Influenza is a Major Contributor to Childhood Pneumonia in a Tropical Developing Country

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Background: Pneumonia is the leading cause of child mortality worldwide. The role of influenza in childhood pneumonia in tropical developing countries is poorly understood. We undertook population-based surveillance among low-income urban preschool children to determine its role in childhood pneumonia.

Methods: Longitudinal prospective active surveillance was conducted among randomly selected households in a poor urban area of Dhaka. Nasopharyngeal washes were collected from 1 in 5 children for influenza culture isolation. Clinical data were collected at clinical presentation and through the illness course.

Results: From April 1, 2004 through December 31, 2007, 12,062 children presented in clinic with eligible febrile and respiratory illnesses, from whom 321 influenza isolates were obtained from 2370 nasopharyngeal washes (13.5%), representing 16,043 child-years of observation (adjusted influenza incidence 102 episodes/1000 child-years). There were 8198 pneumonia episodes during the period (pneumonia incidence 511 episodes/1000 child-years). Ninety influenza-positive children (28%) developed pneumonia during their illness. Among influenza culture-positive children, those with pneumonia were younger than those without (23.4 vs. 29.7 months, ANOVA: $P < 0.001$). Pneumonia was more commonly associated with Influenza A (H3N2) than either A (H1N1) or B infections (age-adjusted relative odds (RO) 2.98, [95% CI: 1.56, 5.71] and 2.75, [95% CI: 1.52, 4.98], respectively). Influenza was associated with 10% all childhood pneumonia.

Conclusions: Influenza is a major contributor to childhood pneumonia both through high influenza infection incidence and high pneumonia prevalence among infected children. Its contribution to early childhood pneumonia appears under-appreciated in high pneumonia-endemic tropical settings. Influenza vaccine trials against childhood pneumonia are warranted.

Key Words: influenza, pneumonia, children, urban

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Pneumonia is, globally, the primary cause of child mortality, causing 19% of 10.6 million deaths among children <5 years, or 2 million deaths per year in 2000 to 2003.[1] Reducing pneumonia mortality would substantially aid achieving the Millennium Development Goal 4 of reducing the 1990 child mortality rate by two-thirds.[2] Pneumonia is also the primary cause of childhood death in Bangladesh.[3] The role of influenza in childhood pneumonia is poorly understood.[4] Influenza is a leading cause of childhood morbidity in temperate countries,[5,6] and a cause of outpatient visits and hospitalization worldwide.[7–9] Influenza-associated complications, including pneumonia and hospitalization rates, among healthy preschool aged children, particularly those <2 years, approximate those of older children 5 to 17 years and adults with underlying chronic conditions,[5,8,10] suggesting that young children are particularly vulnerable to influenza complications. Influenza is also a major source of mortality globally.[11] Uncertainty persists about influenza's contribution to childhood pneumonia in tropical and subtropical regions,[12] particularly developing countries, where the burden is highest, limiting efforts to evaluate influenza-specific interventions, like vaccines, to reduce childhood pneumonia.[13]

We undertook this study to determine the incidence, seasonality, virus-type distribution, and clinical presentation, including pneumonia, of influenza among poor urban children <5 years in Dhaka, Bangladesh, an area with a documented high pneumonia burden.[14]

MATERIALS AND METHODS

The study was conducted in Kamalapur, a low-income urban area in southeast Dhaka, where the International Centre for Diarrheal Disease Research, Bangladesh (ICDDR,B) has conducted surveillance since 1998. It comprises 7 communities in 4 municipal wards with 200,000 residents in a 2.4 km^2 area with a median household income <US $80.00/mo, a mean education of 6.6 years for men and 5.1 for women. Children receive routine vaccines of Bacille Calmette Guenin (BCG), Diptheria, pertusssis, tetanus (DPT), and oral polio through the Expanded Programme of

