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Aetiology and risks factors associated with the fatal outcomes of childhood pneumonia among hospitalised children in the Philippines from 2008 to 2016: a case series study

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ABSTRACT

Objective Pneumonia remains the leading cause of hospitalisations and deaths among children aged <5 years. Diverse respiratory pathogens cause acute respiratory infections, including pneumonia. Here, we analysed viral and bacterial pathogens and risk factors associated with death of hospitalised children.

Design A 9-year case series study.

Setting Two secondary-care hospitals, one tertiary-care hospital and one research centre in the Philippines.

Participants 5054 children aged <5 years hospitalised with severe pneumonia.

Methods Nasopharyngeal swabs for virus identification, and venous blood samples for bacterial culture were collected. Demographic, clinical data and laboratory findings were collected at admission time. Logistic regression analyses were performed to identify the factors associated with death.

Results Of the enrolled patients, 57% (2876/5054) were males. The case fatality rate was 4.7% (238/5054), showing a decreasing trend during the study period (p<0.001). 55.0% of the patients who died were either moderately or severely underweight. Viruses were detected in 61.0% of the patients, with respiratory syncytial virus (27.0%) and rhinovirus (23.0%) being the most commonly detected viruses. In children aged 2–59 months, the risk factors significantly associated with death included age of 2–5 months, sensorial changes, severe malnutrition, grunting, central cyanosis, decreased breath sounds, tachypnoea, fever (≥38.5°C), saturation of peripheral oxygen <90%, infiltration, consolidation and pleural effusion on chest radiograph. Among the pathogens, adenovirus type 7, seasonal influenza A (H1N1) and positive blood culture for bacteria were significantly associated with death. Similar patterns were observed between the death cases and the aforementioned factors in children aged <2 months.

Conclusion Malnutrition was the most common factor associated with death and addressing this issue may decrease the case fatality rate. In addition, chest radiographic examination and oxygen saturation measurement should be promoted in all hospitalised patients with pneumonia as well as bacteria detection to identify patients who are at risk of death.

Strengths and limitations of this study

- A large sample size of more than 5000 patients studied over a longer duration of 9 years in a lower-middle-income country.
- The study tested almost 100% of nasopharyngeal samples collected from patients for 13 different viruses.
- Oxygen saturation measurement using pulse oximetry was obtained from 99% of all patients enrolled in the study.
- Chest radiographs were available and interpretable from 4452 (88%) patients.
- Limited findings for bacterial culture identification due to lower sampling rate for blood culture among fatal cases.

BACKGROUND

Pneumonia is the most important cause of childhood mortality in children aged <5 years. It is estimated to cause 896 000 deaths of the total 5.6 million deaths in 2016 alone.[1] Most of these deaths occurred in low-income and middle-income countries (LMIC).[2] Integrated Management of Childhood Illness (IMCI), which was developed by the WHO and UNICEF, has been widely used for the better management of common childhood illnesses, including pneumonia in LMIC. Bacteria are considered to be an important aetiology of childhood pneumonia, and the detection of bacterial pathogens has been associated with deaths.[3 4] Vaccination programmes for

bacterial pathogens[5 6] have also been introduced to reduce the negative impact of childhood pneumonia in several LMIC, including vaccines against *Haemophilus influenzae* type b and *Streptococcus pneumoniae*.[7 8] These vaccines have contributed to the reduction of morality from childhood pneumonia.[1 9 10] Viruses are commonly identified from children with acute lower respiratory infection (ALRI), including pneumonia. At least 26 viruses are known to cause childhood pneumonia,[11] and respiratory syncytial virus (RSV) is one of these common viruses detected from children with ALRI. The most recent estimates on the global burden of RSV indicate that 33.1 million episodes of RSV-associated ALRI with 59 600 in-hospital deaths among children of age <5 years in 2015.[12] Influenza virus (IFV) infection has also been shown to have a significant impact on children worldwide, with an estimated 28 000–111 500 deaths in children aged <5 years.[13] Other common viruses identified from ALRI include rhinovirus (RV), human metapneumovirus (HMPV), parainfluenza virus (PIV) and adenovirus (ADV).[14–16] More recently, enterovirus D68 (EV-D68) was found to be associated with ALRI.[17] However, the impact of these viral infections on childhood pneumonia mortality remains to be adequately characterised.

Some risk factors and clinical signs, including nutritional status,[2 18 19] low birth weight,[20] hypoxia, cyanosis and grunting,[21 22] and radiological findings,[23] are well described as the predictors of death in childhood pneumonia. Nonetheless, further reduction of mortality due to childhood pneumonia requires a better understanding of the association between death and viral infections and requires an update of all factors associated with death in general. The present study aimed to define the aetiological, demographic and environmental factors and clinical findings associated with mortality due to childhood pneumonia among hospitalised children in the Philippines.

METHODS

Study sites

The present study was conducted across four hospitals in the Philippines which include the Biliran Provincial Hospital (BPH), Eastern Visayas Regional Medical Center (EVRMC), Ospital ng Palawan (ONP) and Research Institute for Tropical Medicine (RITM). BPH is the only hospital in Biliran Island with 50 paediatric beds and four emergency rooms. EVRMC is a tertiary-care government hospital for the Eastern Visayas Region with a 250-bed capacity including 50 paediatric beds. ONP is a secondary referral government hospital in Palawan Island with 40 beds in the paediatric department and 10 beds in the intensive care unit. RITM is a specialised tertiary-care hospital in Metro Manila with 50 beds. In the Philippines, tertiary hospitals are referral facilities for patients needing tertiary care, such as intensive and emergency care, mechanical ventilation and major surgeries. Secondary hospitals are for patients who need hospitalisation for simple cases, such as fever, diarrhoea and pneumonia not requiring emergency care. The study periods varied among the hospitals, with that for BPH from September 2012 to March 2016, for EVRMC from June 2008 to January 2015, for ONP from August 2012 to February 2015 and for RITM from September 2012 to January 2015.

Study design

This was a case series study of hospitalised children with pneumonia in the Philippines evaluating associated risk factors for fatal outcome.

Study patients

Children aged 8 days to <5 years who were hospitalised in the above mentioned medical facilities with acute respiratory symptoms were assessed using the IMCI algorithm by trained study physicians.[6] Patients who were assessed to have severe pneumonia or very severe pneumonia by the IMCI algorithm were enrolled in the study. In 2014, the IMCI algorithm for acute respiratory infection was revised,[24] and children with chest indrawing are no longer diagnosed as severe pneumonia cases and are not required to be hospitalised. However, this new algorithm was not widely implemented in the Philippines during the study period, and we continued to recruit patients with chest indrawing and those with danger signs based on the previous IMCI algorithm. Exclusion criteria included children aged less than 8 days old or 5 years or more, children admitted for another illness and who had developed symptoms of pneumonia during hospitalisation, children who had been admitted to another hospital within the last 3 days prior to the present admission and children who had prior hospital admission without 1-week symptom-free period when readmitted to the hospital.

