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Burden of Influenza in Less Than 5-Year-Old Children Admitted to Hospital with Pneumonia in Developing and Emerging Countries: A Descriptive, Multicenter Study

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Abstract. This descriptive 4-year study reports the proportion of detection of influenza viruses in less than 5-year-old children hospitalized for pneumonia in eight developing and emerging countries and describes clinical and microbiological characteristics of influenza-related pneumonia cases. Hospitalized children presenting radiologically confirmed pneumonia aged 2–60 months were prospectively enrolled in this observational standardized study. Mean proportion of isolated influenza virus was 9.7% (95% confidence interval: 7.9–11.8%) among 888 pneumonia children analyzed, with moderate heterogeneity between countries—ranging from 6.2% in Cambodia to 18.8% in Haiti. The clinical characteristics of children with influenza-related pneumonia were not substantially different from those of other pneumonia cases. Influenza A H1N1-related pneumonia cases appeared as more severe than pneumonia cases related to other strains of influenza. *Streptococcus pneumoniae* was detected more often in blood samples from influenza-related cases than in those without detected influenza viruses (19.7% versus 9.5%, $P = 0.018$). Influenza-related pneumonia is frequent among children less than 5 years old with pneumonia, living in developing and emerging countries. Influenza might be a frequent etiologic agent responsible for pneumonia or a predisposing status factor for pneumococcal-related pneumonia in this population.

INTRODUCTION

Influenza is a major cause of mortality and morbidity in young children worldwide. According to a meta-analysis published in 2011,[1] a total of one million severe, acute, lower respiratory infections and between 28,000 and 111,500 deaths may be attributable annually to influenza-associated infections in children younger than 5 years, with 99% of these deaths occurring in developing countries. Influenza viruses are recognized as risk factors for secondary bacterial infections or co-colonizations[2] or as etiological agents of viral pneumonia.[3] Therefore, detection of influenza viruses in upper respiratory samples from children with pneumonia might be related to one of these phenomena or both.

The burden of influenza has been determined in industrialized countries, with attack rates reaching between 10% and 20% during seasonal outbreaks or higher during pandemics,[4] but data from developing and emerging nations remain scarce.[5] We conducted a descriptive study of less than 5-year-old children hospitalized because of pneumonia in developing and emerging countries. The main objective was to estimate the age- and country-stratified proportion of influenza-related pneumonia in this population. Secondary objectives were the description of clinical and microbiological characteristics of—particularly bacterial coinfections in—influenza-related pneumonia cases.

MATERIALS AND METHODS

This descriptive investigation was based on pneumonia cases provided by a large, multicenter, prospective case–control study carried out between the end of 2009 and the beginning of 2014 in nine settings from eight developing and emerging countries: Cambodia, China, Haiti, India (two settings), Madagascar, Mali, Mongolia, and Paraguay. The participating sites were members of the Global Approach to Biological Research, Infectious Diseases and Epidemics in Low-income Countries network established by Fondation Mérieux.[6] The protocol, sites, and initial results of the prospective study have been reported in detail elsewhere.[7] This study is an ancillary analysis of the previously collected data.[8,9] Briefly, incident cases of 2- to 60-month-old children hospitalized with a suspected pneumonia were identified by study clinicians at each participating site and assessed for eligibility. Pneumonia cases were defined by the following criteria:

- Cough and/or dyspnea;
- tachypnea, as delineated by the WHO (breathing rate ≥ 50 cycles per minute in children 2–12 months of age and ≥ 40 cycles per minute in children 12–59 months of age)[9];
- first symptoms appearing within the last 14 days; and
- radiological confirmation of pneumonia, as per WHO guidelines, including primary end-point pneumonia or other infiltrates.[10]

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Patients who met the inclusion criteria and from whom signed informed consent was obtained from their parents or legal guardians were included in the study.

Demographic characteristics, medical history, vital signs, clinical symptoms, and biological parameters at admission were recorded prospectively for each patient on a standardized data collection form. Data quality was monitored and evaluated by each site and by the same scientists of the Emerging Pathogens Laboratory (Lyon, France).

Specimens (nasal swabs/aspirates and blood) were collected in the first 48 hours of patient hospitalization. Biological samples were taken before in-hospital administration of antibiotics. Whole blood allowed complete blood count and culture, and a standard semiquantitative real-time multiplex polymerase chain reaction (RT-PCR) assay was performed for the identification of *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* type B.[11,12] C-reactive protein and procalcitonin were quantified in serum. Respiratory specimens were tested for the detection of viruses and bacteria by another RT-PCR assay with a panel of 19 viruses and five bacteria (fast-track diagnostics respiratory pathogens 21 plus; Fast-track Diagnostic, Esch-sur-Alzette, Luxembourg). A centralized, blinded polymer chain reaction (PCR) respiratory quality control panel was provided to all sites to ensure procedure validation on-site before the specimens were processed locally.

