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Epidemiology of community-acquired pneumonia among hospitalised children in Indonesia: a multicentre, prospective study

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ABSTRACT

Objective To identify aetiologies of childhood community-acquired pneumonia (CAP) based on a comprehensive diagnostic approach.

Design 'Partnerships for Enhanced Engagement in Research-Pneumonia in Paediatrics (PEER-PePPeS)' study was an observational prospective cohort study conducted from July 2017 to September 2019.

Setting Government referral teaching hospitals and satellite sites in three cities in Indonesia: Semarang, Yogyakarta and Tangerang.

Participants Hospitalised children aged 2–59 months who met the criteria for pneumonia were eligible. Children were excluded if they had been hospitalised for >24 hours; had malignancy or history of malignancy; a history of long-term (>2 months) steroid therapy, or conditions that might interfere with compliance with study procedures.

Main outcome(s) measure(s) Causative bacterial, viral or mixed pathogen(s) for pneumonia were determined using microbiological, molecular and serological tests from routinely collected specimens (blood, sputum and nasopharyngeal swabs). We applied a previously published algorithm (PEER-PePPeS rules) to determine the causative pathogen(s).

Results 188 subjects were enrolled. Based on our algorithm, 48 (25.5%) had a bacterial infection, 31 (16.5%) had a viral infection, 76 (40.4%) had mixed bacterial and viral infections, and 33 (17.6%) were unable to be classified. The five most common causative pathogens identified were *Haemophilus influenzae* non-type B (N=73, 38.8%), respiratory syncytial virus (RSV) (N=51, 27.1%), *Klebsiella pneumoniae* (N=43, 22.9%), *Streptococcus pneumoniae* (N=29, 15.4%) and Influenza virus (N=25, 13.3%). RSV and influenza virus diagnoses were highly associated with Indonesia's rainy season (November–March). The PCR assays on induced sputum (IS) specimens captured most of the pathogens identified in this study.

Conclusions Our study found that *H. influenzae* non-type B and RSV were the most frequently identified pathogens causing hospitalised CAP among Indonesian children aged 2–59 months old. Our study also highlights the importance of PCR for diagnosis and by extension, appropriate use of antimicrobials.

Trail registration number NCT03366454

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Prospective multisite study conducted over 27 months.
⇒ Used a comprehensive diagnostic approach (culture, molecular testing and paired serological assays) to identify causative pathogens from routinely collected specimens (blood, sputum and nasopharyngeal swabs).
⇒ The relatively small sample size, geographical limitation to the island of Java and observational design limit generalisability and causal inference.
⇒ We did not collect lung aspirates or pleural fluid specimens, which are preferred for determination of pneumonia aetiology, and did not include healthy control children, limiting ability to estimate the adjusted population attributable fraction for each pathogen.
⇒ Several cases of pneumonia were attributed to unknown aetiology, which could be due to administration of antibiotics before culture, poor sputum quality, limited bacterial and viral panels, lack of fungal testing or another factor.

INTRODUCTION

Pneumonia is the leading infectious cause of child mortality, with a greater burden in low-income and middle-income countries (LMICs).[1] In Indonesia, pneumonia contributed to 15% of childhood deaths and was the second leading cause of death among children under 5 years in 2017.[2] Indonesian practice guidelines are adapted from the WHO guidelines, which are based on 1970s–1990's data showing bacteria such as *Haemophilus influenzae* type b (Hib) and *Streptococcus*

pneumoniae caused the majority of fatal pneumonias in children.[3–5] Therefore, empiric antibiotics are considered first-line treatment for children with community-acquired pneumonia (CAP).[6–8] Despite evidence that appropriate antibiotics are lifesaving, rational selection of antibiotics for pneumonia is hampered by low adherence to guidelines and scarcity of point-of-care diagnostics.[9–11] Consequently, healthcare providers, particularly those in LMIC, are likely to overtreat non-bacterial pneumonia with antibiotics.[11 12]

Several recent studies of CAP in children have highlighted the role of viral aetiologies. Increased recognition of viral aetiologies of CAP is likely due to both enhanced molecular diagnostic capacity and wide deployment of Hib and pneumococcal conjugate vaccines (PCV).[13 14] Treatment of non-bacterial pneumonia with antibiotics may engender avoidable antimicrobial resistance. Thus, current data on the aetiologies of childhood pneumonia is needed and should be regularly evaluated to inform vaccination policies, empiric management decisions and targeted treatment.[12]

From a diagnostic standpoint, direct demonstration of organisms by culture (or staining) of lung aspirates has been the standard for determining microbial aetiology of CAP.[15] In the current era, many use less-invasive biological specimens (eg, blood, naso/oropharyngeal secretions, bronchoalveolar lavage or induced sputum (IS)) and employ diverse methods (eg, culture, PCR, antigen detection or paired serology) to identify organisms.[16] However, such comprehensive methods are costly and often require specialised equipment and human resources, limiting feasibility in low-resource settings.[17 18]

Prospective community-based cohort studies that define pathogen(s) causing CAP in Indonesian children are scarce. We conducted a 'Partnerships for Enhanced Engagement in Research-Pneumonia in Paediatrics (PEER-PePPeS)' study, which aimed to identify aetiologies of childhood CAP using comprehensive diagnostic methods.

METHODS

Study design and study sites

PEER-PePPeS was a multisite observational cohort study (ClinicalTrials.gov Identifier: NCT03366454) seeking to determine aetiologies of CAP among children aged 2–59 months in Indonesia. The study was conducted by the Indonesia Research Partnership on Infectious Disease (INA-RESPOND) and enrolled participants initially at three government referral teaching hospitals in three provinces: Kariadi Hospital (Central Java), Sardjito Hospital (Yogyakarta) and Tangerang District Hospital (Banten), as shown in online supplemental file 1). Satellite sites located near the primary sites were added during the study to facilitate subject recruitment.

Study definitions

In this study, pneumonia in children was defined as cough or fever with at least one of the following: shortness of breath (indicated by at least one of the following signs: head bobbing; nasal flaring; chest indrawing or intercostal retracting), tachypnea, grunting, crackles, rhonchi, decreased vesicular breath sounds, bronchial breath sounds or chest X-ray findings consistent with pneumonia. Tachypnoea was defined as respiratory rate >50/min for infants 2–12 months and >40/min for children>12–60 months.[19] Abnormal chest X-ray findings consistent with pneumonia were defined as presence of either focal or diffuse infiltrates, a silhouette sign, pleural effusion or air bronchogram.[20] Chest X-rays were read by the paediatrician.

Based on WHO classification and treatment of childhood pneumonia at health facilities (2014 version), for children 2–59 months of age, severe pneumonia is defined as pneumonia (tachypnea and/or chest indrawing) accompanied by presence of any danger signs, including inability to drink, persistent vomiting, convulsions, lethargy or loss of consciousness, stridor in a calm child or severe malnutrition.[19]

Study participants

PEER-PePPeS study enrolled children aged 2–59 months, who were hospitalised between 18 July 2017 and 25 September 2019, and met the definition for pneumonia. Eligible subjects were enrolled within 24 hours of admission. Children were excluded if they had been hospitalised for >24 hours; had a malignancy or history of malignancy; a history of long term (≥2 months) steroid therapy; or conditions that might interfere with compliance with study procedures (eg, very ill patients for whom specimens could not be obtained or living outside the area for which follow-up was practical).

Study procedures

Demographic and anthropometric data, current signs and symptoms, pregnancy history, vaccination status, breastfeeding history, antibiotic and steroid exposure, family history, medical history, risk factors, haematology profiles, chemistry results and chest X-ray (per standard of care) were collected at enrolment. Clinical examination (vital signs, general examination, lung auscultation, SpO2); nasopharyngeal (NP) swab for molecular tests; IS for culture and molecular tests; collection of blood specimens for routine blood count, cultures, molecular tests, serological tests, C reactive protein (CRP) and procalcitonin (PCT) were also performed. We prospectively followed subjects daily until hospital discharge; data on vital signs, respiratory signs, intensive care admission, intubation, complications and treatment were collected. On day 14, we performed clinical examinations and collected convalescent sera for serology tests; subjects discharged before day 14 returned to clinic for their evaluation. We conducted a telephone interview on day 30 (±4 days) to assess clinical outcome.

This study used several widely available bacterial and viral respiratory molecular pathogen panels and serological assays.[21–24] NP and IS specimens were tested with a

PCR panel that included 12 viruses (influenza A, influenza B, adenovirus, enterovirus, bocavirus, respiratory syncytial virus (RSV) A, RSV B, human metapneumovirus (hMPV), rhinovirus, parainfluenza virus (PIV) 1–4, coronavirus OC43 and coronavirus NL63). NP specimens were evaluated by PCR for five bacteria (*Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis, Staphylococcus aureus* and *Klebsiella pneumoniae*), while IS specimens were tested for nine (*Haemophilus influenzae, Streptococcus pneumoniae, Mycoplasma pneumoniae, Chlamydia pneumoniae, Bordetella pertussis, Moraxella catarrhalis, Staphylococcus aureus, Klebsiella pneumoniae* and *Legionella pneumoniae*). Good quality (<10 squamous epithelial cells per low power field[12]) IS specimens underwent culture and gram stain.[25] For whole blood, qPCR was performed for three bacteria (*Haemophilus influenzae, Streptococcus pneumoniae* and *Staphylococcus aureus*). Serological testing for seven viruses (influenza A, influenza B, adenovirus, parvovirus B19, echovirus/enterovirus, RSV, PIV) and four bacteria (*Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella pneumoniae* and *Bordetella pertussis*) was performed using paired acute-convalescent sera.