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W. Abdullah Brooks was the principal investigator, designed and conducted, the study, analyzed the data, retained access to the data throughout the study and took the lead role in drafting the manuscript. Doli Goswami and Kamrun Nahar contributed to the study design and the daily execution of patient recruitment, surveillance, and clinical operations. Mustafizur Rahman, Nadia Iftekharuddin, and Tasnim Azim designed of the laboratory operations in Dhaka, conducted the tissue culture isolates and viral typing/sub-typing. Tasnim Azim as Head of Virology oversaw and coordinated all stages of these operations. Alexander Klimov, Xiyan Xu and Amanda Balish designed the laboratory operations in Atlanta, and provided technical support to the Dhaka lab as needed. Alicia Fry, Tasnim Azim, Joe Bresee, Alexander Klimov, Carolyn Bridges, and Stephen Luby were senior investigators who assisted with all stages of the design, conduct, analysis, and manuscript preparation of the study. All members contributed to the interpretation of results and the preparation of the manuscript.

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Immunization. Although *Haemophilus influenzae* type b vaccine (Hib) was introduced in July 2009, it was not provided to children during this observation period; and neither protein-conjugate pneumococcal nor influenza vaccines are available in Bangladesh. Respiratory and febrile disease surveillance in Kamalapur has been previously described, along with exposures to infectious and noninfectious respiratory disease risk factors.[14,15] Briefly, 5000 children <5 years were followed longitudinally during weekly home visits by trained field research assistants using standardized questionnaires to elicit both recall and observational data on clinical illness signs for the previous 7 days. Field research assistants were trained in both administration of the standardized questionnaires, and in the detection of clinical signs. Major signs included fever (axillary temperature, ≥38°C), age-specific tachypnea using WHO criteria, danger signs (chest indrawing, lethargy, cyanosis, inability to drink, convulsions), difficult breathing, noisy breathing, and ear pain/discharge. Minor signs included cough, rhinorrhea, sore throat, myalgia/arthralgia, chills, headache, irritability/decreased activity, and vomiting. Field research assistants referred children with 1 major or at least 2 minor signs to the onsite clinic.

In the clinic, project physicians and nurses conducted standardized clinical examinations to make standardized diagnoses of febrile or respiratory illnesses.[14] They collected nasopharyngeal wash (NPW) specimens on every fifth child (20%) with any of the following: documented fever (T ≥38°C) or one of the following standardized clinical syndromes: pneumonia, (age-specific tachypnea[16] plus crepitations on auscultation, ie, fine crackles on inspiration), severe pneumonia (pneumonia plus chest-indrawing), very severe pneumonia (pneumonia with chest-indrawing plus at least one other danger sign[16]), otitis media (OM) (bulging/inflamed tympanic membrane inflammation or suppurative OM if ear discharge was present), upper respiratory infection (or URI defined as documented fever, cough, and rhinorrhea), and meningitis (fever with nuchal rigidity/bulging fontanelle). Blood cultures were collected from all children meeting these criteria for bacterial surveillance, and were reported.[14]

NPWs were performed by attaching a butterfly catheter (needle removed) to a 10 mL syringe containing 5 mL normal saline, placing the child in a 30° semi-Fowler position with the head slightly angled forward,[17] inserting the catheter between 2 and 3 cm into the nares, injecting the saline and immediately applying suction while removing the catheter. A wash was successful if at least 1 mL of aspirate was collected. The NPW was then placed in viral transport medium (containing Dulbecco Modified Eagle Medium), stored, and transported at 4°C to the ICDDR, B virology laboratory within 8 hours.

All children with study diagnoses were provided clinical care, including hospitalization, according to standard WHO recommendations.[16] Field research assistants followed these children daily at home to monitor progress, and referred them back to clinic for failure to improve (no change in presenting illness signs after 72 hours of treatment) or worsening condition (addition of illness signs at anytime). If confirmed in clinic, these events were recorded as treatment failures, and second line therapy was implemented or patients were referred to hospital, according to project physician judgment. At the end of a 7-day disease-free interval, field research assistants referred patients back to clinic for exit interviews with project physicians to assess final diagnosis, clinical course, duration of illness, and outcome. Only trained project physicians made determinations of clinical diagnoses and outcomes, whereas field research assistants simply made referrals based on clinical signs, which required project physician confirmation.

