 per 1000 infant-years). Of note, none of those who received palivizumab after discharge were positive for RSV during the study period.

Clinical Risk Factors

There were no significant differences when comparing the baseline characteristics of infants with RVIs before initial discharge (n = 32) and those who were infected postdischarge (n = 238). Infants infected predischarge had a higher median duration of oxygen therapy (33 days vs 4 days; P < .05) and higher median duration of assisted ventilation (59 days vs 37 days; P < .05).

Based on univariate analysis, clinical risk factors associated with RVIs in our study included gestational age 23–27 weeks, lower birth weight, male sex, presence of histologic
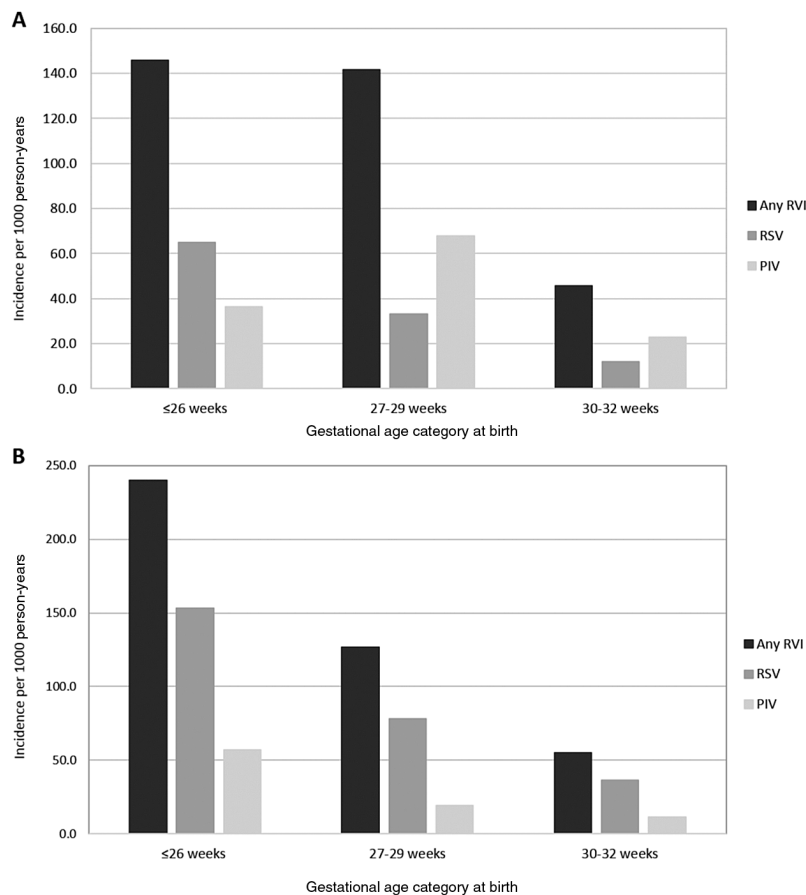
Figure 1. Gestational age-specific incidence of laboratory-confirmed respiratory viral infection (RVI), respiratory syncytial virus (RSV) infection, and parainfluenza virus (PIV) infection predischarge (*A*) and postdischarge (*B*) in preterm infants up to 2 years of age.

chorioamnionitis, vaginal delivery, surfactant usage, postnatal steroid treatment, longer duration of oxygen therapy, longer duration of assisted ventilation, and history of BPD (Table 2). After multivariable adjustment, risk factors that remained significant were gestational age 23–27 weeks (aOR, 1.7; 95% CI, 1.2–2.3), postnatal steroid treatment (aOR, 1.5; 95% CI, 1.0–2.1), and diagnosis of BPD (aOR, 1.7; 95% CI, 1.2–2.4) (Table 3).

DISCUSSION

In this single-center cohort study of preterm infants ≤32 weeks' gestation, 14.5% had acquired at least 1 laboratory-confirmed RVI within the first 2 years of life, representing an overall incidence of 116 per 1000 infant-years. Approximately 1.7% acquired an RVI predischarge, with PIV (36.7%) and RSV (30.6%) the main causative pathogens in-hospital. The majority of RVIs (12.8%) occurred postdischarge, with 61.4% attributable to RSV. Preterm infants in the community were at highest risk of RSV infection requiring hospitalization at 3 to <6 months old with incidence remaining high up to 1 year of age. Risk factors significantly associated with RVI were extremely low gestational age (≤27 weeks), treatment with postnatal steroids, and diagnosis of BPD.