Patient outcomes were grouped into two categories: survived and died. The survived group comprised patients who were discharged, including those discharged against medical advice (DAMA) but with improved conditions. The died group comprised patients with pneumonia who died during the hospitalisation period or were DAMA with a deteriorated condition at their last clinical assessment. We assumed that all DAMA patients with a deteriorated condition were likely to die based on a previous study in the Philippines.[3]

Congenital abnormalities included congenital heart disease, trisomy 21 syndrome, cerebral palsy or other neurodevelopmental conditions and inherited haemolytic anaemia. Tachypnoea was defined as follows: respiratory rate (RR) ≥60 breaths/min in children <2 months, RR ≥50 breaths per min in children aged 2–11 months and RR ≥40 breaths/min in children aged ≥12 months. Tachycardia was defined as heart rate ≥180 beats/min (bpm) for children aged <12 months and ≥140 bpm for children aged ≥12 months. The WHO child growth standards were used to evaluate the nutritional status of children by computing the Z-scores of weight-for-age and height-for-age.[25] Saturation of peripheral oxygen (SpO_2) was measured on admission by using a pulse oximeter

(Handheld Pulse Oximeter PalmSAT 2500A with Finger Clip Sensor [Paediatrics], Nonin Medical). Venous blood samples were also collected. The haemoglobin level of <80 g/L was classified as severe anaemia.

Collection of patient information

A standardised questionnaire was used to collect the sociodemographic and environmental data of households for children recruited only from February 2014 to March 2016. A Simple Poverty Scorecard for the Philippines, developed by Mark Schreiner,[26] was used to assess the socioeconomic status (SES) of the household. This score uses 10 simple questions (the number of children per household; school attendance of the children; female head's education level; employment salary; material of the house's roof and walls; the type of toilet facility; and possession of a refrigerator, television or washing machine) and the scores ranged from 0 to 100. Households with an SES score of <30 were defined as being in extreme poverty. A physical examination was conducted by a trained study physician, which included examination of neck rigidity, sensorial changes, grunting, decreased breath sounds, chest indrawing, rales, central cyanosis and nasal flaring. We considered the following signs as sensorial changes: irritability, drowsiness and stupor. The Glasgow Coma Scale was used for the assessment of coma and impaired consciousness.[27] Glasgow Coma Scale of <9 was considered to indicate severe condition, while the scale of 9–12 was considered to indicate moderate condition.

Assessment of chest X-ray

Anteroposterior and lateral chest radiographs were obtained. The images were interpreted by a designated radiologist trained in the standard interpretation of chest radiographs for the diagnosis of childhood pneumonia, as developed by the WHO Pneumonia Vaccine Trial Investigators' Group.[28] The chest X-ray findings in this study included end-point consolidation; other infiltrate and pleural effusion, and end-point pneumonia was defined as the presence of end-point consolidation or pleural effusion.

Detection of viruses

Nasopharyngeal swabs were obtained from patients and stored at 4°C. The samples were shipped to RITM for processing and virus identification. Viral RNA and DNA were purified using the QIAamp MinElute Virus Spin Kit. Viral RNA was reverse transcribed to complementary DNA by the Moloney murine leukaemia virus reverse transcriptase with random hexamer primers. RSV, HMPV and PIV were detected in the samples by multiplex PCR using two methods. The first method involved detection of RSV and HMPV. The second method involved detection of PIV-1, PIV-2, PIV-3 and PIV-4. The RSV positive samples were further subtyped into RSV-A and RSV-B by performing nested PCR.[29–32] RV and enterovirus (EV) were detected from the clinical samples by targeting 5' non-coding region (NCR). The RV species (A, B, C) and serotypes of EV, including EV-D68, were further identified by sequencing and phylogenetic analysis of 5' NCR. RT-PCR was performed for the detection of IFV A(H1N1) pdm09, IFV A(H3N2) and IFV B.[33] ADV detection was performed by combining viral isolation and neutralisation testing as well as PCR and serotyping by sequencing.[34–36]

Detection of bacteria

Blood drawing for bacterial culture identification was done only when informed consents were obtained from caregivers. One millilitre of venous blood sample was collected from each patient. The method for blood culture identification for bacteria is described elsewhere.[14] We considered the bacterial culture positive if at least one of the following 12 bacteria was identified: *Acinetobacter baumannii, Burkholderia cepacia, Enterobacter aerogenes, H. influenzae, Klebsiella pneumoniae, Staphylococcus aureus, Pseudomonas aeruginosa, P. stutzeri,* other *Pseudomonas species, S. pneumoniae* and *Onchrobactrum anthropi*. Virus-bacteria co-detection was defined positive for at least one virus and one pathogenic bacterium, while virus-virus co-detection was defined as patient with two or more viruses detected. Patients whose samples were negative for any of the target viruses and bacteria were considered negative for all pathogens.

Data analysis

The data were analysed based on two age groups: <2 months and 2–59 months, according to the IMCI guidelines.[6 24] To investigate the aetiological and clinical factors associated with fatal outcomes, a generalised linear model was applied. This model was adjusted for the age of the patients, the year of sampling and the hospitals where the patients were admitted. A second model was also applied, wherein the association of death was evaluated in context of the clinical and radiological findings in six separate groups of children, including those positive for RSV, RV, ADV, EV, bacteria in blood and negative for any viruses. The second model was adjusted for the age of the patients, the year of sampling and the hospitals after matching with the age groups. The extent of association with the fatal outcome in both the models was evaluated by calculating the ORs and 95% CI using a simple exact binomial calculation. Fisher exact test was applied to compare the frequencies, and Welch's t-test or Brunner-Munzel test was used to compare the means and medians of variables between the two groups. A p value <0.05 indicated statistical significance. The comparison of case fatality rates (CFR) by the year of examination was performed using the Cochran-Armitage Test for Trend. Missing data were not included in the analysis. All statistical analyses were performed using the Microsoft R Open V.3.2.4 and Dplyr package.[37]

Patient involvement

No patients were directly involved in the development of the research question, selection of the outcome measures,

design and implementation of the study, or interpretation of the results.

RESULTS

From 2008 to 2016, 5128 children were enrolled in the study (online supplementary figure 1). Of these, the outcome data was available for 5054 (98.6%) children; 74 (1.4%) children were excluded from the analysis due to loss to follow-up, unknown outcome or transferred to another hospital. Out of the 5054 patients analysed, 749 (14.8%) were aged <2 months and 4305 (85.2%) were aged 2–59 months.

The CFR was slightly higher in patients aged <2 months than in those aged 2–59 months (5.3% vs 4.6%) and declined as the age of children increased (table 1). Children aged <24 months accounted for 87.0% of all fatal cases and the highest CFR (7%) was observed in patients aged 2–5 months (table 1). Missing data of each parameter in table 1 are reported in online supplementary table 1.

There were more male patients (n=2876, 56.9%) than female patients (n=2178, 43.1%), although there was no significant association between the gender and outcome in both the age groups. A significant decreasing trend of CFR was observed during the 9-year study period, with the highest CFR of 12.5% recorded in 2008 and the lowest CFR of 2.0% recorded in 2013 (p<0.001) (online supplementary table 2). EVRMC showed the highest CFR among the hospitals in both the patient groups (<2 months, 7.8% and 2–59 months, 5.7%). CFRs were lower in BPH (3.2%) and ONP (2.1%). The presence of congenital abnormalities was significantly associated with the fatal outcome for both the age groups (p<0.05). Severe underweight for age (<−3 SD) was observed in 41.2% of the fatal cases in patients <2 months and in 39.2% of fatal cases in patients aged 2–59 months. The history of child loss in the family was significantly more frequent in fatal cases than in the survived group for children 2–59 months (33.3% vs 10.2%, p=0.003). Charcoal and wood were used as the cooking fuels by 86.5% of patient's families; however, no significant association was noted between the type of cooking fuels and outcomes.