Blood culture, IS culture and Gram stain, routine blood count, CRP, PCT and chest X-ray were performed by the laboratory/radiology department at the hospital site. qPCR and serology assays were performed retrospectively at the INA-RESPOND Reference Laboratory located in Tangerang District Hospital. Details of blood culture, sputum culture, molecular and serology test techniques are shown in online supplemental table 1.

Pathogen identification

Causative bacterial, viral or mixed pathogen for the pneumonia was determined based on an algorithm (PEER-PePPeS rules) for interpretation of microbiological, molecular and serological test results published previously.[12] In brief, we considered all organisms detected by blood culture, detected by whole blood PCR, or that grew from good quality IS specimen in high quantities with a compatible primary Gram stain as potential causative bacterial pathogens. Bacteria commonly considered contaminants were excluded. For the nasopharynx, potential colonising bacteria (eg, *H. influenzae, S. pneumoniae* and *S. aureus*) and potential innocent bystander viruses (eg, bocavirus, adenovirus, non-SARS human CoVs (hCoVs), enterovirus and rhinovirus) were determined to be causative based on a PCR density cut-off and/or serodiagnosis criteria for paired acute and convalescent sera (seroconversion or a two to four-fold increase in antibody titers in the convalescent specimen).[12]

Data collection and statistical analysis

Data were recorded on paper case report forms and entered in duplicate into OpenClinica (OpenClinica, Massachusetts, USA) by research staff. Categorical variables were summarised using absolute values and percentages, and continuous variables as medians and IQRs. Differences in categorical variables were compared using Pearson χ^2 or Fisher's exact test when the expected values in any of the contingency table cells were below 5. Differences in continuous variables were compared using one-way analysis of variance or Kruskal-Wallis H-test for data which did not follow the normal distribution based on Levene's test. Statistical analyses were performed using SPSS software V.23 (IBM). All p values were two sided. Level of significance was set at $p<0.05$.

Patient and public involvement statement

Patients or the public were not involved in study design or study conduct at any stage from inception to completion and dissemination of this project. Patients who met the eligibility criteria as described above were recruited to this study.

RESULTS

Study population

Of 444 children who were hospitalised with CAP, 188 (42.3%) were eligible and enrolled in the study. Of 256 screening failures, 31.8% were due to hospitalisation >24 hours at the time of screening and 22.1% to circumstances that might interfere with the study procedures. Of the 188 enrolled children, 184 (97.9%) had radiologic evidence of pneumonia. 179 (95.1%) subjects completed the study, including 19 (10.1%) who died. Eight subjects (4.3%) were lost to follow-up, and one subject (0.5%) withdrew from the study. The study flow is shown in figure 1.

Demographic and clinical characteristics are presented in table 1. Age, gender, laboratory values and pneumonia severity by WHO classification were similar across the three study sites. The median age was 9 months (IQR 5–20), and 54.7% of subjects were male. The most common comorbid conditions/medical histories were developmental delay (27.7%), congenital heart disease (26.1%), low birth weight (24.4%) and severe malnutrition (18.6%), with subjects from Yogyakarta site having the greatest proportion of those comorbidities. The percentage of subjects who had been vaccinated (age adjusted) against pneumococcus, influenza, Hib-DPT and measles vaccines were 2.1%, 1.1%, 55.9% and 75.0%, respectively.

The most common symptoms were shortness of breath (92.6%), cough (91.0%) and fever (80.9%). Signs noted during the initial examination included intercostal retraction (91.0%), rhonchi (89.4%) and chest indrawing (66.5%). Of 188 subjects, 172 (91.4%) and 167 (88.8%) had CRP and PCT measured with median values of 9.0 (IQR 3.6–28.0; Ref range ≤5) mg/L and 0.2 (IQR 0.1–1.7; Ref range ≤0.15) ng/mL, respectively. Interstitial infiltrate (69.7%) was the most common radiographic finding. 47.3% of cases were classified as severe pneumonia according to the WHO classification system. All 188 enrolled cases were treated with antibiotics, and 150 of them (79.8%) had

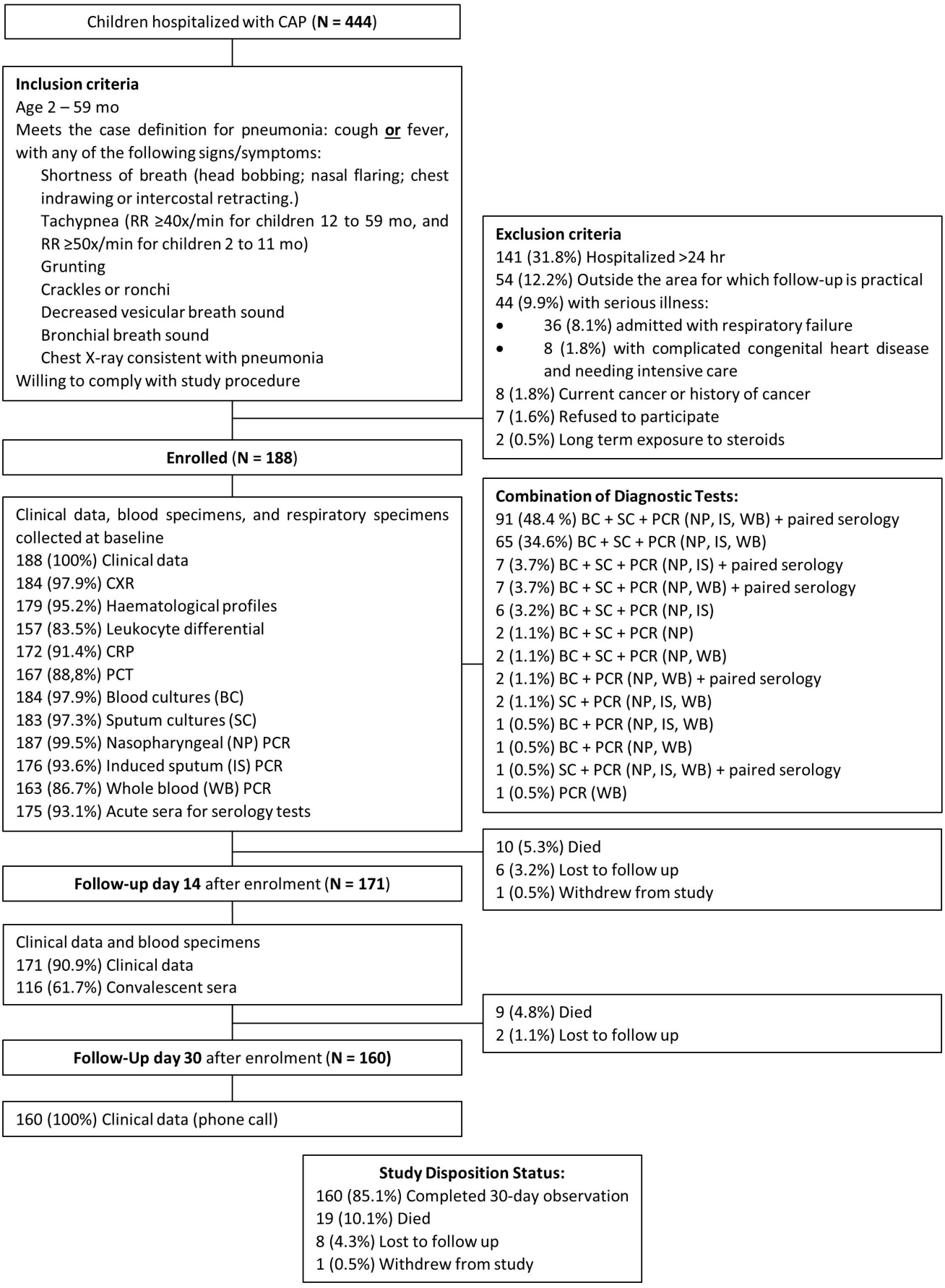

Figure 1 Subject screening, enrolment and monitoring flow chart. CAP, community-acquired pneumonia; CRP, C reactive protein; CXR, chest X-ray; PCT, procalcitonin; RR, respiratory rate.