The 14.5% RVI proportion in our cohort is similar to that reported elsewhere [14, 21]. However, most studies did not include respiratory viruses beyond RSV and the majority did not report beyond the first few months of life. The proportion of RVIs in our inpatient predischarge setting of 1.7% was much lower than the 4%–52% incidence reported in other NICU studies [6, 15, 22]. The higher incidence in previous studies is likely due to the differences in study design, where these studies performed periodic surveillance testing for RVI. Our study included only symptomatic infants with an RVI during their admission. This approach may have missed infants with mild symptoms or who were asymptomatic. Furthermore, differences in testing methodology such as primary usage of multiplex PCR may account for the differences in incidence. Our lower RVI rate could also possibly be attributable to the strict enforcement of infection control policies in our department, which are similar to those in published infection prevention guidelines [17, 23]. Even so, guidelines specific to the neonatal setting is lacking and the effectiveness of most interventions has not been systematically studied. Differences in testing strategy and laboratory methodology also likely accounted for the lack of viral codetection in our study, which has been reported in other pediatric studies [4, 6, 24].
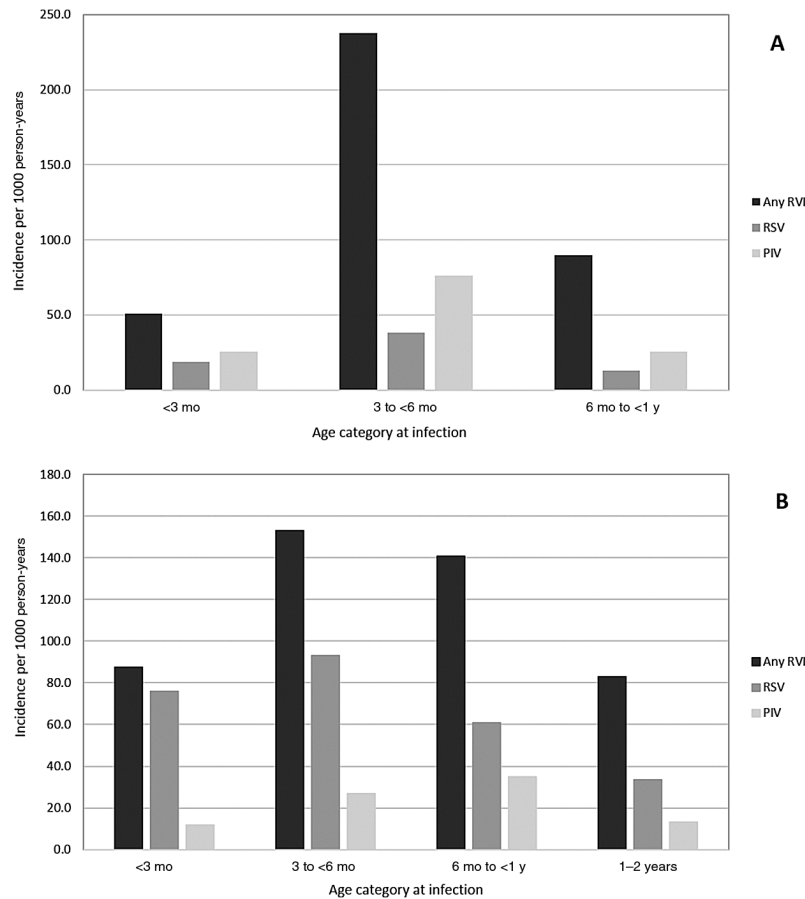
Figure 2. Age-specific incidence of laboratory-confirmed respiratory viral infection (RVI), respiratory syncytial virus (RSV) infection, and parainfluenza virus (PIV) infection predischarge (*A*) and postdischarge (*B*) among preterm infants up to 2 years of age.

Most surveillance studies reporting virus codetection primarily utilized sensitive PCR techniques [25, 26], compared with our 11% respiratory virus detection via PCR.

There is a dearth of data on the epidemiology and burden of RVI in the tropics and we were unable to identify any long-term studies of preterm infants ≤32 weeks' gestation. Previous studies were conducted in temperate regions with seasonal transmission

Table 3. Multivariate Logistic Regression Model for Clinical Variables Associated With Respiratory Viral Infection in the First 2 Years of Life

Characteristic	Respiratory Virus Infected, No. (%)	aOR (95% CI)	P Value
Gestational age 23–27 wk	699 (37.7)	1.7 (1.2–2.3)	<.01
Small for gestational age	209 (11.3)	0.8 (.5–1.3)	.4
Male sex	960 (51.8)	1.2 (.9–1.6)	.1
Histologic chorioamnionitis	630 (34.1)	1.2 (.9–1.6)	.2
Vaginal delivery	646 (34.8)	1.0 (.7–1.3)	.8
Surfactant usage	1049 (56.8)	0.8 (.6–1.1)	.3
Postnatal steroids	382 (20.7)	1.5 (1.0–2.1)	.03
Bronchopulmonary dysplasia	372 (20.1)	1.7 (1.2–2.4)	<.01

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.

of viruses such as RSV and influenza during winter months. It is difficult to extrapolate data from these studies to the tropics as differences in climatic factors and year-round circulation of RSV are likely to affect transmission patterns and exposure risk among preterm infants in tropical regions. Specifically, studies of RSV from temperate countries have reported a broad range of RSV hospitalization rates, from 2% to 19% in preterm infants [27–32]. We found that 7.5% of our preterm infants were hospitalized for RSV in our tropical setting.