In the virology laboratory, NPWs were inoculated into a Madin Darby Canine Kidney cell line monolayer and processed as described elsewhere.[18] Influenza virus strain typing was performed in hemagglutination inhibition tests using hyperimmune type- or subtype-specific antisera. Influenza virus isolates with their NPW specimens were sent to the Influenza Division at Centers for Disease Control and Prevention [CDC] for verification, and virus strain surveillance.

To estimate sample size, we chose clinical pneumonia as a surrogate for clinically important influenza infection. Based on an expected clinical pneumonia incidence of 0.5 episodes/child/yr, a cohort of 4400 children under surveillance would yield 2200 pneumonia episodes/yr. We predicted that 5% of NPWs, using this respiratory disease focused approach, would yield influenza isolates, based on pilot data from this population, in which 16% of children <13 years with fever and respiratory illness had serological evidence of acute influenza infection,[19] compared with 18.8% in a reported cohort study of children <13 years, in which the influenza accounted for 5% of all respiratory infections in children.[20] Under these assumptions, using a 20% sampling frame among all eligible children, we anticipated 22 influenza isolates per year.

Statistical analyses were performed using Stata SE Release 9.2 (Stata Corporation, College Station, TX). A child's observation period began at consent and continued until the child matriculated from the age group or left the cluster. Incidence was calculated as the number of isolates over person-years of observation. Seasonality was plotted as mean incidence per month. Continuous data were compared using analysis of variance (ANOVA) and/or linear regression where appropriate, or where multiple measurements were involved, repeated-measures ANOVA. Categorical variables were analyzed in univariate analysis with by 2×2 tables with calculation of relative odds (odds ratios) and 95% confidence intervals, or Kruskal-Wallis χ^2 test for equality of populations for multiple responses within single covariates. Risk was measured as events over person-time, and compared between groups to determine relative risk. Multivariate modeling of factors associated with clinical illness was done by stepwise forward logistic regression, using all covariates significantly associated with influenza in univariate analysis. Only covariates that remained significant when controlling for age (which affects respiratory rate) were retained in the final model. We adjusted the models for clustering to control for repeat patient visits per episode, used robust variance-covariance estimation, and tested for goodness of fit with either Pearson or Hosmer-Lemeshow methods.[21] Two-sided P values ≤0.05 were considered significant. Kaplan-Meier failure plots were used to show the cumulative hazard of diagnosis of pneumonia versus nonpneumonia among influenza-positive children (y-axis) over patient age in months (x-axis).

The Research Review and Ethical Review Committees of ICDDR,B and the Human Subjects Internal Review Board at CDC approved the study.

Role of the Funding Source

The CDC, one funding source, had a collaborative role in the study design, data collection, data analysis, interpretation of results, and decision to publish this research. The other funding sources had no role in the study. The corresponding author (W.A.B.) had full access to the data and the final responsibility for deciding to submit for publication.

RESULTS

From April 1, 2004 through December 31, 2007, there were 7515 cases of pneumonia, 561 of severe and 122 cases of very severe pneumonia, 11 cases of meningitis, 4214 cases of OM, and

24,696 cases of URI. There were 16,043 child-years of observation during the interval, creating an overall pneumonia incidence of 511 pneumonia episodes/1000 child-years (0.5 episodes/child/yr). The incidences were 35, 8, 263, and 1539 episodes/1000 child-years for severe pneumonia, very severe pneumonia, OM, and URI, respectively.

A total of 12,062 children met criteria for respiratory and febrile illness syndromes and sample collection. (Children had multiple episodes/y and may have had >1 syndrome/illness episode.) Of these, 2370 (19.6%) submitted an NPW for influenza culture. There were no refusals. There were 321 influenza isolates during the period, for an isolation rate of 13.5% and an incidence of 321 influenza episodes/16,043 child-years/0.196 influenza samples/1 eligible samples × 1000 = 101.8 influenza episodes/1000 child-years. The incidence ranged from 6.3 episodes/1000 child-years in January to 258.3 episodes/1000 child-years in May (Figs. 1, 2).