Table 1 Baseline characteristics of subjects

Demographic characteristics	All (N=188)	Semarang (N=47)	Yogyakarta (N=52)	Tangerang (N=89)	P value
Age, median (IQR) months	9 (5–20)	9 (5.5–21)	8 (4–13.3)	11 (5–20)	0.442
Gender, male, (%)	103 (54.7)	29 (61.7)	26 (50)	48 (53.9)	0.493
Household characteristics, (%)					
Low education of parents*	163 (86.7)	37 (78.7)	43 (82.7)	84 (94.3)	0.019
Living in a dense neighbourhood†	121 (64.4)	19 (40.4)	42 (80.8)	60 (67.4)	<0.001
Exposure to cigarette smoke	120 (63.8)	24 (51.1)	27 (51.9)	69 (77.5)	0.001
Sick household contact <14 days	109 (58.0)	22 (46.8)	43 (82.7)	44 (49.4)	<0.001
Living near waste disposal	70 (37.2)	12 (25.5)	29 (55.8)	29 (32.6)	0.004
Attending daycare	4 (2.1)	2 (4.3)	1 (1.9)	1 (1.1)	0.374
Medical history (%)					
Developmental delay	52 (27.7)	16 (34.0)	21 (40.4)	15 (16.8)	0.003
Congenital heart disease	49 (26.1)	16 (34.0)	24 (46.2)	9 (10.1)	<0.001
Low birth weight	46 (24.4)	12 (25.5)	20 (38.5)	14 (15.7)	0.011
Severe malnutrition‡	35 (18.6)	10 (21.3)	13 (25.0)	12 (13.5)	0.205
Premature baby	34 (18.1)	4 (8.5)	16 (30.8)	14 (15.7)	0.012
Neurological disorder	25 (13.3)	5 (10.6)	17 (32.7)	3 (3.4)	<0.001
Tuberculosis (recent/cured)	10 (5.3)	4 (8.5)	2 (3.8)	4 (4.5)	0.588
Asthma	9 (4.8)	3 (6.4)	1 (1.9)	5 (5.6)	0.563
HIV disease§	2 (1.1)	1 (2.1)	1 (1.9)	0 (0)	0.315
Immunisation history, fully vaccinated for age¶ (%):					
Measles	141 (75.0)	38 (80.9)	41 (78.8)	62 (69.7)	0.175
DPT-Hib	105 (55.9)	30 (63.8)	25 (48.1)	50 (56.2)	0.233
Pneumococcus	4 (2.1)	0 (0)	4 (7.7)	0 (0)	0.009
Influenza	2 (1.1)	0 (0)	2 (3.8)	0 (0)	0.132
Symptoms and signs (%)					
Shortness of breath	174 (92.6)	41 (87.2)	48 (92.3)	85 (95.5)	0.214
Cough	171 (91.0)	40 (85.1)	42 (80.8)	89 (100)	<0.001
Intercostal retraction	171 (91.0)	43 (91.5)	52 (100)	76 (85.4)	0.005
Rhonchi	168 (89.4)	42 (89.4)	39 (75.0)	87 (97.8)	<0.001
Fever	152 (80.9)	34 (72.3)	35 (67.3)	83 (93.3)	<0.001
Chest indrawing	125 (66.5)	36 (76.6)	43 (82.7)	46 (51.7)	<0.001
Fast breathing	80 (42.6)	15 (31.9)	43 (82.7)	22 (24.7)	<0.001

Continued

Table 1 Continued

Demographic characteristics	All (N=188)	Semarang (N=47)	Yogyakarta (N=52)	Tangerang (N=89)	P value
SpO_2<90% and/or cyanosis	43 (22.9)	7 (14.9)	17 (32.7)	19 (21.3)	0.098
Diarrhoea	36 (19.1)	6 (12.8)	4 (7.7)	26 (29.2)	0.003
Wheezing	35 (18.6)	9 (19.1)	10 (19.2)	16 (18.0)	1
Vomiting	14 (7.4)	4 (8.5)	5 (9.6)	5 (5.6)	0.595
Inability to drink	13 (6.9)	4 (8.5)	5 (9.6)	4 (4.5)	0.425
Decreased consciousness	7 (3.7)	1 (2.1)	1 (1.9)	5 (5.6)	0.612
Seizure	6 (3.2)	1 (2.1)	0 (0)	5 (5.6)	0.203
Leucocyte count, median (IQR)×10^3/uL	14.0 (10.4–18.9)	14.9 (11.1–18.8)	12.1 (9.8–17.8)	14.0 (10.4–19.0)	0.356
Neutrophil-lymphocyte ratio, median (IQR)	1.4 (0.9–2.8)	1.3 (0.9–2.6)	1.0 (0.6–2.0)	1.9 (1.1–3.2)	0.367
CRP, median (IQR) mg/L	9.0 (3.6–28.0)	11.8 (1.6–23.3)	9.0 (4.9–21.8)	8.4 (1.5–34.1)	0.665
PCT, median (IQR) ng/mL	0.2 (0.1–1.7)	0.2 (0.1–1.5)	0.2 (0.1–1.0)	0.2 (0.1–2.6)	0.912
Severe pneumonia (WHO Classification 2014 version) (%)	89 (47.3)	26 (55.3)	26 (50.0)	37 (41.6)	0.281
CXR findings (%):					
Interstitial infiltrate	131 (69.7)	26 (55.3)	30 (57.7)	75 (84.3)	<0.001
Alveolar infiltrate	125 (66.5)	41 (87.2)	44 (84.6)	40 (44.9)	<0.001
Pleural effusion	5 (2.7)	1 (2.1)	2 (3.8)	2 (2.2)	0.85
Antibiotic administration prior to blood culture (%)	150 (79.8)	39 (83.0)	49 (94.2)	62 (69.7)	0.002

*Low education of parents was defined by highest level of parents' formal education being high school diploma or less.
†A densely populated neighbourhood was defined as >200 people/km^2 or <8 m^2/person in the subject's home.
‡Severe malnutrition was defined as weight for height below −3 SD from the median of the WHO Child Growth Standards.
§Subjects were tested for HIV infection if a parent/guardian provided consent and a specimen was available (n=160).
¶Full vaccination was defined as being up to date for age per vaccination schedule at study enrolment.
CRP, C reactive protein; CXR, chest X-ray; PCT, procalcitonin.

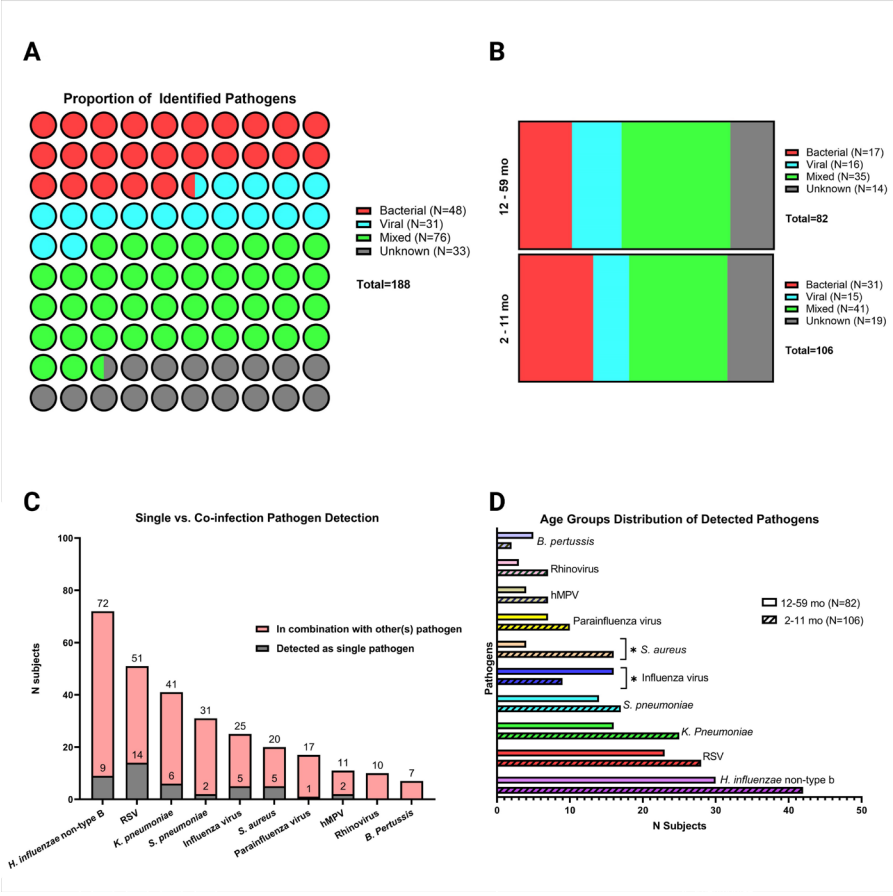

Figure 2 Pathogen distribution. (A) Overall proportion of identified viral/bacterial/mixed pathogen, (B) Viral/bacterial/mixed pathogens by age group, (C) pattern of detection of the ten most identified pathogens, (D) distribution of 10 most identified pathogens by age group. *P<0.05. hMPV, human metapneumovirus; RSV, respiratory syncytial virus.

received 1–2 doses of antibiotics prior to collection of blood culture in the emergency unit, with the combination of ampicillin and gentamicin (34.6%), cefotaxime (17.0%) and ceftriaxone (14.4%) being the three most frequent regimens used. Details of antibiotic regimens administered before blood culture, including dosage and given frequency, are presented in online supplemental table 2.

Detection of pathogens

Blood and sputum cultures were performed on specimens from 184 (97.9%) and 183 (97.3%) subjects, respectively. A total of 150 (79.8%) children received antibiotics prior to collection of blood for culture. Seventy-five (41.0%) sputum culture isolates were analysed from specimens meeting the required quality criteria. An NP or OP swab was obtained from 187 (99.5%) subjects, IS for PCR from 176 (93.6%), whole blood for PCR from 163 (86.7%) and paired acute-convalescent serum specimens for serology from 116 (61.7%) (figure 1).