Among the findings of physical examination, rales and chest indrawing were the most common signs in both the age groups (table 2). On admission, 19.1% (968/5054) of fatal patients had fever (>38.5°C), and the fever was significantly more frequent in the died group than in the survived group of both age groups. Sensorial changes were recorded in 28.0% of the fatal cases; these changes were significantly more frequent in the died group than in the survived group of both the age groups (p<0.001). Glasgow Coma Scale <9 was also significantly associated with fatal outcome in children aged 2–59 months (p<0.001). The prevalence rate of hypoxaemia was 13.0% (654/5023). Among the respiratory signs, grunting, decreased breath sounds, central cyanosis, apnoeic episode and SpO_2 <90% were more commonly observed in the died group than in the survived group of both the age groups.

The proportion of patients with severe anaemia (<80 g/L) was significantly higher in the died cases of both the age groups (p<0.01), while the mean haemoglobin level was significantly lower only in the patients aged 2–59 months (100.3 vs 110.2 g/L; p<0.001) (table 2). Missing data of each parameter in table 2 are reported in online supplementary table 3.

A total of 4498 children had chest radiographs; of these, 4452 showed interpretable results. At least one abnormal finding was observed in 1711 (38.4%) chest radiographs. Among the died cases, 41.6% patients showed end-point pneumonia, 5% had consolidation, 35% had infiltrations and 3.4% had pleural effusion. These findings were significantly more common in the died cases than in the survived cases, except for pleural effusion in children aged <2 months.

Of the 5054 nasopharyngeal swabs, 61.0% tested positive for at least one virus. RSV was the most common viral pathogen, which was detected in 27.0% (1352/5054), of which 135 (10.0%) reported co-infection with other viruses. Rhinovirus was the second-most common viral pathogen, which was detected in 23.0% (1156/5054) of the cases, of which 173 (17.6%) had dual co-infection infections with other viruses. The RSV positive rate was significantly lower in the died cases of the 2–59 months age group. A similar trend was also observed in patient group aged <2 months; however, the difference was not statistically significant. The positive rates of RSV-A, RSV-B and HMPV were also significantly lower in the died cases than in the survived cases among the patients aged 2–59 months. On the other hand, the positive rate of ADV, specifically for ADV-7, was significantly higher in the died cases than in the survived cases for the patient aged 2–59 months, while the CFRs of ADV and ADV-7 were 10.7% and 24.0%, respectively. The positive rate for EV-D68 was higher in the died cases than in the survived cases, although the difference was not statistically significant (table 3).

A total of 3018 blood samples were cultured for bacterial identification. The overall positivity rate for any pathogenic bacteria in the blood samples was 1.6% (49/3018), and the CFR among the blood culture-positive cases was 18.3% (9/49). The most commonly identified bacterial pathogen was *B. cepacia* (26.5%, n=13), followed by *S. pneumoniae* (22.4%, n=11) and *A. baumannii* (n=5) (table 4). The positive rates for blood culture were significantly higher in the died cases than in the survived cases from both the age groups. Among the died cases from the patient group of 2–59 months, the identified bacteria included *P. aeruginosa* (n=2), *S. pneumoniae* (n=2), methicillin-resistant *Staphylococcus aureus* (n=2), *A. baumannii* (n=1), *B. cepacia* (n=1) and *K. pneumoniae* (n=1), while *A. baumannii* and *K. pneumoniae* were identified in the died cases of age <2 months (table 3).

In the univariate analysis, the demographic, clinical and laboratory findings significantly associated with death

Table 1 Demographic, socioeconomic and environmental characteristics of children hospitalised with severe pneumonia, stratified by age group and outcome

	Children aged <2 months				Children aged 2–59 months			
	Survived	Died	CFR	P value	Survived	Died	CRF	P value
	n=709	n=40	5.3		n=4107	n=198	4.6	
Age group								
Less than 1 month	286 (40.3)	17 (42.5)	5.6	0.860				<0.001
1 month	423 (59.7)	23 (57.5)	5.2					
2–5 months					1011 (25.2)	76 (38.4)	7.0	
6–11 months					1064 (25.9)	50 (25.3)	4.5	
12–35 months					1677 (40.8)	59 (29.8)	3.4	
36–59 months					355 (8.6)	13 (6.7)	3.5	
Gender								
Female	285 (40.2)	17 (42.5)	5.6	0.900	1786 (43.5)	90 (45.5)	4.8	0.490
Male	424 (59.8)	23 (57.5)	5.1		2321 (56.5)	108 (54.5)	4.5	
Hospital admitted								
BPH	215 (30.3)	3 (7.5)	1.4	<0.001	795 (19.4)	26 (13.1)	3.2	<0.001
EVRMC	380 (53.6)	32 (80.0)	7.8		2429 (59.1)	148 (74.7)	5.7	
ONP	88 (12.4)	4 (10.0)	4.3		712 (17.3)	15 (7.6)	2.1	
RITM	26 (3.7)	1 (2.5)	3.7		171 (4.2)	9 (4.6)	5.0	
Congenital abnormalities								
Yes	8 (1.1)	3 (2.5)	27.3	0.010	33 (0.8)	9 (4.6)	6.2	<0.001
No	691 (98.9)	37 (92.5)			4035 (99.2)	187 (95.4)		
Height(h)-for-age								
−2 SD≤h≤2 SD	251 (59.1)	5 (45.5)	2.0	0.350	1213 (53.9)	33 (48.5)	2.6	0.320
−3 SD≤h<−2 SD	63 (14.8)	1 (9.1)	1.6		397 (17.6)	10 (14.7)	2.5	
h<−3 SD	111 (26.1)	5 (45.5)	4.3		642 (28.5)	25 (36.8)	3.7	
Weight(w)-for-age								
−2 SD≤w≤2 SD	511 (78.7)	15 (44.1)	2.9	<0.001	2424 (61.2)	82 (43.3)	3.3	<0.001
−3 SD≤w<−2 SD	86 (13.3)	5 (14.7)	5.5		764 (19.3)	36 (18.6)	4.5	
w<−3 SD	52 (8.0)	14 (41.2)	21.2		776 (19.6)	76 (39.2)	8.9	
Duration of hospitalisation	8 (6–9)	3.5 (1–8.2)		<0.001	4 (3–6)	1 (−3)		<0.001
Environmental factors*								
	n=184	n=4			n=904	n=23		
SES								