Continuous variables were reported as median and interquartile range (IQR) with comparisons by the Mann–Whitney *U* test. Categorical variables were computed as number of individuals and percentage, with χ^2 or Fisher's exact test as appropriate for comparison. Calculated proportion rates of influenza-related pneumonia represented mean occurrence over the study period. They were reported per 100 patients with their 95% confidence interval (CI). Statistical analysis was undertaken with Stata version 13.0 (StataCorp., College Station, TX).

RESULTS

Overall, 86 influenza-related pneumonia cases were observed among 888 pneumonia children analyzed. Mean influenza proportion in less than 5-year-old children with pneumonia was 9.7% (95% CI: 7.9–11.8%). Country-stratified influenza proportion rates ranged from 6.2% (95% CI: 3.3–10.6%) in Cambodia and 6.2% (95% CI: 2.3–13.3%) in Madagascar to 18.8% (95% CI: 12.1–27.3%) in Haiti, as shown in Figure 1. No substantial seasonality was retrieved, neither on overall data nor after stratification by geographical area (Supplemental Figure 1A–E).

Influenza proportion in children with pneumonia was homogeneous in different age strata (9.7% in children aged 2–11 months, 9.7% in children aged 12–23 months, and 9.6% in children aged 24–60 months; $P = 0.99$). Figure 2 reports country- and age-stratified proportions of influenza-related pneumonia. In the 2- to 11-month-old group, influenza proportions ranged from 4.0% (95% CI: 0.7–12.6%) in Mali to 25.7% (95% CI: 12.4–16.3%) in Haiti. It ranged from 0% (95% CI: 0–10.1%) in Madagascar to 23.7% (95% CI: 2.2–39.0%) in India in the 12- to 23-month-old group and between 3.5% (95% CI: 0.2–15.8%) in Paraguay and 21.9% (95% CI: 10.1–38.5%) in Haiti in the 24- to 60-month-old group.

Table 1 enumerates the characteristics of influenza-related pneumonia cases in comparison to pneumonia cases without identified influenza viruses. No statistically significant differences in demographics, vital signs, and clinical symptoms were

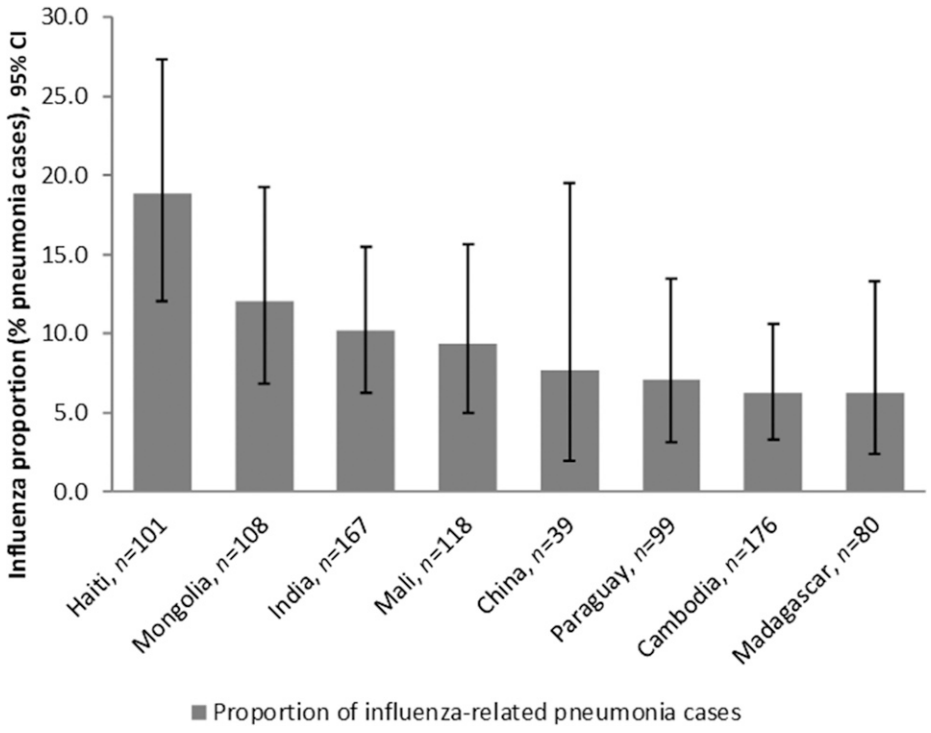
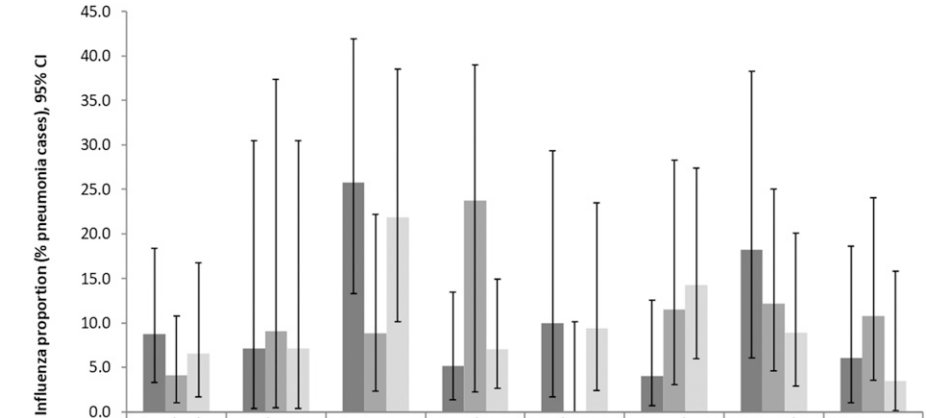