The PEER-PePPeS algorithm was used to determine the causative pathogen(s) from those identified by culture, molecular and serological assay. Among the 188 study participants, 48 (25.5%) had bacterial infection, 31 (16.5%) had viral infection, 76 (40.4%) were of mixed bacterial and viral aetiology, and 33 (17.6%) were of unknown aetiology (figure 2A). Mixed infection, the most common overall aetiology, was seen in 38.7% of 2–11 months and in 42.7% of 12–59 months (figure 2B). Mixed infection was also the predominant aetiology across all study sites (online supplementary file 2). *H. influenzae* non-type B (N=73, 38.8%), RSV (N=51, 27.1%), *K. pneumoniae* (N=43, 22.9%), *S. pneumoniae* (N=29, 15.4%), influenza virus (N=25, 13.3%), *S. aureus* (N=20, 10.6%), PIV (N=17, 9.0%), hMPV (N=11, 5.8%), Rhinovirus (N=10, 5.3%) and *B. pertussis* (N=7, 3.7%) were the top ten pathogens identified, more commonly appearing in mixed infection as opposed to as a sole pathogen (figure 2C). Influenza virus was significantly higher in the age group 12–59 months vs 2–11 months (N=16, 64%, p=0.027), while *S. aureus* was significantly more common in 2–11 months vs 12–59 months (N=16, 80%, p=0.024). Though not statistically significant, other pathogens trended toward more frequent detection in age group 2–11 mo (except *B. pertussis*) (figure 2D). Among 76 mixed infection cases, RSV +*H. influenzae* non-type B was the most common coinfection (N=22, 28.9%), followed by RSV +*S. pneumoniae* (N=10, 13.2%), influenza virus +*H. influenzae* non-type B (N=10, 13.2%), RSV +*K. pneumoniae* (N=9, 11.8%) and PIV+*H. influenzae* non-type B (N=9, 11.8%) (data not shown).

We observed no difference in pathogen distribution by pneumonia severity based on WHO classification system (online supplemental table 3 and online supplemental fig 3). By pathogen, there was no significant difference in distribution between pneumonia severity status or mortality, except for *S. pneumoniae* which was found in significantly more severe cases using the WHO system (p=0.033) (online supplemental table 3).

A comparison of positivity rates for each causative pathogen by detection method is shown in table 2. Overall, PCR captured more bacterial pathogens than culture and more viral pathogens than acute-convalescent paired serology. Paired serology was generally helpful in identifying atypical bacteria, such as *C. pneumoniae* and *L. pneumophila* and upper respiratory tract viruses, such as Rhinovirus and Enterovirus. When comparing blood and IS culture, IS yielded more positive bacterial pathogen results. Similarly, IS PCR captured more pathogens than NP/OP PCR.

Mortality

Nineteen (10.1%) of the 188 subjects died during the 30-day study period. Seven (36.8%) of these 19 were male, and most (N=17, 89.5%) were less than 1 year old. Among the 19 deceased subjects, median study duration was 12 (IQR 4–17.5) days; 8 (42.1%) were admitted to ICU and 6 (31.6%) received mechanical ventilation. Twelve (63.2%) died due to respiratory failure, three (15.8%) due to sepsis and three (15.8%) for unknown reasons after discharge (data not shown). Most deaths occurred in the 2–11 mo age group compared with the 12–59 mo age group (78.9% vs 21.1%, p=0.036). Causative pathogens for deceased subjects were bacterial-only in seven (36.8%), viral-only in two (10.5%), mixed in five (26.3%) and unknown in five subjects (26.3%). There were no significant differences in pathogen distribution between subjects that survived and died. *H. influenzae* non-type B was the most common pathogen identified in deceased subjects (N=8, with the case fatality rate (CFR) in this study of 11.0%), followed by *K. pneumoniae* (N=6, CFR of 13.9%), influenza virus (N=3, CFR of 12.0%), *B. pertussis* (N=2, CFR of 28.6%) and RSV (N=2, CFR of 3.9%) (online supplemental table 3). Pre-existing conditions among deceased subjects included congenital heart disease (N=10, 52.6%), severe malnutrition (N=7, 36.8%) and developmental delay (N=7, 36.8%). A clinical summary of the fatal cases is shown in online supplemental table 4.

Seasonality

During the 27-month study period, infections caused by RSV and influenza were seen year-round with peak activity occurring during the wet season (November to March) in Indonesia (66.7%, p<0.001; and 64.0%, p=0.012, respectively). However, there was little variation in detection of the most common respiratory bacterial infections by month and season. *H. influenzae* non-type B shows peaks in August (N=12, 16.4%) and March (N=11, 15.1%), while *K. pneumoniae* and *S. pneumoniae* fluctuate at lower levels throughout the year (figure 3).

DISCUSSION

PEER-PePPeS, a prospective multisite study, characterised the current epidemiology of CAP in children 2–59 months in Indonesia. No recent prospective Indonesian studies address this topic. Our study found: (1) mixed bacterial and viral infection is the most frequent (N=76, 40.4%) cause of childhood CAP, irrespective of age group and pneumonia severity; (2) bacterial infections were common (66% of cases) with *H. influenzae* non-b type, *K. pneumoniae* and *S. pneumoniae* as the three most common bacterial aetiologies; (3) viral pathogens were also common (57% of PEER-PePPeS subjects), with 16.5% of cases attributed to virus only and RSV and Influenza Virus being the most common viruses identified and (4) PCR on IS specimens was the most sensitive assay for pathogen identification.

While our findings are consistent with other studies, clinical significance of mixed infection remains controversial. It is unclear if both agents act as true pathogens.[22 26] PEER-PePPeS did not demonstrate a correlation of mixed infection with pneumonia severity and 30-day mortality. Many deaths occurred at a younger age (<1 year old) and with comorbidities, such as congenital heart disease and severe malnutrition, similar to previous reports.[27 28] Such factors should be considered in prevention and management of childhood pneumonia to reduce mortality rate.

In recent years, there has been an increased focus on the role of respiratory viruses in childhood pneumonia, partly attributable to use of conjugate pneumococcal and Hib vaccines and increased detection by PCR.[21 22 29 30] In PEER-PePPeS, viruses were found in 57% of subjects (virus only +mixed infection), with 16.5% of cases attributed to virus only. Thus, many patients probably received unnecessary antibiotics when covered empirically per current Indonesian guidelines. Improving ability to discriminate between viral and bacterial infections would facilitate optimisation of antibiotic administration and counter antimicrobial resistance.[31]

RSV and influenza virus were the most commonly detected viruses in this study and may be associated with Indonesia's wet/rainy season.[32–34] A high prevalence of RSV was also observed in the GABRIEL and PERCH international case–control studies of childhood pneumonia aetiology.[22 30] In terms of mixed infections, we found that RSV +*H. influenzae* non-type B and RSV +*S. pneumoniae* were most common. Since respiratory viruses such as RSV can predispose to secondary bacterial infections, particularly *S. pneumoniae* and *H. influenzae*,[35] and conversely bacteria can increase RSV susceptibility,[35 36] these coinfections highlight the need for optimising RSV surveillance, prevention and treatment.

Though influenza virus also increases risk for secondary bacterial infections and is a major cause of childhood morbidity and mortality worldwide, data from developing

Table 2 Causative pathogens per PEER-PePPeS rules by detection method

Pathogen	N	Blood culture N (%)	IS culture N (%)	Whole blood PCR N (%)	NP / OP PCR N (%)	IS PCR N (%)	Serology test N (%)
Gram-positive cocci bacteria							
Streptococcus pneumoniae	29	1 (3.4)	3 (10.3)	--	21 (72.4)	28 (96.6)	
Staphylococcus aureus	20	--	7 (35)	--	11 (55)	19 (95)	
Streptococcus mitis	4	--	4 (100)				
Streptococcus pyogenes	1	--	1 (100)				
Gram-negative cocci bacteria							
Moraxella catarrhalis	2	--	2 (100)		2 (100)	2 (100)	
Gram-negative rods bacteria							
Haemophilus influenzae non-type b	73	--	--	8 (10.9)	60 (82.2)	71 (98.6)	
Klebsiella pneumoniae	43	--	17 (39.5)		2 (4.7)	34 (79.1)	
Bordetella pertussis	7	--	--			7 (100)	
Escherichia coli	5	1 (20)	4 (80)				
Pseudomonas aeruginosa	4	--	4 (100)				
Acinetobacter baumannii	3	--	3 (100)				
H. inf type b	2	--	--	--	--	2 (100)	
Neisseria meningitidis	1	1 (100)	1 (100)				
Atypical-bacteria							
Chlamydia pneumoniae	5	--	--			--	5 (100)
Mycoplasma pneumoniae	5	--	--			5 (100)	1 (20)
Legionella pneumophila	1	--	--			--	1 (100)
Virus							
RSV	51				36 (70.6)	45 (88.2)	10 (19.6)
RSV A	15				10 (66.7)	13 (86.7)	
RSV B	36				26 (72.2)	32 (88.8)	
Influenza virus	25				16 (64)	22 (88)	9 (36)
inf A (H1N1)	7				7 (100)	7 (100)	7 (70)
inf A (H3N2)	3				3 (100)	3 (100)	
inf B	14				6 (42.9)	12 (85.7)	2 (14.3)
PIV	17				16 (94.1)	15 (88.2)	3 (17.6)

Continued

Table 2 Continued

Pathogen	N	Blood culture N (%)	IS culture N (%)	Whole blood PCR N (%)	NP / OP PCR N (%)	IS PCR N (%)	Serology test N (%)
PIV 1	5				5 (100)	4 (80)	3 (17.6)
PIV 2	0				--	--	
PIV 3	11				10 (90.9)	10 (90.9)	
PIV 4	1				1 (100)	1 (100)	
hMPV	11				5 (45.5)	10 (90.9)	
Rhinovirus	10				10 (100)	6 (60)	4 (40)
Enterovirus	5				3 (60)	3 (60)	3 (60)
Bocavirus	3				2 (66.7)	3 (100)	
hCoV-NL63	2				2 (100)	2 (100)	

Grey box indicates the assay was not performed.
hMPV, human metapneumovirus; IS, induced sputum; NP, nasopharyngeal; PIV, parainfluenza virus; RSV, respiratory syncytial virus.

countries is scarce.[37] In a previous Indonesian study of hospitalised patients with a SARI, the prevalence of the influenza virus was 10.6% in children under 5 years old, and was never diagnosed during hospitalisation.[38] PEER-PePPeS confirms the need for improved diagnostic strategies, management optimisation and influenza vaccination in children. Of note, our study was conducted before identification of COVID-19 in Indonesia,[39] so did not address the role of COVID-19 in childhood pneumonia.

