

High burden of respiratory viral infection-associated mortality among critically ill children

Dear Editor,

Acute lower respiratory infections (ALRIs) are a leading cause of under-5 mortality globally—two-thirds could be attributable to respiratory viral infections (RVIs).^{1,2} The burden of paediatric RVIs in settings of tropical climate with year-long virus circulation is relatively underreported.^{3,4} Previous studies in these areas have estimated that around 8–11% of RVI-associated ALRI admission required intensive care.^{5,6}

In this study, we describe the burden and epidemiology of RVI-associated mortalities among critically ill patients admitted to a paediatric intensive care unit (PICU) in Singapore.

We conducted a retrospective single-centre cohort study of children ≤ 18 years admitted to a 16-bedded PICU from 1 January 2010 to 31 December 2019. RVI-associated mortality was defined as any PICU mortality occurring with laboratory-confirmed RVI within 14 days prior to the certified date of mortality. Each case was reviewed and verified individually, to confirm that an RVI was either the primary cause or a significant contributor to the mortality as recorded by the clinical team in medical charts. The study team was blinded to all causes of death information at the time of data matching. Nosocomial RVI was defined as an infection with positive viral testing >72 hours of hospital admission. Pre-existing patient comorbidities were classified as complex chronic conditions (CCC) or non-complex chronic conditions (NCCC), to gauge the severity of individual comorbidities.⁷

RVI detection was by direct fluorescent antibody and/or polymerase chain reaction at the discretion of the admitting physician. The RVI-associated mortality rate (per 1,000 admissions) was calculated thus:

$$\frac{\text{no. of PICU RVI-associated mortality} \times 1000}{\text{total PICU admissions}}$$

Poisson regression was performed to determine the significance of RVI-associated mortality trends over the study period using SAS version 9.4 (SAS Institute Inc, Cary, US). A P value of <0.05 was considered statistically significant. This study received ethical approval from the Singapore Health Services (SingHealth CIRB Ref No. 2019/2686).

Results. A total of 6,101 paediatric patients were admitted to our PICU over the study period, with an

overall PICU mortality rate of 5.6% (339/6,101). Of these, 19.8% (67/339) were determined to have an RVI-associated mortality as per our case definition above (overall rate 11 per 1,000 PICU admissions). RVI was a listed cause of death by the clinical team in 59 of the 67 (88.1%) patients. The other 8 cases had an RVI diagnosed around the time of respiratory support escalation, increased inotropic support or deterioration of their overall clinical course. The RVI-associated mortality rate increased significantly from 9.4 to 15.2 over the study period (F-test $P=0.03$) (Supplementary Fig. S1 in online Supplementary Material). Children with RVI-associated mortality had a median age of 3.5 years (interquartile range [IQR] 0.5–8), with 45/67 (67.1%) being <5 years. The median interval between RVI detection and mortality was 5 days (IQR 2–8), and the median length of hospital stay prior to death was 8 days (IQR 3–15).

Fifty-five (82.1%) of the 67 patients with RVI-associated mortality required mechanical ventilation during admission (Table 1). Forty (59.7%) patients had pre-existing comorbidities and 9 (13.4%) were palliative care patients. Of patients with pre-existing comorbidities, 39 had CCCs, under these most common categories: neuromuscular (30.6%), respiratory (20.8%), oncologic (12.5%) and cardiovascular (12.5%). A total of 23/67 (34.3%) patients were born preterm (mean birth gestation 29 weeks): 8/23 (34.8%) had chronic lung disease and 4/23 (17.4%) had cerebral palsy.

The primary documented causes of death among the patients were: infection ($n=53$, 79.1%), cardiovascular ($n=6$, 9.0%), oncologic ($n=3$, 4.5%), respiratory ($n=2$, 3.0%), neuromuscular ($n=2$, 3.0%) and gastrointestinal ($n=1$, 1.5%). Among the 53 patients with infection as a primary cause of death, 7 (13.2%) had a bacterial infection and positive blood culture within 3 days of the RVI diagnosis. The positive bacterial cultures included *Pseudomonas aeruginosa* ($n=3$), *Streptococcus pneumoniae* ($n=1$), *Staphylococcus aureus* ($n=1$), *Klebsiella pneumoniae* ($n=1$) and *Mycobacterium bovis* ($n=1$).