FIGURE 1. Country-stratified proportions of influenza-related pneumonia among less than 5-year-old children with pneumonia. Columns and error bars refer to proportions of influenza-related pneumonia among less than 5-year-old children with pneumonia, with their 95% confidence interval (CI).



	Cambodia	China	Haiti	India	Madagascar	Mali	Mongolia	Paraguay
2–11 months	8.8	7.1	25.7	5.2	10.0	4.0	18.2	6.1
12–23 months	4.1	9.1	8.8	23.7	0.0	11.5	12.2	10.8
24–60 months	6.5	7.1	21.9	7.0	9.4	14.3	8.9	3.4

FIGURE 2. Country- and age-stratified proportions of influenza-related pneumonia among less than 5-year-old children with pneumonia. Columns and error bars refer to proportions of influenza-related pneumonia among less than 5-year-old children with pneumonia with their 95% confidence interval (CI).

observed between the two groups. White blood cell (WBC) and neutrophil counts were significantly lower in influenza-related pneumonia cases ($P < 0.001$ and $P = 0.002$, respectively).

Supplemental Table 1 lists age-stratified characteristics of influenza-related pneumonia cases compared with pneumonia cases without identified influenza viruses. In the 2- to 11-month-old and 12- to 23-month-old age groups, few significant differences in characteristics were observed. In the 24- to 60-month-old age group, wheezing, diminished breathing sounds, and rhonchi were identified less frequently in influenza-related pneumonia cases compared with pneumonia cases without identified influenza viruses ($P = 0.044$, $P = 0.038$, and $P = 0.01$, respectively); in addition, convulsions occurred more often ($P = 0.03$) and WBC and neutrophil counts were lower ($P < 0.001$ and $P = 0.002$, respectively).

Overall, influenza A virus was found in nasal swabs and aspirates in 60/86 patients (69.8%) and 24/86 patients (27.9%) were found with H1N1 influenza A virus. Influenza B virus was detected in 26/86 patients (30.2%). Influenza A (including A H1N1) and B virus proportions were not different by age groups ($P = 0.58$, 0.53, and 0.40, respectively). By country, proportions of influenza A virus among detected influenza viruses ranged from 33.3% in China to 100% in Mali ($P = 0.004$). Influenza A H1N1–related pneumonia cases seemed to be more severe than pneumonia cases related to other strains of influenza. For these patients, a decrease in breathing sounds was observed ($P = 0.03$), the median breathing rate was higher (57.5 versus 52 cycles/minutes, $P = 0.02$) and arterial oxygen saturation was lower (93.5% versus 96%, $P = 0.005$), but median delay between symptoms and hospitalization was higher for influenza A H1N1–related cases (7 versus 5 days, $P = 0.023$) (Supplemental Table 2).