Among influenza infections, there were 7 bacterial coinfections (blood isolates). These included 1 coagulase-negative *Staphylococcus* (pneumonia), 2 *Moraxella catarhallis* (upper respiratory infection and fever without localizing signs), 1 *Pseudomonas aeruginosa* (pneumonia), 2 *Salmonella* Typhi, and 1 *Salmonella* Paratyphi (all enteric fever).

Influenza was present year-round, with 2 distinct influenza A peaks (Fig. 3)–an A (H3N2) peak from April to June (premonsoon season), and an A (H1N1) peak from June through September (monsoon season); both during the warm spring and summer months. Influenza B viruses circulated year-round.

Influenza A accounted for 60% of all influenza viruses, with A (H1N1) subtypes accounting for 31%, A (H3N2) 29%, and influenza B viruses 40% (Table 1). Although the influenza A virus tallies are similar, during the final 12 months of observation (January 1, 2007–December 31, 2007), 61 of 122 isolates (50%) were H3N2 and 27 (22%) were H1N1.

Compared with children with febrile or respiratory illnesses who were influenza-negative, influenza-positive children were older (Table, Supplemental Digital Content 1, http://links.lww.com/INF/A237). The median ages for influenza-positive and influenza-negative patients were 24.2 months (95% CI: 21.6, 27.8) and 19.5 months (95% CI: 18.5, 20.4), respectively. At presentation, influenza patients were significantly more likely to complain of fever, headache, body pain (myalgia), rhinorrhea, and loss of appetite (anorexia) than were children without influenza (Table, Supplemental Digital Content 1, http://links.lww.com/INF/A237). Influenza-positive children were 32% more likely to complain of diarrhea, although this was not

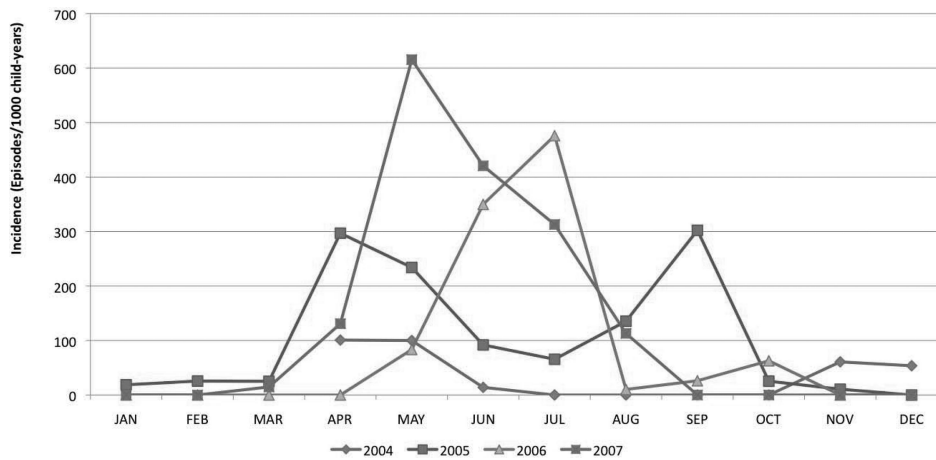

FIGURE 1. Incidence of Influenza by year among children <5 years: Kamalapur, April 2004 to December 2007.