Influenza (22.7%), adenovirus (17.3%), respiratory syncytial virus (RSV) (16.0%) and rhinovirus (16.0%), accounted for 72.0% of all RVIs detected. Eight patients (11.9%) had virus coinfection, with rhinovirus ($n=6$, 37.5%) and bocavirus ($n=3$, 18.8%) the most common viruses isolated in these cases. Twenty-one

Table 1. Characteristics of patients with respiratory viral infection-associated mortalities

Characteristics	No. (%) N=67
Male sex	38 (56.7)
Preterm birth (<37 weeks gestation)	23 (34.3)
Age at time of infection	
≤30 days	1 (1.5)
30 days – 1 year	23 (34.3)
2–5 years	21 (31.3)
6–10 years	10 (14.9)
11–18 years	12 (17.9)
Mechanical ventilation during admission	55 (82.1)
Presence of pre-existing comorbidities	40 (59.7)
1 condition	11 (16.4)
2 conditions	10 (14.9)
>2 conditions	19 (28.4)
Palliative care	9 (13.4)
Nosocomial infection	21 (31.3)
Types of complex chronic condition	22 (30.6)
Neuromuscular	15 (20.8)
Respiratory	9 (12.5)
Cardiovascular	9 (12.5)
Oncologic	8 (11.1)
Genetic	5 (6.9)
Gastrointestinal	1 (1.4)
Metabolic	1 (1.4)
Immunologic	1 (1.4)
Haematologic	1 (1.4)
Endocrinology	

patients (31.3%) had nosocomial RVI, predominantly with adenovirus (33.3%), RSV (19.0%) and rhinovirus (19.0%). When stratified by the most common infecting RVI pathogen, the median age of infection was: influenza (6 years, IQR 3–12), adenovirus (4.5 years, IQR 2–9), RSV (0.9 year, IQR 0.5–3) and rhinovirus (2 years, IQR 1–6). Among those who were born premature (n=23), the most common RVI pathogens were influenza (n=6, 26.1%), adenovirus (n=6, 26.1%) and RSV (n=4, 17.4%).

Discussion. The burden of RVI-associated mortality among critically ill children in our setting was high, accounting for up to 20% of all PICU mortality. A significant proportion of these patients were born preterm (34.3%) and had comorbid conditions (60.0%). The overall PICU RVI-associated mortality rate of 1.1% in our study is at the lower end of previously reported rates of 0.3–17%.^{5,6,8,9} The predominance of influenza (22.7%), adenovirus (17.3%) and rhinovirus (16.0%) in our cohort differs from previous reports that described a predominance of RSV infections (38–49.0%).^{6,7} Almost all previous reports on the

incidence of RVI-associated mortalities were from facilities located in regions with temperate or subtropical climates. Additionally, differences in viral distribution between studies could be attributed to differences in the study population (exclusion of children with comorbidities), climate³ and vaccination rates.⁷ Although seasonal influenza vaccination is recommended for pregnant mothers and children aged 6–59 months in Singapore, studies have found that the uptake was only about 10% and 15%, respectively.¹⁰ Additionally, the local rates of palivizumab vaccination among eligible preterm infants have been reported to range from 17–39% annually.¹¹

The median age of RVI-associated mortality among children with influenza and RSV in our cohort was 5.7 years and 0.9 year, respectively, which is similar to previous studies.^{6,12} In a study of 49 children in Hong Kong, the reported age of RVI-associated mortality was 5.6 years and 1.2 years for influenza and RSV, respectively.⁶ Neuromuscular conditions were the most prevalent comorbidity seen in this cohort of RVI-associated mortalities. Patients with neuromuscular weakness may have respiratory muscle involvement, resulting in suboptimal pulmonary mechanics and a weaker cough reflex, leading to a higher predisposition to atelectasis, aspiration pneumonia and respiratory failure.

The small sample size, retrospective study design, lack of data on the usage of antiviral medications or vaccinations, and the limited granular clinical details limit the overall generalisability and the ability to delineate the risk factors associated with such mortalities. However, the 10-year duration of this study from the largest PICU in Singapore provides a reasonable estimate of the mortality burden among critically ill children living in a tropical climate with year-long transmission of such viruses. The high RVI burden from RSV and influenza in this population of patients could potentially be mitigated by improved influenza vaccination rates and the effective use of monoclonal antibodies such as palivizumab against RSV.

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