Table 2 depicts the microorganisms detected from blood and respiratory samples. Viral coinfections were observed in 46/86 (53.5%) of the influenza-related pneumonia group and viral–bacterial coinfection/co-colonizations in 61/86 (70.9%). Blood RT-PCR assay was frequently more positive for *S. pneumoniae* in the influenza-related pneumonia group (13/66 [19.7%] versus 61/645 [9.5%], $P = 0.018$), whereas association was negative for other viral infections (respiratory syncytial virus and rhinovirus).

DISCUSSION

Our objective was to ascertain the proportion of influenza virus–related infections in upper respiratory samples from children less than 5 years of age with pneumonia in developing and emerging countries. We observed that the mean proportion was 9.7%, with moderate variations by country—ranging from 6.2% to 18.8%—potentially because of local outbreaks. These data are consistent with the findings of Walker et al.,[3] who estimated that influenza viruses are detected in 4.1–17.2% of pneumonia cases. Another study carried out in Pakistan in 2010–2011 reported a proportion of 5.3% of influenza A–related pneumonia in a population of less than 2-year-old children.[13]

No relevant characteristics were associated with influenza-related pneumonia cases in the 2- to 11-month-old and 12- to 23-month-old age groups. In the 24- to 60-month-old age group, lower WBC and neutrophil counts might support a viral etiology of pneumonia.[14] The higher proportion of seizures is known to be associated with influenza.[15] The lower proportion of rhonchi or wheezing and the diminished breathing sounds observed in the influenza-related pneumonia group were not clearly retrieved in literature. Indeed, no specific symptom permits to distinguish clearly viral from bacterial pneumonia.[14,16] The observed differences may be partly explained by the large number of clinical signs collected or because both influenza-related pneumonia cases and pneumonia cases without influenza detection were affected by mixed viral and bacterial infections in varying proportions. In addition, as observed elsewhere,[13,17] results displayed that influenza A H1N1–related cases were more severe than pneumonia cases related to other strains of influenza. The crude mortality rate was not higher in influenza-related pneumonia cases. The role of influenza viruses in childhood mortality is not fully understood,[1] but some authors, however, report that influenza results in a substantial burden on health-care services, particularly in developing countries.[1] The literature shows that the clinical characteristics of children with lower respiratory tract

TABLE 1

Demographics at hospital admission, medical history, vital signs, clinical symptoms, and biological parameters of influenza-related pneumonia cases compared with pneumonia cases without detected influenza viruses

