*Clinical Infectious Diseases*

MAJOR ARTICLE

# Individual-level Association of Influenza Infection With Subsequent Pneumonia: A Case-control and Prospective Cohort Study

**John Kubale,[1] Guillermina Kuan,[2] Lionel Gresh,[3] Sergio Ojeda,[3] Amy Schiller,[1] Nery Sanchez,[3] Roger Lopez,[4] Eduardo Azziz-Baumgartner,[5] Steph Wraith,[1] Eva Harris,[6] Angel Balmaseda,[4] Jon Zelner,[1,a] and Aubree Gordon[1,a]**

[1]Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, Michigan, USA, [2]Sócrates Flores Vivas Health Center, Ministry of Health, Managua, Nicaragua, [3]Sustainable Sciences Institute, Managua, Nicaragua, [4]Laboratorio Nacional de Virología, Centro Nacional de Diagnóstico y Referencia, Ministry of Health, Managua, Nicaragua, [5]Centers for Disease Control and Prevention, Atlanta, Georgia, USA, and [6]Division of Infectious Diseases and Vaccinology, School of Public Health, University of California, Berkeley, California, USA

***Background.*** Pneumonia is a leading cause of mortality worldwide. Influenza may result in primary pneumonia or be associated with secondary bacterial pneumonia. While the association with secondary pneumonia has been established ecologically, individual-level evidence remains sparse and the risk period for pneumonia following influenza poorly defined.

***Methods.*** We conducted a matched case-control study and a prospective cohort study among Nicaraguan children aged 0–14 years from 2011 through 2018. Physicians diagnosed pneumonia cases based on Integrated Management for Childhood Illness guidelines. Cases were matched with up to 4 controls on age (months) and study week. We fit conditional logistic regression models to assess the association between influenza subtype and subsequent pneumonia development, and a Bayesian nonlinear survival model to estimate pneumonia hazard following influenza.

***Results.*** Participants with influenza had greater risk of developing pneumonia in the 30 days following onset compared to those without influenza (matched odds ratio [mOR], 2.7 [95% confidence interval {CI}, 1.9–3.9]). Odds of developing pneumonia were highest for participants following A(H1N1)pdm09 illness (mOR, 3.7 [95% CI, 2.0–6.9]), followed by influenza B and A(H3N2). Participants' odds of pneumonia following influenza were not constant, showing distinct peaks 0–6 days (mOR, 8.3 [95% CI, 4.8–14.5] days) and 14–20 (mOR, 2.5 [95% CI, 1.1–5.5] days) after influenza infection.

***Conclusions.*** Influenza is a significant driver of both primary and secondary pneumonia among children. The presence of distinct periods of elevated pneumonia risk in the 30 days following influenza supports multiple etiological pathways.

**Keywords.** influenza; pneumonia; incidence; cohort study; global health.

Despite progress in reducing morbidity and mortality, the global burden of pneumonia remains substantial, particularly among children in low- and middle-income countries [1]. Influenza is an important contributor to pneumonia burden [2]. This may occur directly, as primary viral pneumonia [3], or indirectly through secondary bacterial pneumonia [4]. Seasonal influenza peaks coincide with, or are followed by, peaks of pneumonia, suggesting population-level association [5, 6]. Additionally, investigations of the 1918 and 2009 influenza pandemics make the case for secondary bacterial infections being drivers of mortality during influenza pandemics [4, 7–11]. Laboratory studies have established plausible biological mechanisms through which influenza infection may lead to increased susceptibility to secondary bacterial pneumonia [12–14]. However, substantial gaps in the literature remain that can only be addressed through large participant-level epidemiologic studies [15, 16].

Previous large-scale studies focused on individuals hospitalized for pneumonia. Though community comparisons strengthen some studies' findings, respiratory samples were often collected concurrently with pneumonia diagnosis (cross-sectional), limiting causal inference. Studies that addressed the limitations of cross-sectional analysis faced different challenges, specifically small sample size [17] and seasonal confounding [18].

We used a nested, matched case-control study and Bayesian time-to-event modeling to explore the risk of developing pneumonia following symptomatic influenza infection in a prospective cohort of Nicaraguan children aged 0–14 years.

## METHODS

### Ethics Statement

The study was approved by the institutional review boards of the Nicaraguan Ministry of Health, the University of Michigan, and the University of California, Berkeley. Written

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[a]J. Z. and A. G. contributed equally to this work.