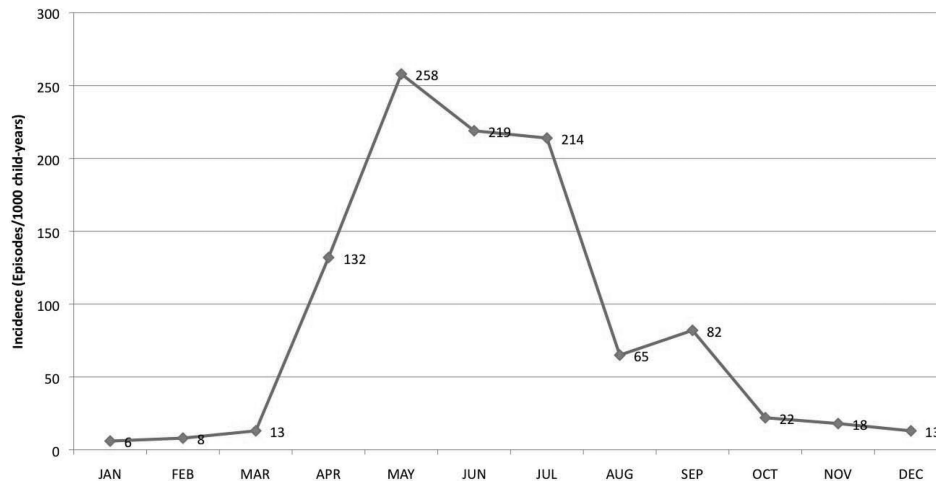

FIGURE 2. Incidence of Influenza among children <5 years: Kamalapur, April.

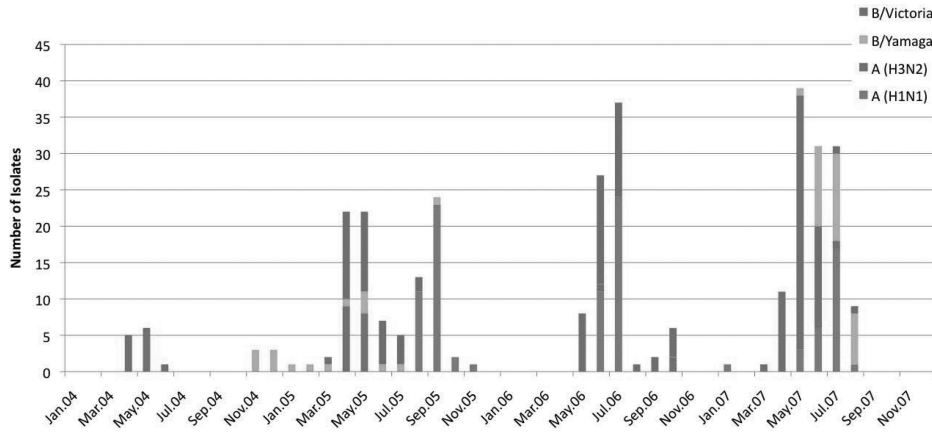

FIGURE 3. Distribution of Influenza viruses among children <5 years: Kamalapur, April 2004 to December 2007.

TABLE 1. Distribution of Viruses by Type

Virus	No. Isolates	Percent
A/H1N1	99	31
A/H3N2	93	29
B/Victoria/1/87 lineage	82	25.5
B/Yamagata/16/88 lineage	47	14.5
Total	321	100

TABLE 2. Diagnoses Among Influenza Culture Positive Patients (N = 321)

Diagnostic Category	Preliminary Diagnosis*		Final Diagnosis†	
	Number	Percent	Number	Percent
Pneumonia	65	20.2	88	27.4
Severe pneumonia	1	0.3	2	0.6
Bronchiolitis	5	1.6	1	0.3
Sinusitis	4	1.2	4	1.2
Otitis media	10	3.1	14	4.4
Upper respiratory infection (URI)	165	51.4	167	52.1
Enteric fever	42	13.2	3‡	1.0
Fever without localizing signs (FWLS)	8	2.5	21	6.5
Other	21	6.5	21	6.5
Total	321	100	321	100

*Diagnosis at presentation visit.
†Diagnosis at exit interview.
‡Confirmed by blood culture isolation of *Salmonella enterica* serovar Typhi and Paratyphi.