We also found that 66% of cases were caused by bacterial infection (bacteria only +mixed infection). Overall, *H. influenzae* non-type B was the most common bacteria implicated, followed by *K. pneumoniae* and *S. pneumoniae*. *H. influenzae* non-type B predominance was also observed in a Malaysian study, where 90% of enrolled children were vaccinated against Hib as part of the national immunisation programme.[24] With Indonesia's moderate (56.4%) Hib vaccine coverage, high incidence of *H. influenzae* non-type B may represent its true prevalence or strains not covered by Hib vaccine.[40] This finding agrees with current data that non-typeable *H. influenzae* (NTHi) can cause significant illness, and argues for strengthening paediatric diagnostic laboratory capacity.

Our identification of *K. pneumoniae* as the second most common bacterial aetiology is consistent with high carriage rates (~7%) in healthy Indonesian children. Carriage has been related to poor food and water sanitation and may give rise to pneumonia, especially in children with malnutrition.[41] Given *K. pneumoniae's* potential for antibiotic resistance and high virulence of some strains, proactive detection and management strategies should be prioritised.[42]

The relatively low prevalence (15.4%) of *S. pneumoniae* in PEER-PePPes was surprising since carriage rates are high and PCV coverage low in Indonesia.[43] Low prevalence has also been reported from Malaysia, where PCV coverage is 8.7%[24] and in the PERCH study, reflecting temporal shifts in childhood pneumonia aetiologies.[22] As only 4.8% of PEER-PePPeS subjects had received PCV, vaccination alone cannot account for the low *S. pneumoniae* prevalence. Antibiotic exposure prior to specimen collection may have reduced colonisation density and lowered the yield of *S. pneumoniae* by both culture and PCR.[44] Moreover, our panel did not include *S. pneumoniae* paired serology, which may be useful to increase pneumococcal diagnosis in young children.[45] Nonetheless, *S. pneumoniae* remains an important aetiological agent of severe/complicated CAP globally.[46] Our finding that *S. pneumoniae* was significantly associated with severe cases by the WHO classification system supports the need for ongoing surveillance, vaccination and prevention of transmission between adults and children.

Inclusion of several pathogen identification strategies in PEER-PePPes demonstrates the differential utility of assays and specimen types. Our findings highlight the value of molecular assays, especially in culture-negative cases where microorganisms may be nonrecoverable in culture due to prior antibiotics or presence of otherwise

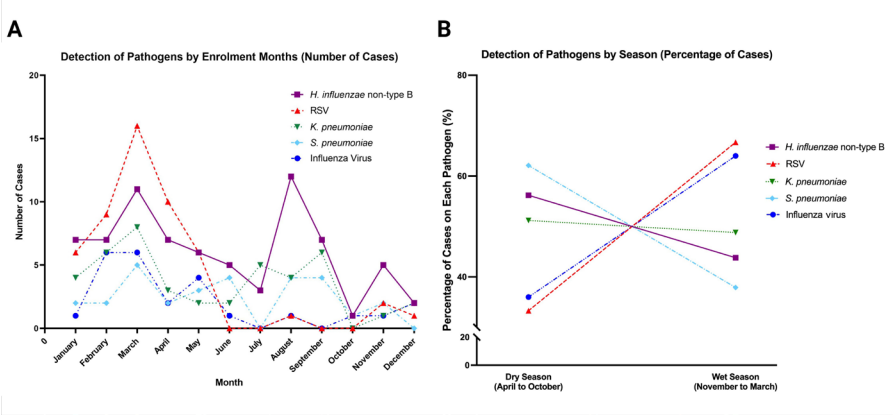

Figure 3 Distribution of the (A) monthly count and (B) seasonal pattern of infection caused by *Haemophilus influenzae* non-type B, RSV, *Klebsiella pneumoniae*, *Streptococcus pneumoniae* and influenza virus during a 27-month study period. RSV, respiratory syncytial virus.

difficult to culture bacteria.[47 48] PCR is also less laborious and can identify genes associated with antibiotic resistance, though conventional culture methods are required to confirm phenotypic resistance.[49 50] Even with the limited PCR panels used in our study, molecular assays had greater sensitivity for identification of bacterial pathogens than blood or sputum culture.

Although sensitive for detection, PCR does not provide information regarding infectiousness or viability. Genome fragments from dead organisms may be detected, often at a low level, even after clinical resolution.[48] Furthermore, negative results may occur due to differential viral kinetics along the respiratory tract. Lower respiratory tract specimens, such as IS, should be sought as they originate from the site of infection.[12 13] Accordingly, we observed a higher yield from PCR on IS than NP specimens. We also found that the use of paired serologies increased the diagnostic yield and was useful for pathogen confirmation, particularly in the setting of innocent bystander viruses and atypical bacteria.[12]

PEER-PePPeS used a comprehensive approach for pathogen detection to increase diagnostic yield. It also enrolled patients over a 27-month study period, facilitating assessment of seasonality. However, our study has several limitations. First, the relatively small sample size, and observational design may limit generalisability and causal inference. Second, most subjects (79.8%) received antibiotics before specimen collection in accordance with national guidelines. To address this, we enrolled subjects within 24 hours of admission, and specimens were collected as soon as possible to minimise the effects of antibiotics on culture results. Third, we did not enrol healthy control children, limiting the ability to estimate the adjusted population attributable fraction of each pathogen.[29 30] A healthy control group could have revealed baseline carriage rates, minimising overattribution of disease to non-pathogenic organisms.[21 22 29 30] Fourth, we did not collect lung aspirates or pleural fluid specimens, which are superior for determination of pneumonia aetiology.[15] Fifth, several subjects had pneumonia of unknown aetiology; this may have been due to administration of antibiotics before culture which could reduce sensitivity, poor IS quality, the limited panel of bacterial and viral pathogens tested, lack of fungal testing, or currently unrecognised causes of paediatric pneumonia.

In conclusion, the epidemiology of childhood CAP is constantly evolving in step with social and environmental factors and thus, should be regularly assessed. Our study found that *H. influenzae* non-type B and RSV were the most common pathogens causing hospitalised CAP among Indonesian children aged 2–59 months old, reflecting temporally dynamic aetiologies of childhood CAP; studies from the 1970s–1990s mainly detected *S. pneumoniae* and *H. influenzae* type B as the most important causes of childhood pneumonia in LMICs.[3–5] PCR on IS demonstrated the best sensitivity for pathogen identification. We recommend incorporating molecular assays for pathogen detection, preferably multiplexed point-of-care assays, into practice guidelines. Improvements in Indonesia's lab infrastructure during the COVID-19 pandemic can be leveraged to facilitate use of molecular assays for evaluation of childhood CAP. Optimisation of pathogen detection to understand changing childhood CAP epidemiology will also inform public policy on prevention and management.

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DL, HK, ATA, MK, AN, C-YL and CL assisted with manuscript writing, analysis and interpretation of data. All authors contributed to manuscript development, edited for critical conten and have approved the final version. HK acts as guarantor for the final manuscript.

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SUPPLEMENTARY MATERIALS.

Supplementary Table 1. Microbiological, Molecular and Serologic Methods

No.	Assays	Procedures
1.	Gram stain	Gram-stained smears were obtained from the most purulent portion of each induced sputum specimen. The good quality specimen was defined as <10 squamous epithelium per low-power field (magnification, 100×) [1]. The procedure of the Gram stain required four basic steps that include applied a primary stain (crystal violet) to a heat-fixed smear, followed by the addition of a mordant (Gram's Iodine), rapid decolorization with alcohol, acetone, or a mixture of alcohol and acetone and lastly, counterstained with safranin [2]. The Gram-stained smears interpreted as follows: Gram-positive lancet-shaped diplococci (GPDC) suggest *Streptococcus pneumoniae*; Gram-positive diplococci (GPDC) or cocci in chains suggest *Streptococcus pyogenes*; Gram-positive cocci in clusters (GPC-cluster) suggest *Staphylococcus aureus*; Gram-negative coccobacilli (GNCB) suggest *Hemophilus influenzae*, *Bordetella pertussis* or *Acinetobacter baumannii*; Gram-negative diploccoci (GNDC) suggest *Moraxella catarrhalis*; large Gram-negative rods (GNR-large) suggest *Klebsiella pneumoniae* or *Escherichia coli*; and small Gram-negative rods (GNR-small) suggest *Pseudomonas aeruginosa* [3].
2.	Induced Sputum Culture	The most purulent portion of induced sputum was inoculated onto sheep blood, chocolate, and MacConkey agars, streaked out using a standard 4-quadrant streaking method, and incubated at 35°C for 48 hours. Cultures were examined at 24 hours and 48 hours, and predominant bacteria were identified and quantified according to the farthest quadrant with visible colonies (first quadrant, scanty; second quadrant, 1+; third quadrant, 2+; fourth quadrant, 3+) [4]. Then, the predominant bacteria isolates were inoculated into the appropriate VITEK identification strip using the VITEK® 2 COMPACT (BioMérieux, Germany). Briefly, a bacterial suspension was adjusted to a McFarland standard of 0.50 in a solution of 0.45 % sodium chloride using DensiLameter. The time between preparation of the solution and filling of the card was always less than 1 h. Analysis was done using the identification card and automatically read every 15 min. Bacteria identification and antibiotic susceptibility testing results were analyzed using the VITEK 2 software according to the manufacturer's instructions [5].
3.	Blood Culture	Up to 2 mL of blood samples (2 bottle sets) were collected and sent to the site laboratory with standardized procedures. Blood cultures were incubated for at least 5 days, unless positive, using automated systems (BacT/ALERT in Tangerang Hospital; BACTEC at other sites) [6]. Organisms were identified according to standard microbiological methods as described in induced sputum culture section. The following organisms were considered to be contaminants when identified in blood cultures: Coagulase-negative *staphylococci*, *Micrococcus* spp., *Propionibacterium* spp., Alpha-hemolytic streptococci (except