Correspondence: A. Gordon, School of Public Health, University of Michigan, 1415 Washington Heights, Ann Arbor, MI 48109 (gordonal@umich.edu).

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informed consent was obtained from a parent/guardian of all participants. Verbal assent was obtained from children aged ≥6 years.

#### Study Population and Sample Collection

Study participants were from 2 prospective cohorts of Nicaraguan children, the Nicaraguan Influenza Birth Cohort and the Nicaraguan Pediatric Influenza Cohort. Participants were pooled as they were enrolled from the same population and shared the same data collection methods. The resulting cohort included children aged 0–14 years who participated in the study between 2011 and 2018. The methods employed in these studies have been described in detail previously [19, 20]. In brief, healthy children were enrolled when brought to Health Center Sócrates Flores Vivas (HCSFV) or were recruited through home visits. A detailed clinical history and sociodemographic survey were collected on enrollment and yearly thereafter. Nicaragua introduced the 13-valent pneumococcal conjugate vaccine (PCV13) in 2010 with a 3-dose schedule (2, 4, and 6 months) and a catch-up dose for children aged 12–24 months. By the end of 2012, nearly 100% of infants were appropriately vaccinated for their age [21].

Nasal and oropharyngeal swabs were collected from all children meeting the testing definition. Study nurses and physicians are available at HCSFV 24 hours/day, 365 days/year, and parents agreed to bring their child to HCSFV at the first sign of fever. The criteria for sample collection and testing were illness onset within 4 days, fever or reported fever, and rhinorrhea and/or cough for children aged ≥2 years, or fever or reported fever for children aged <2 years [19]. Respiratory samples were also collected/tested for influenza for any child presenting with clinical pneumonia or severe respiratory illness (ie, requiring transfer to hospital).

#### Laboratory Methods

RNA was extracted from swabs (QIAamp Viral RNA Mini Kit, Qiagen) and tested for influenza A and B using validated Centers for Disease Control and Prevention (CDC) reverse-transcription polymerase chain reaction (RT-PCR) protocols [22]. Influenza A–positive samples were subtyped according to CDC protocols [19]. Samples were not tested for bacterial pathogens and influenza B lineage was not considered in this analysis.

#### Data Collection and Case Definitions

Yearly surveys assessing household and participant-level risk factors were completed in March–April, before the typical start of seasonal influenza transmission in June [19]. With each visit to the study health center, a comprehensive medical consultation form was completed. These data were also collected at follow-up visits, which were scheduled until the participant's illness clears, with frequency of visits depending on severity.

Study physicians identified cases of clinical pneumonia among those presenting to the clinic using age-specific guidelines for rapid breathing from the Nicaraguan Ministry of Health based on the Integrated Management of Childhood Illness approach (Supplementary Table 1) [23]. Parents reported the onset date of symptoms, which was used as the start of the influenza episode in all subsequent analyses. Diagnosis date was used to define pneumonia onset. Pneumonia episodes occurring within 0–6 days of influenza illness onset were considered cases of likely primary viral pneumonia, while those occurring ≥7 days after influenza onset were considered likely secondary bacterial pneumonia [17].

#### Statistical Analysis

Two study designs were employed: a nested, matched case-control study and a prospective cohort study. Conditional logistic regression models were fit using the *survival* package, survival models were fit with the *brms* package for Bayesian regression modeling with *Stan*, and figures were generated with *ggplot2* and the *tidybayes* packages for R 3.6.1 software [24–27].

#### Matched Cases and Controls

Pneumonia cases were matched to up to 4 controls on age (months) and study week ensuring the appropriate risk set was used when assigning controls. Controls were selected from the cohort at large after excluding those with a pneumonia diagnosis in the previous 45 days (Figure 1). Children were able to serve as a case (if distinct episode) or control multiple times if they met the previously described criteria.

To explore the relationship between influenza subtype and risk of pneumonia in the 30 days following onset, a conditional logistic regression model was fit (model 1) with categorical variable ($s_{ik}$) indicating no influenza, H3N2, H1N1pdm09, or influenza B for case $i$ in pair $k$. To assess the risk period for pneumonia following symptomatic influenza infection, a separate conditional logistic regression model was fit (model 2), with categorical variable ($w_{ik}$) assessing the risk of pneumonia in 0–6, 7–13, 14–20, and 21–30 days following pneumonia infection. Those without influenza in the 30 days prior to the case's pneumonia diagnosis were the reference group.