statistically significant. Influenza patients were less likely to initially complain of lower airway obstruction symptoms (difficult or fast breathing) or of ear infection. There were no differences in prior hospitalization rates, immunizations, or underlying illnesses; however, among previously hospitalized children, influenza-positives had a longer wellness interval since last hospitalization than other children. Multivariate analysis showed that history of fever (relative odds: 5.79; 95% CI: 2.64, 12.71) and rhinorrhea (RO: 2.06; 95% CI: 1.37, 3.11) were independently associated with influenza infection; while histories of difficult breathing (RO: 0.23; 95% CI: 0.16, 0.33) and ear discharge (RO: 0.52; 95% CI: 0.30, 0.90) showed independent negative association.

Compared with children who were influenza-negative (Table, Supplemental Digital Content 2, http://links.lww.com/INF/A238), influenza-positive children were significantly more likely on examination to have fever, higher mean pulse pressure, pharyngeal inflammation, altered mental status (irritability or lethargy), and less likely to have lower airway obstructive findings, or inflamed or suppurating tympanic membranes. Their convalescent weight-for-age, compared by repeated measures analysis of variance, was lower. Multivariate analysis showed that fever (RO: 1.71; 95% CI: 1.45, 2.01) and nasal discharge (RO: 1.72; 95% CI: 1.28, 2.30) were independently associated with influenza infection at presentation; while tachypnea (RO: 0.96; 95% CI: 0.94, 0.98), OM (RO: 0.81;95% CI: 0.70, 0.93), and abnormal auscultation findings (crepitations and/or wheezes) (RO: 0.86; 95% CI: 0.77, 0.96), were negatively associated.

Table 2 compares initial and final diagnoses among influenza-positive patients. Twenty-four children with nonpneumonia preliminary diagnoses (URI 12, OM 2, bronchiolitis 4, sinusitis 1, enteric fever 1, and other 4) progressed to pneumonia. One child diagnosed with pneumonia progressed to severe pneumonia, leaving a net increase of 23 pneumonia cases, or 35% above the original 65 cases. By comparison, 1047 versus 1152 influenza-negative children had preliminary versus final diagnoses of pneumonia, for a net pneumonia increase of 105 (10%), suggesting a greater pneumonia progression risk for children with influenza (RR: 1.46; 95% CI: 0.94, 2.27; $P = 0.105$). Although not used as a diagnosis, influenza-like illness defined as temperature ≥37.8°C and cough or sore throat was present in 236 (73.5%) influenza-positive children at presentation. Among influenza-positive pneumonia patients (Fig., Supplemental Digital Content 3, http://links.lww.com/INF/A239), the mean age was 23.4 months (SD: 13.2) (range, 4.7–55.0), and among influenza nonpneumonia patients 29.7 months (SD: 15.6) (range: 2.5–59.1) (ANOVA $P < 0.001$). Figure, Supplemental Digital Content 4, http://links.lww.com/INF/A240, shows that 66% of the pneumonia diagnoses occurred among children less than 2 years old. The 2 influenza severe pneumonia cases were 8.6 and 18.3 months (mean: 13.5 months, SD: 6.8). Among the 66 influenza-positive children with initial pneumonia/severe pneumonia diagnoses, 26 (39%) had chest roentgenogram findings consistent with pneumonia at presentation (interstitial infiltrates 17, alveolar infiltrates 9). Adjusting for the sampling frame, the incidence of influenza-specific pneumonia was 28.6 episodes/1000 child-years.