No.	Assays	Procedures
		pneumococcus, *Streptococcus anginosus*, and *Streptococcus mitis*), *Enterococcus* spp., *Corynebacterium* spp. (diphtheroids), *Bacillus* spp. (except *Bacillus anthracis*), *Pseudomonas* spp. (except *Pseudomonas aeruginosa*), *Stomatococcus, Aeroccocus, Neiserria subflava, Veillonella* spp., other environmental non-fermenting Gram negative rods, and *Candida* spp [7].
4.	Viral RNA Extraction	Viral RNA was extracted from viral transport media (VTM) containing respiratory swab as well as sputum, using the QIAamp Viral RNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. Briefly, 140 µl of VTM or sputum coat was lysed in 560 of carrier RNA-containing AVL buffer, followed by the binding of viral RNA to the QIAamp membrane. Contaminants were removed from viral RNA in two separate washing steps using two different wash buffers, AW1 and AW2. Viral RNA was eluted in 60 µl of AVE buffer and kept in -80^{o} C if not directly used [8,9].
5.	Bacterial DNA Extraction	Bacterial DNA was extracted from viral transport media (VTM) containing respiratory swab as well as sputum, using the QIAamp® DNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. Briefly, 20 µl of QIAGEN Protease and 200 µl of VTM or sputum coat was lysed in 200 of AL buffer, followed binding of DNA to the QIAamp membrane. Contaminants were removed from DNA in two separate washing steps using two different wash buffers, AW1 and AW2. Bacterial DNA was eluted in 200 µl of AE buffer and kept in -80^{o} C if not directly used
6.	qPCR for Respiratory Viruses	The realtime PCR for respiratory virus detection was done followed the protocol of Beld et al., 2004 and Jansen et al., 2011. Positive control is a synthetic plasmid carrying the nucleotide sequence of the detection target. Primers, probes, and positive controls were synthesized and purified by an outside vendor (Integrated DNA Technologies, Iowa, US). Realtime PCR was done using the TaqManTM Fast Virus 1-Step Master Mix (Thermo Fisher Scientific; Cat#: 4444432) in an Applied Biosystems 7500 Fast Realtime PCR System (Thermo Fisher Scientific, MA, US). The reaction mixture composition was 1X TaqManTM Fast Virus 1-Step Master Mix, 0.5 µM of each primer, 0.25 µM probe, and 4 µl RNA, in a total 20 µl volume. The cycle condition was 50^{o} reverse transcription for 5 minutes, 95^{o} C initial denaturation for 20 seconds, followed by 45 cycles of denaturation (95^{o} C, 3 seconds) and annealing/elongation (55^{o} C, 30 seconds). Realtime PCR works correctly when the positive control demonstrates the amplification curve and the template-free (negative) control demonstrates no amplification curve (no Ct values) [8,9].
7.	qPCR for Respiratory Bacteria	In real-time PCR (qPCR) a portion of bacterial DNA genome specific to the pathogen(s) of interest is amplified using a specific pair of primers and probes for each bacteria, that were selected from the available literature [10–14]. A detector (TaqMan® probe) is used in the reaction. Mastermix is prepared in a 1.5-ml tube for total reaction. qPCR assays were carried out in a total volume of 20 µL, comprising 10 µL of TaqMan® Fast Universal PCR Master Mix, 1.4 µL of nuclease-free water (Promega), 3.6 µL of oligonucleotide mixtures, and 4 µL of

No.	Assays	Procedures
		DNA extract. The cycle condition was 95° C initial denaturation for 20 seconds, followed by 45 cycles of denaturation (95° C, 3 seconds) and annealing/elongation (58° C, 30 seconds). Realtime PCR works correctly when the positive control demonstrates the amplification curve and the template-free (negative) control demonstrates no amplification curve (no Ct values)
8.	Serology Test	Assays were obtained from SERION ELISA classic kit (Institut Virion/Serion Laboratories, Germany) and used according to the insert of SERION kit. SERION ELISA classic is a qualitative and quantitative immunoassay for detecting human antibodies in serum or plasma with their corresponding antigen. The indirect enzyme immunosorbent assay in this kit was coated with specific antigens of the pathogen of interest. Patient sera are diluted in a rheumatoid factor and then diluted in Sample Diluent (containing phosphate with tween 20 and Bromphenol blue) and incubated in the coated microwells to bind serum antibody to the solid-phase antigen. The microwells are then washed to remove unreacted serum proteins, and enzyme conjugate (anti-human IgA, IgG, or IgM APC_Alkaline phosphatase) is added to label the bound antibody. After further incubation, the microwells are washed to remove unbound APC Conjugate. The pNPP (para-nitrophenyl phosphate) substrate is then added to quantitate the Conjugate-bound p-nitrophenyl phosphate portion. The colorless substrate p-nitrophenyl phosphate is then converted into the colored product p-nitrophenol. The signal intensity of this reaction product is proportional to the concentration of the analyte in the serum antibody. This timed reaction is interrupted with a Stop Solution (sodium hydroxide). Color intensity (Absorbance) is measured at a wavelength of 405nm on a microtiter plate reader or spectrophotometer within 15 minutes of adding the stop solution. Antibody activities are calculated by the SERION evaluation software [15].

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Supplementary Table 2. Antibiotic regimens administered prior to blood culture

Antibiotic Regimen, (Dose)	All sites (N=188), Administered Dose(s) prior to blood culture, N (%)	Semarang (N=47) Administered Dose(s) prior to blood culture, N (%)	Yogyakarta (N=52) Administered Dose(s) prior to blood culture, N (%)	Tangerang (N=89) Administered Dose(s) prior to blood culture, N (%)
Ampicillin (50 mg/kg IV q6hr) + Gentamicin (2 – 7.5 mg/kg IV q24hr)	65 (34.6) 1x: 45 (24.0) 2x: 20 (10.6)	25 (53.2) 1x: 20 (42.6) 2x: 5 (10.6)	40 (76.9) 1x: 25 (48.1) 2x: 15 (28.8)	0 (0)
Cefotaxime (50 – 100 mg/kg IV q6hr)	32 (17.0) All received 1 dose	0 (0)	0 (0)	32 (36.0) All received 1 dose
Ceftriaxone (50 mg/kg IV q12hr)	27 (14.4) All received 1 dose	0 (0)	0 (0)	27 (30.3) All received 1 dose
Ampicillin (50 mg/kg IV q6hr)	14 (7.4) 1x: 10 (5.3) 2x: 4 (2.1)	5 (10.6) All received 1 dose	9 (17.3) 1x: 5 (9.6) 2x: 4 (7.7)	0 (0)
Gentamicin (2 – 7.5 mg/kg IV q24hr)	3 (1.6) 1x: 2 (1.1) 2x: 1 (0.5)	3 (6.4) 1x: 2 (4.3) 2x: 1 (2.1)	0 (0)	0 (0)
Ceftazidime (50 – 100 mg/kg IV q8hr)	3 (1.6) All received 1 dose	0 (0)	0 (0)	3 (3.4) All received 1 dose
Cefamandole (50 – 100 mg/kg IV q12hr)	2 (1.1) 1x: 1 (0.5) 2x: 1 (0.5)	2 (4.3) 1x: 1 (2.1) 2x: 1 (2.1)	0 (0)	0 (0)
Ceftriaxone (50 mg/kg IV q12hr) + Gentamicin (2 – 7.5 mg/kg IV q24hr)	2 (1.1) All received 1 dose	2 (4.3) All received 1 dose	0 (0)	0 (0)
Amikacin (15 mg/kg IV q8hr) + Cefotaxime (50 – 100 mg/kg IV q6hr)	1 (0.5) All received 1 dose	1 (2.1) All received 1 dose	0 (0)	0 (0)
Amoxicillin syrup (40 mg/kg PO q12hr)	1 (0.5) All received 1 dose	1 (2.1) All received 1 dose	0 (0)	0 (0)

IV = intravenous; PO = peroral; qXhr = given at X hour intervals.

Supplementary Table 3. Pathogen distribution by WHO severity classification status and mortality.