Continued

Table 1 Continued

	Children aged <2 months				Children aged 2–59 months			
	Survived	Died	CFR	P value	Survived	Died	CRF	P value
≤30	83 (46.1)	3 (75.0)	3.5	0.560	504 (55.8)	15 (65.2)	2.9	0.490
>30	97 (53.9)	1 (25.0)	1.0		400 (44.2)	8 (34.4)	2.0	
Past experience of child loss								
Yes	15 (11.4)	0 (0.0)	0.0	1.000	71 (10.2)	7 (33.3)	9.0	0.003
No	117 (88.6)	2 (5.0)	1.7		626 (89.8)	14 (66.7)	2.2	
Number of siblings								
<2	55 (29.7)	2 (50.0)	3.5	0.420	199 (22.1)	3 (13.5)	1.5	0.050
2–3	78 (42.2)	2 (50.0)	2.5		441 (48.9)	8 (34.8)	1.8	
≥4	52 (28.1)	0 (0.0)	0.0		262 (29.0)	12 (52.2)	4.4	
Types of cooking fuel used								
Electricity, petroleum gas and kerosene	26 (14.1)	0	0.0	0.100	121 (12.8)	2 (8.7)	1.7	0.780
Charcoal and wood	158 (85.9)	4 (100.0)	2.5		775 (86.5)	21 (91.3)	2.6	

n (%) of children unless stated otherwise.
Duration of hospitalisation is presented as median with IQR.
Congenital abnormalities including Down syndrome and congenital heart disease.
*Analysis from February 2014 to March 2016. Past experience of child loss included all causes of death.
BPH, Biliran Provincial Hospital; CFR, case fatality rate (%); EVRMC, Eastern Visayas Regional Medical Center; ONP, Ospital Ng Palawan; SES, socioeconomic status.

Table 2 Clinical and laboratory findings of children hospitalised with severe pneumonia, stratified by age group and outcome

	Children aged <2 months				Children aged 2–59 months			
	Survived n=709	Died n=40	CFR 5.3	P value	Survived n=4107	Died n=198	CFR 4.6	P value
Clinical findings								
Neck rigidity								
Yes	2 (0.4)	0 (0.0)	0.0	1.000	6 (0.1)	2 (2.7)	25.0	0.008
No	457 (99.6)	12 (100.0)			2433 (99.9)	71 (97.3)		
Sensorial changes								
Yes	26 (4.1)	10 (26.3)	27.8	<0.001	146 (4.0)	51 (28.8)	25.9	<0.001
No	608 (95.9)	28 (73.7)			3466 (96.0)	126 (71.2)		
Glasgow Coma Scale								
Severe	1 (14.3)	1 (50.0)	50.0	0.140	2 (3.6)	5 (55.6)	71.4	<0.001
Moderate	6 (85.7)	1 (50.0)			54 (96.4)	4 (44.4)		
Grunting								
Yes	4 (0.9)	2 (18.2)	33.3	<0.001	13 (0.5)	6 (8.2)	31.6	<0.001
No	455 (99.1)	9 (81.8)			2427 (99.5)	67 (91.8)		
Yes	15 (2.1)	4 (10.0)	21.1	0.010	81 (2.0)	12 (6.1)	12.9	<0.001
No	694 (97.9)	36 (90.0)			4022 (98.0)	186 (93.9)		
Wheezing								
Yes	91 (12.8)	9 (22.5)	9.0	0.130	1454 (35.4)	84 (42.6)	5.5	0.040
No	618 (87.2)	31 (77.5)			2650 (64.6)	113 (57.4)		
Chest indrawing								
Yes	704 (99.3)	38 (95.0)	5.1	0.050	4080 (99.4)	196 (99.0)	4.6	0.730
No	5 (0.7)	2 (5.0)			23 (0.6)	2 (1.0)		
Rales								
Yes	693 (97.7)	39 (97.5)	5.3	1.000	4083 (99.5)	197 (99.5)	4.6	1.000
No	16 (2.3)	1 (2.5)			21 (0.5)	1 (0.5)		
Central cyanosis								
Yes	22 (3.1)	8 (20.0)	26.7	<0.001	45 (1.1)	47 (23.9)	51.1	<0.001
No	687 (96.9)	32 (80.0)			4056 (98.9)	150 (76.1)		
Apnoeic episode								
Yes	3 (0.4)	3 (7.5)	50.0	<0.001	2 (0.5)	14 (7.1)	87.5	<0.001
No	706 (99.6)	37 (92.5)			4098 (99.5)	183 (92.9)		

Continued

Table 2 Continued

	Children aged <2 months				Children aged 2–59 months			
	Survived n=709	Died n=40	CFR 5.3	P value	Survived n=4107	Died n=198	CFR 4.6	P value
Nasal flaring								
Yes	183 (39.9)	8 (66.7)	4.2	0.110	996 (40.8)	39 (53.4)	3.8	0.040
No	276 (60.1)	4 (33.3)			1444 (59.2)	34 (46.6)		
Tachypnoea								
Yes	594 (84.4)	35 (92.1)	5.6	0.250	3428 (83.8)	169 (91.4)	4.7	<0.001
No	110 (15.6)	3 (7.9)			663 (16.2)	16 (8.6)		
SpO_2 <90%								
Yes	75 (10.7)	14 (35.0)	15.7	<0.001	494 (12.1)	71 (36.0)	12.6	0.005
No	629 (89.3)	26 (65.0)			3588 (87.9)	126 (64.0)		
Tachycardia								
Yes	61 (8.7)	4 (10.3)	6.2	0.770	1373 (33.8)	69 (35.6)	4.8	0.640
No	640 (91.3)	35 (89.7)			2691 (66.2)	125 (64.4)		
Fever >38.5°C								
Yes	23 (3.2)	11 (27.5)	32.4	<0.001	862 (21.0)	72 (36.4)	7.7	<0.001
No	686 (96.8)	29 (72.5)			3245 (79.0)	126 (63.6)		
Chest radiographs findings								
End-point pneumonia								
Yes	40 (5.6)	11 (27.5)	15.5	<0.001	1155 (31.7)	81 (50.9)	6.6	<0.001
No	669 (94.4)	29 (72.5)			2493 (68.3)	72 (47.1)		
Consolidations								
Yes	40 (6.5)	11 (31.4)	21.6	<0.001	366 (9.9)	49 (32.0)	11.8	<0.001
No	572 (93.5)	24 (68.6)			3286 (90.1)	104 (68.0)		
Infiltrations								
Yes	120 (19.6)	13 (37.1)	9.8	0.020	1301 (35.6)	70 (45.8)	5.1	0.010
No	493 (80.4)	22 (62.9)			2351 (64.4)	83 (54.2)		
Pleural effusions								
Yes	1 (0.2)	1 (2.9)	50.0	0.100	25 (0.7)	7 (4.6)	21.9	<0.001
No	612 (99.8)	34 (97.1)			3630 (99.3)	146 (95.4)		
Chest X-ray								
Negative	473 (77.3)	14 (40.0)	2.9	<0.001	2159 (59.2)	58 (37.9)	2.6	0.001