TABLE 3. Final Clinical Diagnoses by Virus Type (N = 321)

Clinical Diagnosis	H1N1 N (%)	H3N2* N (%)	Influenza B N (%)	Total
Severe pneumonia	0 (0)	1 (1.1)	1 (0.8)	2 (0.6)
Pneumonia	20 (20.2)	41 (44.1)	27 (20.9)	88 (27.4)
Bronchiolitis	0 (0)	1 (1.1)	0 (0)	1 (0.3)
Sinusitis	0 (0)	3 (3.2)	1 (0.8)	4 (1.2)
Otitis media	5 (5.1)	3 (3.2)	6 (4.7)	14 (4.4)
Upper respiratory infection	58 (58.5)	34 (36.5)	75 (58.1)	167 (52.0)
Enteric fever	0	0	1	1 (0.3)
Fever without localizing signs	7 (7.1)	2 (2.2)	12 (9.3)	20 (6.2)
Other	9 (9.1)	8 (8.6)	7 (5.4)	24 (7.5)
Total	99 (100)	93 (100)	129 (100)	321 (100)

*Bonferroni-adjusted ANOVA indicated that patients with H3 were significantly younger (24.2 mo, SD: 14.1) than those with H1 (30.5 mo, SD: 15.1; $P = 0.012$), but not those with influenza B (28.7 mo, SD: 15.7; $P = 0.082$). Ages between patients with H1 and influenza B did not differ significantly ($P = 1.000$).

There were significant differences in clinical syndrome by virus type (Table 3). Influenza A (H3N2) had the strongest association with pneumonia compared with either influenza B (crude RO: 2.98 [95% CI: 1.59, 5.62]; $P < 0.001$) or A (H1N1) (crude RO: 3.11 [95% CI: 1.57, 6.24]; $P < 0.001$). The age-adjusted relative odds for pneumonia and influenza A (H3N2) versus influenza B was 2.75, [95% CI: 1.52, 4.98]; and for A (H3N2) versus A (H1N1) was 2.98, [95% CI: 1.56, 5.71].

Among influenza cases, 227 children (71%) fully recovered, 86 (27%) recovered with disability (reactive airways disease including new-onset recurrent wheezing and/or night-time coughing), 1 continued to be ill with chronic recurrent OM, 3 outmigrated before their exit interviews, but showed clinical recovery, and 4 were lost to follow-up. There was 1 hospitalization (14.9-month-old H3N2-infected male with pneumonia and severe hypoxia [SPO_2 86%]) but no deaths. Recovery among influenza-negative children (71%) and other illness outcomes did not differ significantly from those of influenza-positive children (Kruskal-Wallis χ^2 $P = 0.988$). Severe pneumonia patients should have been hospitalized,[16] but most refused and were administered parenteral antibiotics as outpatients. There were no differences in the likelihood of developing reactive airways disease between influenza and noninfluenza patients, or between influenza viruses (data not shown).

Influenza was associated with 10% of all pneumonias among children <5 years of age in this community (Table, Supplemental Digital Content 5, http://links.lww.com/INF/A241), and a substantial fraction of URI, sinusitis, and fever without other localizing signs.

DISCUSSION

This population-based study found a high influenza infection incidence of over 10% per year among children <5 years, and that 28% of children with influenza had pneumonia, indicating that influenza is a major source of childhood pneumonia in this low-income tropical urban setting. That nearly 10% of all childhood pneumonia was associated with influenza, supported by the high childhood pneumonia incidence, underscores influenza's role as a substantial contributor to overall childhood illness. Identification of influenza by tissue culture isolation likely underestimates true burden,[22] making these conservative estimates. Importantly, this study found that influenza patients who developed pneumonia, irrespective of virus type, were significantly younger (<24 months) than those who did not, and that two-thirds of this pneumonia occurred before age 24 months. This corroborates findings elsewhere that influenza complications, including pneumonia, are more likely in younger children.[5,7] These are the first population-based data from Bangladesh to document high contribution of influenza to childhood respiratory infection, and combined with hospital reports from India,[23] Thailand,[24] and subtropical Hong Kong[7] suggest that influenza contributes considerably to childhood pneumonia throughout this tropical and subtropical region, particularly where pneumonia is highly prevalent. Influenza's contribution to childhood pneumonia in the developing world has likely been markedly under-appreciated.