Pathogens	WHO Classification System		*p-value*	Mortality Outcome		*p-value*
	Severe (N=89)	Non-severe (N=99)		Died (N=19)	Alive (N=169)	
Causative Pathogen						
H. influenzae non-type b	31 (34.8%)	42 (42.4%)	0.286	8 (42.1%)	65 (38.5%)	0.757
RSV	25 (28.1%)	26 (26.3%)	0.778	2 (10.5%)	49 (29.0%)	0.086
K. pneumoniae	15 (16.9%)	28 (28.3%)	0.062	6 (31.6%)	37 (21.9%)	0.388
S. pneumoniae	19 (21.3%)	10 (10.1%)	0.033	1 (5.2%)	28 (16.6%)	0.317
Influenza virus	9 (10.1%)	16 (16.2%)	0.223	3 (15.8%)	22 (13.0%)	0.723
S. aureus	8 (9.0%)	12 (12.1%)	0.487	0 (0.0%)	20 (11.8%)	0.230
PIV	8 (9.0%)	9 (9.1%)	0.981	1 (5.3%)	16 (9.5%)	1.000
hMPV	6 (6.7%)	5 (5.1%)	0.622	1 (5.3%)	10 (5.9%)	1.000
Rhinovirus	7 (7.9%)	3 (3.0%)	0.196	1 (5.3%)	9 (5.3%)	1.000
B. pertussis	4 (4.5%)	3 (3.0%)	0.709	2 (10.5%)	5 (3.0%)	0.150
Infection Type						
Bacterial pathogen	17 (19.1%)	31 (31.3%)	0.055	7 (36.8%)	41 (24.3%)	0.268
Viral pathogen	16 (18.0%)	15 (15.2%)	0.602	2 (10.5%)	29 (17.2%)	0.744
Mixed pathogen	38 (42.7%)	38 (38.4%)	0.547	5 (26.3%)	71 (42.0%)	0.186
Unknown pathogen	18 (20.2%)	15 (15.2%)	0.361	5 (26.3%)	28 (16.6%)	0.337

Differences in categorical variables were compared using Pearson χ2 or Fisher's exact test when the expected values in any of the contingency table cells were below 5.

Supplementary Table 4. Summary of fatal cases.

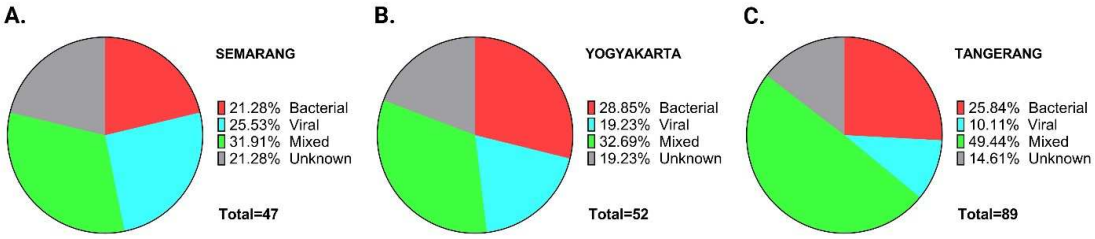
Case, Site, Gender (Age, mo)	Medical History	Signs and Symptoms (SS), Vital Signs (VS), Laboratory parameter (Lab) at admission	CXR	Causative Pathogen	ABX during Hospitalization	Hospitalization status	Cause of Death
#01, SMG, Male (4)	Recurrent pneumonia, congenital heart disease, severe malnutrition	• **SS:** Cough, fever, dyspnea, chest indrawing, intercostal retraction, rhonchi • **VS:** 38°C, RR 44x/min, SpO_2 97% • **Lab:** Hb 9.6 g/dL, WBC 24.1 $\times10^9$/L, PLT 350 $\times10^9$/L, NLR 4.63, CRP 25.70 mg/L, PCT 2.41 ng/mL	Alveolar infiltrate	Rhinovirus, *H. influenzae non-type b*	Ampicillin, Gentamicin, Ceftriaxon, Cefoperazone Sulbactam	On mechanical ventilator ICU admission (25 days) Died on Day-26	Cardiopulmonary failure Sepsis
#02, SMG, Female (23)	Recurrent pneumonia, congenital heart disease, incomplete NIP (DPT-Hib), malnutrition, developmental delay	• **SS:** Cough, fever, dyspnea, chest indrawing, intercostal retraction, rhonchi • **VS:** 37.5°C, RR 56x/min, SpO_2 95% • **Lab:** Hb 10.6 g/dL, WBC 14.1 $\times10^9$/L, PLT 405 $\times10^9$/L, NLR 9.63, CRP 14.90 mg/L, PCT 0.37 ng/mL	Alveolar and interstitial infiltrates	Influenza A (H1N1)	Ampicillin, Gentamicin, Metronidazole, Ceftriaxon, Meropenem	On mechanical ventilator ICU admission (9 days) Died on Day 21	Cardiopulmonary failure
#03, SMG, Female (11)	Low birth weight, congenital heart disease, incomplete NIP (Measles), severe malnutrition, developmental delay	• **SS:** Cough, fever, dyspnea, diarrhea, nasal flaring, chest indrawing, intercostal retraction, rhonchi • **VS:** 38.3°C, RR 45x/min, SpO_2 96% • **Lab:** Hb 8.1 g/dL, WBC 15.9 $\times10^9$/L, PLT 677 $\times10^9$/L, NLR 1.87	Alveolar and interstitial infiltrates	Influenza A (H3N2), *B. pertussis, H. influenzae non-type b, K. pneumoniae*	Ampicillin, Gentamicin, Azithromycin	On nasal cannula Died on day 19	Cardiopulmonary failure
#04, SMG, Male (45)	Recurrent pneumonia, frontometaphysea l dysplasia syndrome,	• **SS:** Cough, fever, dyspnea, nasal flaring, intercostal retraction, rhonchi, wheezing • **VS:** 36.7°C, RR 40x/min, SpO_2 99%	Alveolar infiltrate	Unknown	Ampicillin, Gentamicin	On Nasal cannula Died on day 2	Respiratory failure

Case, Site, Gender (Age, mo)	Medical History	Signs and Symptoms (SS), Vital Signs (VS), Laboratory parameter (Lab) at admission	CXR	Causative Pathogen	ABX during Hospitalization	Hospitalization status	Cause of Death
	epilepsy, developmental delay	• **Lab:** Hb 13.7 g/dL, WBC 11.3 $\times 10^9$/L, PLT 277 $\times 10^9$/L, NLR 0.98, CRP 0.10 mg/L, PCT 0.05 ng/mL					
#05, SMG, Male (5)	Premature birth, low birth weight, recurrent pneumonia, congenital heart disease, incomplete NIP (DPT-Hib)	• **SS:** Cough, dyspnea, nasal flaring, chest indrawing, intercostal retraction, • **VS:** 36.8°C, RR 30x/min, SpO_2 98% • **Lab:** Hb 10.9 g/dL, WBC 12.4 $\times 10^9$/L, PLT 396 $\times 10^9$/L, CRP 0.80 mg/L, PCT 128 ng/mL	Alveolar infiltrate	*K. pneumoniae*	Ampicillin, Gentamicin	On Simple mask ICU admission (1 day) Died on day 6	Cardiopulmonary failure
#06, SMG, Female (3)	Recurrent pneumonia, incomplete NIP (DPT-Hib), malnutrition	• **SS:** Cough, dyspnea, chest indrawing, intercostal retraction, rhonchi • **VS:** 36.7°C, RR 42x/min, SpO_2 99% • **Lab:** Hb 8.2 g/dL, WBC 16 $\times 10^9$/L, PLT 499 $\times 10^9$/L, ANC 6.7, NLR 0.76, CRP 13.10 mg/L, PCT 0.28 ng/mL	Alveolar infiltrate	Unknown	Ampicillin, Gentamicin, Vancomycin, Metronidazol, Meropenem	On mechanical ventilator ICU admission (7 days) Died on day 18	Septic shock, respiratory failure
#07, YGY, Female (10)	Congenital heart disease, incomplete NIP (DPT-Hib, and Measles), severe malnutrition, developmental delay	• **SS:** Cough, fever, dyspnea, head bobbing, chest indrawing, intercostal retraction, rhonchi • **VS:** 39.0 °C, RR 64x/min, SpO_2 96% • **Lab:** Hb 10.1 g/dL, WBC 12.1 $\times 10^9$/L, PLT 415 $\times 10^9$/L, ANC 6.0, NLR 1.15, CRP 4.90 mg/L, PCT 0.11 ng/mL	Alveolar infiltrate	hMPV, RSV A	Ampicillin, Gentamicin, Ceftriaxone, Cotrimoxazole	On mechanical ventilator/ ICU admission (13 days) Died on day 17	Sepsis, Pulmonary crisis due to pulmonary hypertension
#08, YGY, Female (3)	Low birth weight, congenital heart disease, incomplete NIP (DPT-Hib), severe malnutrition	• **SS:** Cough, fever, dyspnea, chest indrawing, intercostal retraction, rhonchi • **VS:** 37.2 °C, RR 49x/min, SpO_2 56% • **Lab:** Hb 9.7 g/dL, WBC 11.3 $\times 10^9$/L, PLT 115 $\times 10^9$/L, ANC 7.0, NLR 1.92	Alveolar and interstitial infiltrates	Unknown	Ampicillin, Ceftriaxone	On nasal cannula Hospital discharge on day 10 Died on day 29 (outside hospitalization)	Acute Respiratory Distress Syndrome
#09, YGY, Female (5)	Congenital heart disease, incomplete NIP (DPT-Hib), severe malnutrition	• **SS:** Cough, dyspnea, inability to drink, nasal flaring, chest indrawing, intercostal retraction, rhonchi • **VS:** 37.0 °C, RR 60x/min, SpO_2 96% • **Lab:** Hb 10.3 g/dL, WBC 26.9 $\times 10^9$/L, PLT 788 $\times 10^9$/L, ANC 18.5, NLR 2.97	Alveolar and interstitial infiltrates	*H. influenzae non-type b, K. pneumoniae*	Ampicillin, Gentamicin	On nasal cannula Died on day 15	Aspiration, mucous hypersecretion
#10, YGY, Male (6)	Recurrent pneumonia, congenital heart disease, tuberculosis, incomplete NIP (DPT-Hib)	• **SS:** Cough, fever, dyspnea, nasal flaring, chest indrawing, intercostal retraction, rhonchi, wheezing • **VS:** 37.3 °C, RR 50x/min, SpO_2 89% • **Lab:** Hb 11.6 g/dL, WBC 13.3 $\times 10^9$/L, PLT 189 $\times 10^9$/L, ANC 3.7, NLR 0.48, CRP 4.90 mg/L, PCT 0.08 ng/mL	Alveolar and interstitial infiltrates, pleural effusion	*K. pneumoniae*	Ampicillin, Gentamicin, Ceftriaxone	On non-rebreather mask Died on day 4	Septic shock
#11, TRG, Female (5)	Premature birth, developmental delay	• **SS:** Cough, fever, dyspnea, nasal flaring, rhonchi, wheezing • **VS:** 37.5 °C, RR 48x/min, SpO_2 31% • **Lab:** Hb 8.5 g/dL, WBC 12.1 $\times 10^9$/L, PLT 208 $\times 10^9$/L, ANC 8.6, NLR 3.23, CRP 0.91 mg/L, PCT 0.74 ng/mL	Alveolar infiltrate	*A. baumannii* (MDR)	Cefotaxime	On Nasal cannula Hospital discharge on day 7 Died on day 17 (outside hospitalization)	Unknown death
#12, TRG, Female (2)	Incomplete NIP (DPT-Hib)	• **SS:** Cough, fever, dyspnea, diarrhea, skin rash, intercostal retraction, rhonchi, wheezing • **VS:** 37.6 °C, RR 63x/min, SpO_2 93% • **Lab:** Hb 10.5 g/dL, WBC 13.6 $\times 10^9$/L, PLT 289 $\times 10^9$/L, ANC 10.2, NLR 3.95, CRP 175.30 mg/L, PCT 0.7 ng/mL	Alveolar and interstitial infiltrates	Unknown	Ceftriaxone, Ceftazidime, Azithromycin	On Nasal cannula Died on day 8	Sepsis
#13, TRG, Female (2)	Incomplete NIP (DPT-Hib)	• **SS:** Cough, fever, dyspnea, nasal flaring, chest indrawing, intercostal retraction, rhonchi • **VS:** 36 °C, RR 45x/min, SpO_2 96% • **Lab:** Hb 7.8 g/dL, WBC 21.2 $\times 10^9$/L, PLT 563 $\times 10^9$/L, ANC 16.5, NLR 3.9, CRP 280.30 mg/L, PCT 0.09 ng/mL	Alveolar and interstitial infiltrates, pleural effusion	Influenza B, *S. mitis* (MDR)	Ceftazidime	On non-rebreather mask ICU admission (3 days) Died on day 3	Respiratory Failure