Continued

Table 2 Continued

	Children aged <2 months				Children aged 2–59 months			
	Survived n=709	Died n=40	CFR 5.3	P value	Survived n=4107	Died n=198	CFR 4.6	P value
Positive	139 (22.7)	21 (60.0)	13.1		1490 (40.8)	95 (62.1)	6.0	
Complete blood counts results								
Haematocrit (%)	36.0 (7.7)	38.0 (7.8)		0.430	34.0 (4.6)	31.0 (5.9)		<0.001
Haemoglobin (g/L)	120.0 (25.0)	123.0 (27.0)		0.400	112.0(15.0)	103.0 (19.0)		<0.001
WBC count (10^9/L)	11.1 (6.5)	15.3 (14.6)		0.04	12.2 (6.2)	13.1 (11.2)		0.004
Neutrophils (10^9/L)	4.4 (2.7)	10.3 (9.1)		0.06	7.17 (4.9)	9.86 (8.8)		0.010
Platelets (10^9/L)	358 (140)	280 (141)		0.08	362 (160)	365 (196)		0.850
Severe anaemia <80 g/L								
Yes	4 (0.6)	2 (5.6)	33.3	<0.010	93 (2.4)	18 (9.7)	51.8	<0.001
No	666 (99.4)	34 (94.4)			3810 (97.6)	168 (90.3)		

n (%) of children unless stated otherwise.
Rate of each parameter was calculated without the missing values.
Anaemia was defined when haemoglobin was <80 g/L. Wheeze: wheeze on stethoscope.
In complete blood counts results, mean (SD) were presented.
CFR, case fatality rate (%); SD, SD in each standardised units; SpO_2, saturation of peripheral oxygen; WBC, white blood cells.

Table 3 Detection and outcome associations of pathogens in hospitalised children with pneumonia, stratified by age group

	Children aged <2 months						Children aged 2–59 months					
	Survived	Died		CFR	OR	AOR		Died		CFR	OR	AOR
	(%)	(%)	P value	(%)	(95% CI)	(95% CI)	Survived (%)	(%)	P value	(%)	(95% CI)	(95% CI)
Pathogens	(n=709)	(n=40)					(n=4107)	(n=198)				
RSV	190 (26.9)	6 (15.0)	0.070	3.1	0.48 (0.18 to 1.08)	0.47 (0.17 to 1.07)	1002 (24.4)	19 (9.6)	<0.001	1.9	0.33 (0.2 to 0.52)	0.31 (0.19 to 0.5)
RSV–A	105 (14.9)	5 (12.5)	0.860	4.5	0.82 (0.28 to 1.96)	0.62 (0.2 to 1.53)	576 (14.0)	10 (5.1)	<0.001	1.7	0.33 (0.16 to 0.59)	0.28 (0.13 to 0.5)
RSVB	69 (9.8)	1 (2.5)	0.210	1.4	0.24 (0.01 to 1.12)	0.35 (0.02 to 1.69)	365 (8.9)	6 (3.0)	0.006	1.6	0.32 (0.13 to 0.67)	0.37 (0.14 to 0.78)
Untyped RSV	16	0					61	3				
IFV	8 (1.1)	0 (0.0)	1.000	0.0			154 (3.7)	9 (4.5)	0.700	5.5	1.22 (0.57 to 2.3)	1.58 (0.73 to 3.01)
IFV A	5 (0.7)	0 (0.0)	1.000	0.0	–	–	96 (2.3)	6 (3.0)	0.690	5.9	1.31 (0.5 to 2.77)	1.63 (0.62 to 3.53)
IFV A(H1N1) seasonal	1 (0.1)	0 (0.0)	1.000	0.0	–	–	6 (0.1)	4 (2.0)	<0.001	40.0	14.09 (3.58 to 49.74)	6.79 (1.68 to 24.73)
IFV A (H1N1) pdm09	–	–	–	–	–	–	25 (0.6)	0 (0.0)	0.530	0.0		
IFV A(H3N2)	2 (0.3)	0 (0.0)	1.000	0.0	–		54 (1.3)	2 (1.0)	0.960	3.6	0.77 (0.12 to 2.48)	1.39 (0.22 to 4.6)
IFV B	3 (0.4)	0 (0.0)	1.000	0.0	–	–	52 (1.3)	3 (1.5)	1.000	5.5	1.2 (0.29 to 3.29)	1.62 (0.39 to 4.55)
Untyped influenza	0	0					0	0				
RV	167 (23.6)	4 (10.0)	0.070	2.3	0.36 (0.11 to 0.91)	0.35 (0.1 to 0.89)	774 (18.8)	38 (19.2)	0.970	4.7	1.02 (0.7 to 1.45)	0.99 (0.68 to 1.41)
RV–A	73 (10.3)	2 (5.0)	0.410	2.7	0.46 (0.07 to 1.53)	0.33 (0.05 to 1.11)	279 (6.8)	20 (10.1)	0.100	6.7	1.54 (0.93 to 2.43)	1.3 (0.78 to 2.08)
RV–B	15 (2.1)	0 (0.0)	0.720	0.0	–	–	34 (0.8)	5 (2.5)	0.030	12.8	3.1 (1.05 to 7.34)	2.04 (0.68 to 5)
RV–C	52 (7.4)	2 (5.0)	0.800	3.7	0.66 (0.11 to 2.25)	0.71 (0.11 to 2.5)	383 (9.3)	10 (5.1)	0.050	2.5	0.52 (0.25 to 0.93)	0.57 (0.28 to 1.03)
Untyped RV	27	–					78				–	
Enterovirus	10 (1.4)	1 (2.5)	0.490	9.1	1.79 (0.1 to 9.69)	2.85 (0.15 to 18.22)	60 (1.5)	3 (1.5)	1.000	4.8	1.04 (0.25 to 2.83)	1.18 (0.28 to 3.29)
EV–D68	4 (0.6)	1 (2.5)	0.640	20.0	4.51 (0.23 to 31.37)	5.07 (0.23 to 45.75)	39 (0.9)	3 (1.5)	0.670	7.1	1.60 (0.38 to 4.47)	1.67 (0.4 to 4.8)
ADV	3 (0.4)	0 (0.0)	1.000	0.0	4.52 (0.23 to 31.45)	3.03 (0.15 to 23.07)	41 (1.0)	8 (4.0)	<0.001	16.3	4.18 (1.79 to 8.57)	3.95 (1.65 to 8.37)
ADV–7	1 (0.1)	0 (0.0)	1.000	0.0	–	–	19 (0.5)	6 (3.0)	0.020	24.0	10.66 (3.68 to 27.77)	11.44 (3.77 to 31.38)
HMPV	8 (1.1)	2 (5.0)	0.170	20.0	4.6 (0.68 to 19.14)	6.03 (0.83 to 29.1)	161 (3.9)	2 (1.0)	0.050	1.1	0.25 (0.04 to 0.79)	0.3 (0.05 to 0.95)
PIV	13 (1.8)	1 (2.5)	1.000	7.1	1.37 (0.07 to 7.15)	1.67 (0.09 to 9.69)	110 (2.7)	6 (3.0)	0.940	5.2	1.14 (0.44 to 2.4)	1.54 (0.59 to 3.33)
Multiple infections (virus–virus)	37 (5.2)	2 (5.0)	1.000	5.1	0.95 (0.15 to 3.28)	0.87 (0.14 to 3.18)	178 (4.3)	7 (3.5)	0.710	3.8	0.81 (0.34 to 1.62)	0.71 (0.3 to 1.44)
Negative for viruses	271 (38.5)	24 (60.0)	0.007	8.1	2.41 (1.27 to 4.71)	2.5 (1.29 to 4.99)	1627 (38.1)	106 (52.3)	<0.001	6.1	1.14 (0.44 to 2.4)	1.73 (1.29 to 2.32)
Missing cases for testing	2	0					0	0				
Bacteria sample tested	n=447	n=11					n=2465	n=77				
Bacteria	5 (1.1)	2 (18.2)	0.010	28.5	19.64 (2.58 to 106.01)	7.83 (6.39 to 110.45)	35 (1.4)	7 (9.0)	<0.001	16.7	7.02 (2.78 to 15.49)	5.08 (1.8 to 12.78)