Characteristics	Influenza positive among pneumonia cases (N = 86)	Influenza negative among pneumonia cases (N = 802)	P
Demographics at admission*			
Male gender	53 (61.6)	474 (59.1)	0.65
Country			0.024
Cambodia	11 (12.8)	165 (20.6)	
China	3 (3.5)	36 (4.5)	
Haiti	19 (22.1)	82 (10.2)	
Lucknow, India	13 (15.1)	83 (10.4)	
Vadu, India	4 (4.7)	67 (8.4)	
Madagascar	5 (5.8)	75 (9.4)	
Mali	11 (12.8)	107 (13.3)	
Mongolia	13 (15.1)	95 (11.9)	
Paraguay	7 (8.1)	92 (11.5)	
Age, months, median (IQR)	36 (25–48)	34 (27–45)	0.50
Weight, kg, median (IQR)	9 (7.2–10.5)	9 (7–11)	0.86
Height, cm, median (IQR)	80 (73–87)	77 (66.3–88)	0.074
Body mass index, median (IQR)	14.9 (13.5–15.8)	15.1 (13.6–17.0)	0.20
Mid-upper arm circumference, median (IQR)	14 (13–15.5)	14 (12–16)	0.72
Weight-for-height Z-score ≤ 2 SD	16/55 (29.1)	127/517 (24.6)	0.46
Weight-for-height Z-score ≤ 3 SD	8/55 (14.6)	61/517 (11.8)	0.55
Medical history*			
Heart condition	2/85 (2.4)	37/801 (4.2)	0.57
Lung disease	12/75 (16.0)	93/629 (14.8)	0.73
Tuberculosis	1/85 (1.2)	5/788 (0.6)	0.46
Asthma	0/85 (0.0)	17/789 (2.2)	0.40
Pneumonia	23/69 (33.3)	182/555 (32.8)	1.00
Other lung disease	0/74 (0.0)	24/620 (3.9)	0.10
HIV positive	0/76 (0.0)	9/682 (1.3)	0.61
Contact since 2009 with other persons affected by tuberculosis	1/71 (1.4)	13/581 (2.2)	1.00
Contracted a cold or pharyngitis during prior 2 weeks	13/72 (18.1)	151/621 (24.3)	0.31
Contracted influenza during prior 2 weeks	8/71 (11.3)	82/600 (16.7)	0.71
Prior treatment of fever†	56/86 (65.1)	573/791 (72.4)	0.17
Prior antibiotics treatment†	45/73 (61.6)	398/628 (63.4)	0.77
Referred from another health-care center	12/74 (16.2)	90/615 (14.6)	0.73
Time period between symptoms and hospitalization, days, median (IQR)	5 (4–8)	5 (3–7)	0.21
Vital signs at admission			
Temperature, °C, median (IQR)	38.5 (37.6–38.9)	38.3 (37.7–38.8)	0.74
Breathing rate, cycles/minute, median (IQR)	55 (48–60)	54 (46–60)	0.81
Cardiac rate, beats/minute, median (IQR)	136 (120–152)	136 (121–152)	0.60
Systolic blood pressure, mm of Hg, median (IQR)	90 (84–93)	90 (84–98)	0.24
Diastolic blood pressure, mm of Hg, median (IQR)	60 (57–68)	60 (55–68)	0.99
Arterial oxygen saturation, %, median (IQR)	95 (92–97)	95 (92–97)	0.82
Clinical symptoms at enrollment*			
Dyspnea	83/86 (96.5)	754/799 (94.4)	0.40
Cough	85/86 (98.8)	793/800 (99.1)	0.79
Cyanosis	8/85 (9.4)	77/799 (9.6)	0.95
Lower chest indrawing			
Dullness to percussion	24/84 (28.6)	205/795 (25.8)	0.58
Pulmonary crackles	61/85 (71.8)	546/799 (68.3)	0.52
Wheezing	23/86 (26.7)	258/796 (32.4)	0.28
Rhonchi	25/79 (31.7)	267/705 (37.9)	0.28
Diminished breathing sounds	16/79 (20.3)	207/704 (29.4)	0.088
Prostration or lethargy	23/74 (31.1)	155/632 (24.5)	0.22
Convulsions	6/75 (8.0)	24/634 (3.8)	0.086
Rhinopharyngitis	17/75 (22.8)	141/632 (22.3)	0.94
Otitis	1/75 (1.3)	9/634 (1.4)	0.95
Conjunctivitis	0/86 (0.0)	15/799 (1.9)	0.20
Skin rash	3/75 (4.0)	18/636 (2.8)	0.57
Inability to drink	13/86 (15.1)	99/797 (12.4)	0.48
Vomiting	17/86 (19.8)	153/798 (19.2)	0.89
Diarrhea	14/86 (16.3)	113/800 (14.1)	0.59
H1N1 vaccination in 2009	3/52 (5.8)	17/480 (3.5)	0.42
PCV13 vaccination	3/68 (4.4)	18/546 (3.3)	0.63
Oxygen therapy	33/74 (44.6)	294/627 (46.9)	0.71
Evolution during hospitalization			
Duration of hospitalization, day, median (IQR)	6 (3–10)	6 (2–10)	0.73
Duration of fever, day, median (IQR)	4.5 (3–7)	4 (3–6)	0.15
Duration of oxygen requirements, day, median (IQR)	2.5 (1.5–3)	2 (1–4)	0.85
Death	3/80 (3.8)	18/770 (2.3)	0.44

(continued)

TABLE 1
Continued

Characteristics	Influenza positive among pneumonia cases (*N* = 86)	Influenza negative among pneumonia cases (*N* = 802)	*P*
Biological parameters			
Procalcitonin, ng/mL, median (IQR)	0.43 (0.10–2.20)	0.47 (0.09–3.50)	0.49
C-reactive protein, mg/L, median (IQR)	30.0 (8.0–96.0)	26.0 (7.2–88.0)	0.62
White blood cell count, mm^3, median (IQR)	11,300 (7,600–16,200)	15,400 (10,200–23,300)	< 0.001
Neutrophil count, mm^3, median (IQR)	3,775 (2,204–7,507)	6,383 (3,274–11,400)	0.002

HIV = human immunodeficiency virus; IQR = interquartile range; PCV = pneumococcal conjugate vaccine; SD = standard deviation.
* Reported as number/number with available data (%).
† For the current illness.

infections are dependent on the carriage of specific pathogens in the nasopharynx.[2,18] *Streptococcus pneumoniae* was detected more frequently in blood samples from influenza-related cases, with a high detection rate (70.9%) of viral–bacterial co-colonizations found. As previously mentioned in the literature, it suggests that influenza viruses may be considered as precursors of bacterial pneumonia or as etiological agents of pneumonia.[19] These data bring additional information to the findings of Klein et al.,[20] in which co-colonization rates range between 2% and 65%. Proportions of *S. pneumoniae* identified in respiratory samples were also higher in influenza-related pneumonia cases compared with pneumonia cases without influenza detection (67.4% versus 35%). It may be explained by the increased rate of pneumococcal colonization in the study population. Indeed, most study participants were not vaccinated with pneumococcal conjugate vaccine (PCV) at the time of its completion.