Viruses such as PIV, influenza, and HMPV were important contributors to infection and rehospitalization of our preterm infants, accounting for 30% of diagnosed RVIs. This concurs with previous observations of PIV and HMPV as important pathogens in this population [11, 12, 14, 33]. Specifically, apart from RSV, we noted PIV and rhinovirus to be common in the predischarge period, accounting for up to 45% of all RVIs [8]. There is limited information on the incidence and morbidity of PIV infections in preterm infants, with most reports coming from outbreaks. PIV infections can result in lower respiratory tract infections with significant morbidity [34, 35]. However, in comparison to RSV, symptoms of PIV were reportedly less severe, with less hypoxia and less need for intensive care [12].

Data on burden and age-specific distribution of RSV will be critical in informing RSV immunization public health policy and prioritization of research. Our high RSV infection incidence in the <6-month age groups highlights the substantial burden and risk of RSV for preterm infants <33 weeks in the tropics. The most advanced RSV vaccine has just entered a phase 3 trial and started recruitment to assess the effectiveness of maternal immunization to protect infants [36]. Unfortunately, a maternal immunization strategy is unlikely to benefit very preterm babies as transplacental transfer of antibodies mainly occurs around 34 weeks' gestation. There is an urgent need to develop RSV vaccines that are immunogenic and safe for very preterm infants to be administered soon after delivery.

From August 2012 onward, palivizumab was available to eligible infants in our setting according to established guidelines [37]. However, due to the high cost, uptake was only about 15% of eligible infants during the study period. Although none of those who received palivizumab developed RSV, we are unable to make any conclusions regarding its effectiveness as our study was not designed to address this question. Recent progress in monoclonal antibodies with extended half-life (up to 5 months) could significantly improve current RSV immunoprophylaxis strategy [38]. Importantly, it could help meet the need for year-round protection of preterm infants in the tropics. Protection beyond 6 months of age may be useful in view of our finding of high RSV incidence from 6 months to 1 year.

We identified that infants who were born at ≤27 weeks' gestation, treated with postnatal steroids, and/or have BPD were at increased risk of developing RVI within the first 2 years of life [5, 6]. The association of postnatal steroid treatment and RVI has not been previously described and is likely an indicator of severe underlying lung disease related to prematurity. For our analysis, we only included perinatal and predischarge factors and were unable to analyze the contribution of social and environmental factors that may lead to RVIs postdischarge [9]. Unlike other studies, we did not find sex, chorioamnionitis, or SGA status to be significant risks for RVI in our cohort [39, 40]. While we did find a higher proportion of infants with RVIs having placental chorioamnionitis, this was not significant in the regression analysis. This is in contrast to the recent findings of increased risk of lower respiratory tract infection in infants with histologic chorioamnionitis [40].

The incidence of RVIs in our study is likely an underestimation of the true burden of RVIs in the preterm population as we only included admitted, symptomatic infants who tested positive for a respiratory virus. Our study did not investigate the burden of RVI among nonhospitalized infants in the community. RVI testing based on symptomatology and potential exposures is likely to miss asymptomatic or mildly symptomatic infants. Preterm infants with RVI may present with apnea, and classical symptoms such as fever, cough, and runny nose may not be present. This study also excludes episodes of care sought at other medical facilities. However, we believe our cohort's capture population to be fairly comprehensive due to multiple factors. First, parents are likely to return to the same hospital due to the complex care required of preterm infants, especially for 1–2 years postdischarge and for illnesses requiring hospital admission. Second, a healthcare relationship results from long stays in the NICU and subsequent long-term follow-up postdischarge. Available outpatient service audit data for infants <1250 g show that >80% return for routine neurodevelopmental assessment in our clinics at 2 years of age. Finally, Singapore's small size (approximately 719 km^2) and excellent transport links across the island make it convenient to return to KKH to seek medical care.

CONCLUSIONS

We present data of RVI from a long-term retrospective cohort of preterm infants <33 weeks' gestation from the tropics. The burden of RVI in preterm infants in the tropics was high with 14.5% having had a laboratory-confirmed infection before 2 years of age. Predischarge, RSV and PIV were the main respiratory viruses detected. Postdischarge in the community, RSV was a key causative pathogen, with incidence of infection remaining substantial up to 1 year of age. Risk factors significantly associated with RVI in preterm infants were extremely low gestational age (≤27 weeks), treatment with postnatal steroids, and diagnosis of BPD.

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