Continued

Table 3 Continued

Pathogens	Children aged <2 months						Children aged 2–59 months					
	Survived (%) (n=709)	Died (%) (n=40)	P value	CFR (%)	OR (95% CI)	AOR (95% CI)	Survived (%) (n=4107)	Died (%) (n=198)	P value	CFR (%)	OR (95% CI)	AOR (95% CI)
Negative for all pathogens	163 (36.5)	5 (45.1)	0.810	2.9	0.75 (0.2 to 1.7)	0.75 (0.24 to 1.91)	756 (30.7)	36 (46.7)	0.300	4.5	0.75 (0.24 to 1.91)	0.75 (0.24 to 1.91)
Virus–bacteria co-detection	2 (0.4)	0 (0.0)	1.000	0.0			17 (0.7)	3 (3.9)	0.130	15.0		

Multivariate logistic models were adjusted by age in week, year of sampling and hospitals.
ADV, adenovirus; ADV-7, adenovirus 7; AOR, adjusted OR; CFR, case fatality rate (%); EV-D68, enterovirus D68; HMPV, human metapneumovirus; IFV, influenza virus; RSV, respiratory syncytial virus; PIV, parainfluenza virus; RV, rhinovirus.

in both the age groups included severe underweight (weight-for-age <−3 SD), presence of congenital abnormalities, decreased breath sounds, grunting, sensorial changes, central cyanosis, fever (>38.5°C), SpO_2 <90%, anaemia (<80 g/L), endpoint pneumonia and blood culture positive for bacteria (tables 3 and 4). In addition, past experiences of child loss, tachypnoea and pleural effusion were associated with death in children aged 2–59 months. Infection with RSV (OR: 0.33 [95% CI: 0.2 to 0.52]) and HMPV (OR: 0.25 [95% CI: 0.04 to 0.79]) were negatively associated with death in patients aged 2–59 months (tables 3 and 4). In contrast, ADV (OR: 4.18 [95% CI: 1.79 to 8.57]), particularly ADV-7 (OR: 10.66 [95% CI: 3.68 to 27.77]) was positively associated with death in children aged 2–59 months.

After adjustment for age in months, year of sampling and hospital in the multivariate analysis, the following factors were found to be associated with death in both the age groups: severe underweight, presence of congenital abnormalities, decreased breath sounds, grunting, sensorial changes, central cyanosis, SpO_2 (<90%), fever (>38.5°C), anaemia (<80g/L), consolidation, infiltration, positive blood culture for bacteria (tables 3 and 4). Moreover, past experience of child loss, mild underweight (−3 SD ≤w<−2 SD), tachypnoea, tachycardia, ADV, ADV-7 and seasonal IFV A(H1N1) were found to be associated with death in children aged 2–59 months. In contrast, RSV, HMPV and RV-C infections showed decreased odds of death in children aged 2–59 months (tables 3 and 4).

We explored the factors associated with death for cases that were positive for RSV, RV, ADV, EV and blood culture for bacteria and negative for all viruses (table 5). The presence of fever >38.5°C increased the odds of death in patients infected with RV, ADV, EV and bacteria and in patients who tested negative for viruses. The presence of hypoxaemia increased the odds of death in patients infected with RSV, RV and ADV. The presence of infiltration increased the odds of death in patients infected by RSV, ADV and EV. Interestingly, pleural effusion was associated with death in the group of patients who were tested negative to all viruses.

DISCUSSION

We recorded a significant decrease in the CFR among the patients hospitalised with severe pneumonia during the 9-year study period. We also identified the risk factors associated with the deaths to be age of 2–5 months, sensorial changes, severe malnutrition, grunting, central cyanosis, decreased breath sounds, tachypnoea, wheezing, fever (≥38.5°C), SpO_2 <90%, lung infiltration, consolidation and pleural effusion. Infection with ADV, seasonal influenza A(H1N1) and positive blood culture for bacteria were also found to be associated with mortality.

The overall CFR of children hospitalised with severe pneumonia in the present study was 4.7%; this value is similar to that reported by other LMIC.[18 38 39] We also observed a significant decreasing trend of mortality

Table 4 Factors associated with death among hospitalised children with severe pneumonia, stratified by age group

Factors	Children aged <2 months		Children aged 2–59 months	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Age group				
Less than 1 month	Ref.	Ref.	–	–
1 month	0.93 (0.6 to 1.5)	0.9 (0.57 to 1.44)	–	–
2–5 months	–	–	1.73 (1.17 to 2.69)	1.77 (1.19 to 2.75)
6–11 months	–	–	1.29 (0.89 to 1.82)	1.29 (0.89 to 1.82)
12–35 months	–	–	0.97 (0.72 to 1.3)	0.96 (0.72 to 1.29)
36–59 months	–	–	Ref	Ref
Past experience of child loss	NA	NA	4.9 (1.83 to 11.87)	5.42 (1.99 to 13.51)
Weight(w)–for-age				
−2 SD≤w≤2 SD	Ref.	Ref.	Ref	Ref
−3 SD≤w<−2 SD	1.98 (0.63 to 5.25)	1.98 (0.62 to 5.33)	1.41 (0.93 to 2.1)	1.58 (1.04 to 2.35)
w<−3 SD	9.15 (4.15 to 20.12)	9.59 (4.22 to 21.88)	2.93 (2.12 to 4.05)	3.22 (2.3 to 4.51)
Presence of congenital abnormalities	7.0 (1.49 to 25.35)	1.96 (0.08 to 2.43)	5.88 (2.62 to 11.97)	3.12 (1.08 to 8.62)
Decreased breath sounds	5.14 (1.41 to 15.03)	9.81 (2.11 to 46.49)	3.2 (1.64 to 5.76)	5.36 (2.6 to 10.38)
Grunting	25.28 (3.22 to 148.64)	28.65 (2.89 to 259.6)	16.72 (5.73 to 43.71)	14.27 (4.64 to 39.86)
Sensorial changes	1.59 (1.01 to 3.3)	1.79 (1.13 to 3.22)	9.61 (6.63 to 13.78)	8.31 (5.68 to 12.0)
Glasgow Coma Scale <9	6.0 (0.15 to 321.95)	–	45.0 (6.92 to 437.72)	–
Central cyanosis	7.81 (3.07 to 18.33)	6.49 (2.50 to 15.63)	28.24 (18.19 to 43.95)	27.58 (17.55 to 43.5)
Tachypnoea	1.20 (0.35 to 3.13)	2.03 (0.7 to 8.6)	2.04 (1.25 to 3.57)	1.89 (1.15 to 3.34)
Tachycardia	2.16 (0.76 to 9.07)	2.03 (0.56 to 5.84)	1.08 (0.8 to 1.46)	2.09 (1.42 to 3.07)
SpO_2 <90%	4.52 (2.21 to 8.91)	4.69 (2.23 to 9.56)	4.09 (3.0 to 5.54)	5.06 (3.67 to 6.94)
Wheeze	1.97 (0.86 to 4.12)	2.87 (1.11 to 6.87)	1.35 (1.01 to 1.81)	1.55 (1.15 to 2.08)
Fever (>38.5°C)	11.31 (4.9 to 25.07)	11.98 (5.03 to 27.87)	2.15 (1.59 to 2.89)	2.5 (1.83 to 3.38)
Severe anaemia (<80 g/L)	9.79 (1.32 to 52.0)	9.18 (1.18 to 54.0)	4.39 (2.51 to 7.27)	4.04 (2.29 to 6.8)
Endpoint pneumonia	5.55 (2.76 to 11.24)	5.64 (2.74 to 11.68)	2.43 (1.75 to 3.36)	2.67 (1.92 to 3.73)
Consolidation	6.55 (2.91 to 14.08)	5.37 (2.34 to 11.77)	4.23 (2.94 to 6.0)	4.11 (2.84 to 5.88)
Infiltration	2.43 (1.16 to 4.9)	2.70 (1.26 to 5.57)	1.52 (1.1 to 2.11)	1.71 (1.23 to 2.38)
Pleural effusion	18.0 (0.7 to 461.79)	23.0 (0.76 to 949.37)	6.96 (2.74 to 15.54)	6.85 (2.66 to 15.63)