These findings indicate that currently available influenza vaccines could play a role in reducing early childhood pneumonia. Furthermore, our data suggest that preferential attention given to matching for the A (H3N2) component could have the greatest effect on vaccine performance against pneumonia. Because influenza is associated with pneumonia primarily in younger children, a possible strategy would be to vaccinate children before the onset of influenza A season (April) between their first and second years of life.[13]

Importantly, there have been no influenza vaccine trials to test the effect of influenza vaccine on childhood pneumonia in such a setting.

Studies further indicate that influenza viruses can interact with other pathogens, notably pneumococcus, to exacerbate pneumonia burden and severity.[25] Given the recent data from this population and elsewhere on invasive pneumococcal disease,[14,26,27] it is likely that sequential and mixed influenza/pneumococcal pneumonia is most common in the tropical belt. One study reported an overall 31% efficacy of 9-valent conjugate pneumococcal vaccine against viral pneumonia, with 45% efficacy against hospitalization with influenza A-positive pneumonia.[28] It may also be possible that influenza vaccine could prevent influenza-specific, as well as mixed influenza-bacterial and other pneumonia.[13] Mixed influenza- pneumococcal infection was not seen in this study, but the 20% sampling frame for influenza, and the poor sensitivity of blood culture to isolate pneumococcus[27] make such detection unlikely.

One might attribute the high proportion of influenza-positive pneumonia in this setting to poor premorbid health status. However, <1% of these children had underlying medical conditions, and <20% had prior hospitalization. This remained true when analyzed specifically for children with pneumonia, including those <2 years (data not shown). This corroborates similar findings in Western populations.[5] That influenza compromises the health of otherwise healthy children is substantiated by: (1) 7% of children with influenza-mediated URI progressing to pneumonia, suggesting that at least for influenza infection, upper and lower respiratory tract diseases represent an illness spectrum and not separate illnesses; (2) influenza-positive children having a small but significantly lower convalescent weight-for-age compared with noninfluenza positive children, suggesting a measurable nutritional toll. That the difference was determined using repeated measures ANOVA, which accounts for differences in baseline anthropometry, strengthens the case that the finding is statistically significant. To what extent this is clinically meaningful will require further study, but reflects animal data, albeit to a lesser degree,[29] and could have implications for postinfluenza child health in developing countries.

In this population, Influenza A (H3N2) accounted for 47% of all influenza-related pneumonia, and was nearly 3 times more strongly associated with pneumonia than other influenza viruses. Our findings are supported by ecologic analyses in the United States, which show higher rates of hospitalization and mortality

among children and other age groups during influenza A (H3N2) seasonal peaks.[10,30,31] The relationship between influenza A (H3N2) and pneumonia persisted even after controlling for age. Importantly, despite the higher H3N2 risk, all types of influenza were associated with pneumonia.

The year-round influenza circulation, with seasonal peaks of influenza A (H3N2) followed by influenza A (H1N1) during the warm months of April through September, during this study, is inverse to the temperate Northern Hemisphere pattern.[32] The implications for vaccine preparation and infection control remain uncertain.

Limitations of this study included its reliance on tissue culture isolation, which under-estimates burden. In a comparative study using nasal wash specimens from children <5 years, a 3-fold increase in virus detection was reported using Respiratory Multi-Code-Plx Assay over culture.[22] This surveillance was conducted only among preschool-aged children, and may have missed important trends among other age groups. Furthermore, the analysis is confined to a 3 and a half year window in one location. Since influenza circulation may be part of a larger regional network,[33] longer-term trends over a wider area would not have been detected, including interaction with other pathogens whose prevalences may vary cyclically.

This study demonstrates that influenza is a major contributor to childhood pneumonia in this tropical urban setting, both through high infection incidence and high prevalence of pneumonia among infected children. Our findings suggest that influenza may be a major contributor to childhood pneumonia in other tropical and subtropical settings. Its role in global childhood pneumonia is likely under-appreciated. Clinical trials to determine the effect of influenza vaccines on influenza incidence and childhood pneumonia burden in countries with high childhood pneumonia prevalence and pneumonia-associated mortality are warranted.

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