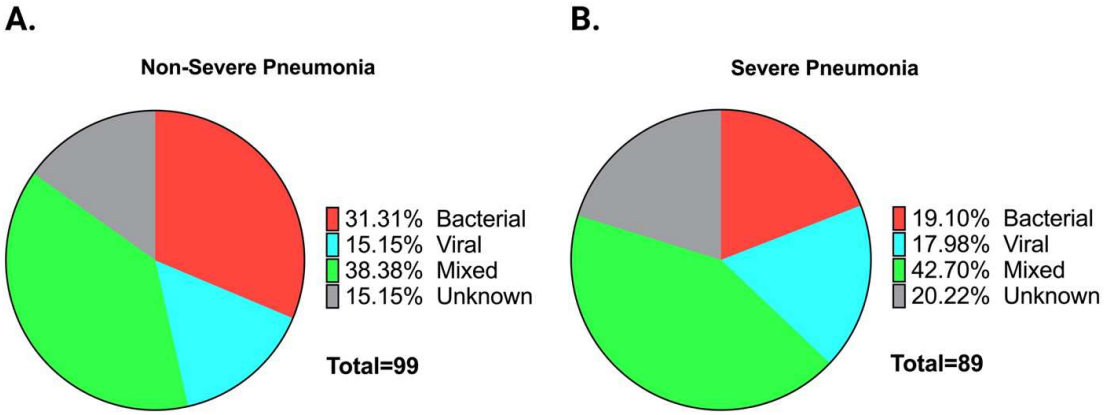
Case, Site, Gender (Age, mo)	Medical History	Signs and Symptoms (SS), Vital Signs (VS), Laboratory parameter (Lab) at admission	CXR	Causative Pathogen	ABX during Hospitalization	Hospitalization status	Cause of Death
#14, TRG, Female (2)	Congenital heart disease, incomplete NIP (DPT-Hib), severe malnutrition	• **SS:** Cough, fever, dyspnea, nasal flaring, chest indrawing, intercostal retraction, rhonchi, wheezing • **VS:** 37 °C, RR 60x/min, SpO_2 76% • **Lab:** Hb 9.5 g/dL, WBC 17.2 $\times10^9$/L, PLT 296 $\times10^9$/L, ANC 8.8, NLR 1.42, CRP 0.70 mg/L, PCT 0.02 ng/mL	Interstitial infiltrate	Unknown	Cefotaxime	On Simple mask Died on day 2	Respiratory Failure
#15, TRG, Male (9)	Incomplete NIP (Measles)	• **SS:** Cough, fever, dyspnea, nasal flaring, chest indrawing, intercostal retraction, rhonchi • **VS:** 37 °C, RR 30x/min, SpO_2 89% • **Lab:** Hb 6.4 g/dL, WBC 25.7 $\times10^9$/L, PLT 801 $\times10^9$/L, ANC 18.5, NLR 3.43, CRP 33.35 mg/L, PCT 0.34 ng/mL	Interstitial infiltrate	*H. influenzae non-type b*	Cefotaxime, Ceftriaxone, Meropenem	On mechanical ventilator ICU admission (8 days) Died on day 12	Meningoencephalitis, Respiratory Failure
#16, TRG, Female (4)	Premature birth, low birth weight, congenital heart disease, incomplete NIP (DPT-Hib)	• **SS:** Cough, fever, dyspnea, diarrhea, chest indrawing, intercostal retraction, rhonchi • **VS:** 38 °C, RR 32x/min, SpO_2 85% • **Lab:** Hb 9.2 g/dL, WBC 16.8 $\times10^9$/L, PLT 224 $\times10^9$/L, ANC 9.4, NLR 2.24, CRP 2.46 mg/L, PCT 2.24 ng/mL	Alveolar and interstitial infiltrates,	*H. influenzae non-type b*, *K. pneumoniae*	Cefotaxime, Gentamicin, Ceftriaxone	On nasal cannula Died on day 11	Unknown death
#17, TRG, Female (20)	Developmental delay, incomplete NIP (DPT-Hib)	• **SS:** Cough, fever, dyspnea, chest indrawing, intercostal retraction, rhonchi • **VS:** 36.3°C, RR 40x/min, SpO_2 75% • **Lab:** Hb 7.0 g/dL, WBC 15.2 $\times10^9$/L, PLT 668 $\times10^9$/L, ANC 9.7, NLR 2.13, CRP 55.10 mg/L	Alveolar and interstitial infiltrates, pleural effusion	*H. influenzae non-type b*, *K. pneumoniae*	Cefotaxime, Gentamicin, Ceftriaxone	On mechanical ventilator ICU admission (3 days) Died on day 8	Septic shock, Cardiopulmonary failure
#18, TRG, Male (4)	Low birth weight, developmental delay, recurrent pneumonia, incomplete NIP (DPT-Hib), severe malnutrition	• **SS:** Cough, fever, dyspnea, nasal flaring, chest indrawing, intercostal retraction, rhonchi • **VS:** 36.7 °C, RR 30x/min, SpO_2 92% • **Lab:** Hb 11.6 g/dL, WBC 20.5 $\times10^9$/L, PLT 433 $\times10^9$/L, ANC 11.9, NLR 2.52, CRP 16.80 mg/L, PCT 20.1 ng/mL	Alveolar and interstitial infiltrates,	PIV 3, *H. influenzae non-type b*, *S. pneumoniae*	Ceftazidime	On non-rebreather mask Died on day 3	Respiratory failure
#19, TRG, Male (15)	Incomplete NIP (DPT-Hib and Measles)	• **SS:** Cough, fever, dyspnea, rhonchi • **VS:** 37.8 °C, RR 52x/min, SpO_2 80% • **Lab:** Hb 9.4 g/dL, WBC 23.6 $\times10^9$/L, PLT 786 $\times10^9$/L, CRP 3.30 mg/L, PCT 0.07 ng/mL	Interstitial infiltrate	RSV B, *B. pertussis, H. influenzae non-type b*	Cefotaxime	On nasal cannula Hospital discharged on day 5 Died on day 20 (outside hospitalization)	Unknown death

Abbreviation. SMG: Semarang site; YGY: Yogyakarta site; TGR: Tangerang site; NIP: mandatory National Immunization Program; DPT-Hib: a combined vaccine of adsorbed diphtheria, tetanus toxoids, acellular pertussis and of *Haemophilus influenzae* type b conjugate vaccines; CXR: chest X-ray; ABX: Antibiotics; RSV: Respiratory Syncytial Virus; hMPV: Human Metapneumovirus; PIV: Parainfluenza Virus; MDR: Multiple drug resistance.

Supplementary Figure 1. PEER-PePPeS Study sites



Supplementary Figure 2. Proportion of Identified Pathogen in each Sites. (A) Semarang, (B) Yogyakarta, and (C) Tangerang



Supplementary Figure 3. Proportion of Identified Pathogen between WHO Severity Status. (A) Non-severe Pneumonia, (B) Severe Pneumonia.