Multivariate logistic models were adjusted by age in month, year of sampling and hospitals.
NA, not applicable; SpO_2, saturation of peripheral oxygen

during the study period, which may be attributed to the improved access to healthcare facilities and the improved management of childhood pneumonia in the past decade. Another possible reason may be the introduction of new vaccines such as *H. influenzae* type b (Hib) vaccines and pneumococcal conjugate vaccines (PCV). These vaccines have been shown to reduce the mortality rate resulting from childhood pneumonia.[7 8] However, in the Philippines, Hib vaccines were introduced in 2010, while PCVs were introduced in 2014 as part of the national immunisation programme of the country.[40] Vaccination coverage for Hib and PCV were estimated at 67% and 35%, respectively, in 2014.[40] Because a decreasing trend in CFR was observed before the introduction of these vaccines, other factors such as improved access to healthcare facilities and improved quality of care are more likely to have contributed to the CFR reduction.

Children aged <24 months accounted for 87.0% of total deaths, which is comparable with the global estimate of 81.0% pneumonia-related deaths occurring in children aged <2 years.[41] Patients of age 2–5 months showed the highest CFR of 7.0%. Similar results have also been reported in a previous study conducted in the Philippines, wherein children of this age group were at risk for pneumonia-associated mortality.[3] The immune system of patients in this age group is not fully functional,[42] and children aged 2–5 months have a lower level of circulating IgG in the blood than in other age groups.[43]

Moreover, we noted an association between the history of child loss in the family among children aged <2–59 months, which may be due to the lack of financial resources in the family, limited access to healthcare facilities or inappropriate health-seeking behaviour of the caretakers, such as self-medication, which may result in

Table 5 Factors associated with death among hospitalised children with severe pneumonia

Factors	RSV AOR (95% CI)	RV AOR (95% CI)	ADV AOR (95% CI)	EV AOR (95% CI)	Bacteria AOR (95% CI)	Negative for viruses AOR (95% CI)
Grunting	1.00 (0.71 to 1.43)	0.91 (0.63 to 1.32)	–	2.79 (1.81 to 4.31)	0.91 (0.47 to 1.79)	4.36 (1.91 to 9.98)
Sensorial changes	2.11 (1.74 to 2.57)	1.19 (0.92 to 1.53)	1.09 (0.87 to 1.35)	1.46 (1.13 to 1.89)	2.11 (1.41 to 3.17)	0.78 (0.69 to 0.87)
Central cyanosis	1.21 (1.02 to 1.45)	1.62 (1.2 to 2.19)	1.25 (0.84 to 1.88)	1.27 (0.91 to 1.76)	1.61 (0.66 to 3.91)	0.81 (0.61 to 1.08)
Alar flaring	1.04 (0.98 to 1.11)	1.01 (0.91 to 1.13)	0.99 (0.79 to 1.25)	1.79 (0.96 to 3.33)	1.1 (0.7 to 1.73)	1.07 (0.94 to 1.23)
Decreased breath sound	0.90 (0.71 to 1.15)	1.46 (0.97 to 2.2)	0.87 (0.54 to 1.40)	0.94 (0.67 to 1.33)	0.68 (0.29 to 1.61)	1.57 (1.05 to 2.35)
Wheezing	0.99 (0.89 to 1.10)	1.12 (0.96 to 1.3)	1.01 (0.84 to 1.19)	8.27 (2.83 to 24.15)	1.04 (0.79 to 1.39)	1.18 (0.98 to 1.42)
Fever (>38.5°C)	1.16 (0.96 to 1.4)	1.95 (1.51 to 2.51)	6.30 (1.57 to 25.21)	7.07 (2.44 to 20.48)	9.48 (1.91 to 47.0)	1.57 (1.22 to 2.03)
Tachypnoea	0.99 (0.88 to 1.1)	1.04 (0.91 to 1.2)	–	–	7.4 (1.06 to 51.67)	1.01 (0.85 to 1.18)
Tachycardia	1.16 (1.02 to 1.33)	1.07 (0.89 to 1.28)	1.41 (0.30 to 6.48)	2.55 (1.10 to 5.89)	0.1 (0.01 to 0.81)	0.82 (0.65 to 1.02)
SpO_2 <90%	1.27 (1.14 to 1.4)	1.29 (1.07 to 1.54)	6.17 (1.49 to 25.42)	1.12 (0.93 to 1.34)	1.17 (0.79 to 1.75)	0.95 (0.78 to 1.14)
Severe anaemia (<80g/dL)	0.86 (0.48 to 1.51)	0.68 (0.38 to 1.2)	–	–	2.58 (1.51 to 4.4)	5.71 (2.92 to 11.17)
Consolidation	1.02 (0.9 to 1.16)	1.13 (0.94 to 1.37)	6.69 (2.11 to 21.22)	1.53 (1.29 to 1.82)	0.97 (0.69 to 1.35)	2.2 (1.69 to 2.88)
Infiltration	1.13 (1.03 to 1.23)	1.07 (0.92 to 1.24)	6.22 (1.98 to 19.51)	1.17 (1.03 to 1.34)	7.84 (1.4 to 44.0)	1.13 (0.98 to 1.32)
Pleural effusion	–	1.33 (1.18 to 1.51)	0.93 (0.57 to 1.50)	0.97 (0.56 to 1.71)	1.05 (0.59 to 1.84)	2.05 (1.07 to 3.95)

Multivariate logistic models were matched with age groups and adjusted by patients age, year of sampling and hospitals.
ADV, adenovirus; AOR, adjusted OR; EV, enterovirus; RSV, respiratory syncytial virus; RV, rhinovirus.

delayed commencement of proper care for children with pneumonia.[44] The increased risk of pneumonia in households using solid cooking fuel and low SES has been well characterised in the past.[26 45–47] However, we did not find any significant associations between these two factors and death. We collected the data on risk factors only from 2014. The scarcity of data and the homogeneous characteristic of patients from lower economic status may explain the lack of significant associations.