The present study had some limitations. First, there was no evidence for seasonality because the study was not designed to assess incidence by season. Cases were recruited for more than 1 year, including the dry and rainy seasons. Even if the previous study found rainy season or low humidity levels were associated with a seasonality of influenza viruses, the latter is less prevalent in tropical than in temperate countries.[21–23] Second, microorganisms involved in pneumonia were detected in upper respiratory samples and those detected may not be the etiological cause of the disease.[24] The multicenter nature of our study and the standardization of data collection are major strengths, reinforcing internal validity. Including incident cases increased the quality of data as well.

CONCLUSION

In conclusion, influenza viruses are frequent in respiratory samples from children with pneumonia in developing and emerging countries with moderate heterogeneity between them. The clinical characteristics of children with influenza-related

TABLE 2
Microorganisms detected in blood and respiratory samples from influenza-related pneumonia children compared with pneumonia children without identified influenza viruses

	Influenza positive among pneumonia children (*N* = 86)	Influenza negative among pneumonia children (*N* = 802)	*P*
Viruses detected in respiratory samples			
Adenovirus	2/86 (2.3)	66/802 (8.2)	0.053
Bocavirus	5/86 (5.8)	77/802 (9.6)	0.33
Coronavirus NL63	0/86 (0.0)	10/802 (1.2)	0.61
Coronavirus 229E	0/86 (0.0)	7/802 (0.9)	1.00
Coronavirus OC43	1/86 (1.2)	19/802 (2.4)	0.71
Coronavirus HKU	0/86 (0.0)	23/796 (2.9)	0.16
Enterovirus	3/86 (3.5)	39/802 (4.9)	0.79
Human metapneumovirus	4/86 (4.7)	72/730 (9.9)	0.22
Parainfluenzae virus 1	3/86 (3.5)	23/802 (2.9)	0.73
Parainfluenzae virus 2	0/86 (0.0)	4/802 (0.5)	1.00
Parainfluenzae virus 3	3/86 (3.5)	54/802 (6.7)	0.35
Parainfluenzae virus 4	4/86 (4.7)	17/802 (2.1)	0.14
Parechovirus	0/86 (0.0)	21/802 (2.6)	0.25
Respiratory syncytial virus	9/86 (10.5)	169/802 (21.1)	0.022
Rhinovirus	5/86 (5.8)	216/802 (26.8)	< 0.001
Viral coinfection/co-colonization	46/86 (53.5)	172/802 (21.5)	< 0.001
Bacteria detected in respiratory samples			
S. pneumoniae	58/86 (67.4)	547/801 (68.3)	0.90
S. aureus	10/86 (11.6)	97/801 (12.1)	1.00
H. influenzae	4/86 (4.7)	43/802 (5.4)	1.00
Mycoplasma pneumoniae	0/86 (0.0)	13/802 (1.6)	0.63
Clamydophila spp.	0/86 (0.0)	4/802 (0.5)	1.00
Viral–bacterial co-colonization	61/86 (70.9)	468/802 (58.4)	0.024
Blood samples			
Blood culture positive for a pathogenic microorganism	0/86 (0.0)	24/802 (3.0)	0.16
RT-PCR positive for *S. aureus*	1/66 (1.5)	12/645 (1.9)	1.00
RT-PCR positive for *S. pneumoniae*	13/66 (19.7)	61/645 (9.5)	0.018
RT-PCR positive for *H. influenzae*	1/66 (1.5)	23/645 (3.6)	0.72

RT-PCR = real-time multiplex polymerase chain reaction.

pneumonia are not substantially different from those of children without identified influenza viruses, but influenza A H1N1–related pneumonia cases were more severe than pneumonia cases with other influenza virus detected in this population. Future studies should assess the utility of influenza vaccination in children from developing countries, to prevent viral and bacterial pneumonia, as demonstrated previously with PCV vaccination obviating influenza hospitalizations in children.[25]

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Note: Supplemental figure and tables appear at www.ajtmh.org.

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