We observed that 55.0% of the patients who died were either moderately or severely underweight. A similar rate of 52.5% has been reported among undernourished patients who died of infectious diseases in LMIC among children aged <5 years.[48] In a hospital-based study conducted in Malawi, the CFR attributed to pneumonia was high among patients with severe malnutrition, despite the general trend of decreasing CFR among patients with pneumonia,[18] which suggest that severely malnourished children with pneumonia require intensive inpatient care.[49] Guidelines for the management of pneumonia in malnourished children should consider this strong association with mortality.

Several clinical factors have been found to be associated with death, including decreased breath sounds, grunting, severe anaemia, central cyanosis and fever (>38.5°C) which are consistent with those reported previously.[18 21] In children aged <2 months, particular attention needs to be given to patients with fever >38.5°C, because of the high CFR of 32.5%. A bacterial infection should be considered in pneumonia cases with fever >38.5°C, as reported elsewhere.[50] Wheeze was associated with death, contrasting with the finding from a previous study in which the presence of wheeze was protective against death.[51] However, in our study, patients infected with EV, particularly EV-D68 showed high CFRs, and there was very strong association between wheezing and fatal outcome in patients with EV (table 5). EV-D68 is known to be more severe in children with asthma or recurrent wheeze.[52] This may contribute to the overall association of wheeze with death.

The prevalence of hypoxaemia (SpO_2 <90%) was 13.0% in this study, which is compatible to the mean rate of hypoxaemia among severe and very severe pneumonia cases reported in a review study.[53] However, in the present study, some patients had received oxygen before SpO_2 measurement, which may have underestimated the prevalence of hypoxia. Hypoxaemia was associated with death in our study, in concordance with earlier findings.[22 54–58] In a multicentre study that included 5 LMIC, the CFR among the hypoxaemic patients was 8.5%,[59] which is lower than the range of CFRs (12.6%–15.7%)%) reported among hypoxaemic patients in this study. Hypoxaemia was associated with viral infections such as RV and RSV as well as with a poor outcome, particularly in ADV infection.[60–64] In this study, hypoxaemia was significantly associated with death in patients infected with RV, RSV and ADV and in those with particularly high adjusted OR for ADV. Central cyanosis was also significantly associated with death for RSV and RV which suggests that hypoxia is particularly important in viral infections (table 5).

In this study, the presence of a positive chest radiograph finding increased CFR. CFR among the consolidation cases was 13.0%, which is the same as the reported mean CFR value of 13% in a multicentre study on childhood pneumonia.[23] The positivity rates for abnormal findings of chest radiograph varied across countries with the type of population and the presence of comorbidities,[23] but the association of endpoint pneumonia and consolidation with death or treatment failure have been consistently reported.[3 57 58] In addition, patients positive for RV and bacteria and negative for any viruses were more likely to die if they showed any abnormal findings by chest radiograph. These findings suggest that, among the patients positive for RV and negative for any viruses, a subset of the patients may have bacterial pneumonia.

Seasonal IFV A (H1N1) had a CFR of 40% in children aged 2–59 months, which was in contrast with the CRF value of 0% for IFV A (H1N1)pdm09. The reason why seasonal IFV A (H1N1) had such a high CFR remains unclear; however, it should be noted that all seasonal IFV A(H1N1) occurred during the period of 2008 to 2009, which was marked by an overall high CFR. ADV-7 had CFR of 24.0% in patients aged 2–59 months which concurs with a similar finding in China.[65] Most cases of ADV-7 in this study occurred between 2008 and 2011, which coincided with the ADV-7 outbreaks in Asia.[65 66] CFR associated with EV-68 (8.5%) was also higher than the average value. The association of EV-68 with severe ALRI, including pneumonia, has been well reported across several studies, including those reporting fatal cases.[17 67–69] RSV was the most common virus identified in the present study, which agrees with some previous reports.[14–16] However, RSV was negatively associated with death; this finding is also similar to those of several studies conducted in hospital settings.[70–73] RV presented with the highest number of deaths in this study. In contrast to RSV, which was significantly and inversely associated with death in children aged 2–59 months, RV did not have any positive or negative associations with deaths. RV is classified into three species: RV-A, B and C. CFRs for RV-A and B were higher than average, but the difference was not statistically significant. The CFR of RV-C was lower in patients aged 2–59 months, which was statistically significant in the univariate analysis. Some studies revealed that RV-C is associated with extremely severe respiratory infections, including deaths.[74] However, our data does not support this association. As mentioned earlier, some RV-positive cases, especially those positive for RV-A and B, may include bacterial pneumonia cases. Further studies are required to define the true causal association of different RVs with pneumonia and deaths due to pneumonia. We also did not observe any increase in the risk of death among patients with multiple viral infections, which is consistent with an earlier report.[75] However, the majority of multiple infections that occurred due to RV, RSV and both the viruses did not increase the risk of death.

Blood culture positive for bacteria was associated with death, as reported elsewhere.[76 77] However, the detection rate was low, which is similar to the findings of a few previously published reports,[78 79] particularly with those conducted in the Philippines, which reported a positivity rate of 1.1%.[80] The possibility of an antimicrobial treatment before admission in hospital may play a role in low positivity rate of blood culture. Although the sensitivity of blood culture for childhood pneumonia is extremely low, there are no alternative to the gold standard in the diagnosis of bacterial pneumonia in children. The difficulty in obtaining proper sputum samples from children also prevented us from identifying the pathogens in patients.[81]

This study has some limitations. First, the inclusion of the DAMA-deteriorated cases as deaths could have increased the CFR value. Second, we started collecting information on the risk factors from 2014 onward. Third, some clinical and laboratory data were missing, especially in fatal cases, because several deaths occurred immediately after hospital admission. Similarly, the sampling rate for blood culture was lower for fatal cases, because the patients died before their samples could be obtained. Despite these limitations, our study had a large sample size of more than 5000 patients studied over a longer duration of 9 years in a lower-middle-income country, which allowed us to accumulate comprehensive data on the demographics, clinical characteristics and aetiology of hospitalised children with severe pneumonia.

CONCLUSION

Our study demonstrated that while the CFR showed a decreasing trend in the past 10 years, severe pneumonia remains a major cause of morbidity and mortality in hospitalised infants and young children. We identified several factors that are associated with mortality, including severe malnutrition, fever >38.5°C, lung infiltration and consolidation on chest radiograph, SpO_2 <90% and respiratory distress syndrome such as central cyanosis, tachypnoea and wheezing. Infection with ADV-7 and seasonal influenza A (H1N1) and positive blood culture for bacteria have been associated with mortality, while infection with RSV and RV was negatively associated with mortality.

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Contributors Conceived and designed the study: HO, SL. Collected clinical data and samples: RT, SL, VT, MS, MS. Performed laboratory diagnosis of pathogens: MO, ESM, MM, MAUI. Analysed the data: BPPD, TK, CD, HO. Drafted the manuscript: BPPD, TK, CD, ES, HO. Critically reviewed and approved the manuscript: all authors.

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