Model 1:

$$logit\,(y_{ik}) = \alpha_k + \beta_1 sex_{ik} + \beta_2\ s_{ik}$$

Model 2:

$$logit\,(y_{ik}) = \alpha_k + \beta_1 sex_{ik} + \beta_2\ w_{ik}$$

#### Bayesian Survival Model

To estimate the daily rate of pneumonia during the 30 days following influenza onset in the entire cohort, we used a discrete time survival model, in which the outcome $y_{it} = 1$ denotes that individual $i$ was diagnosed with pneumonia on day $t$ of the study period, and $y_{it} = 0$ indicates that the individual

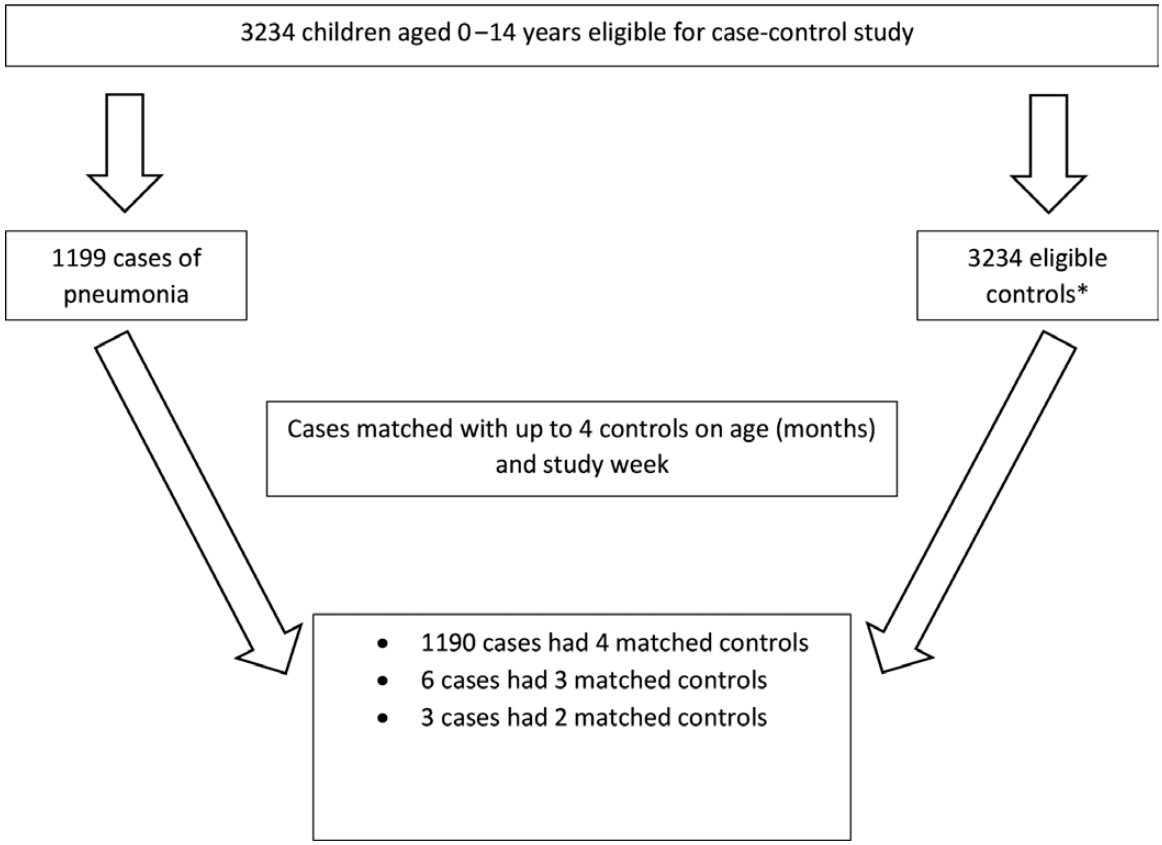


**Figure 1.** Matching scheme for nested matched case-control study. *Controls could not have had an episode of pneumonia within the previous 45 days.

was not. We fit a model with 2 penalized spline terms: for the month of study (1:95), denoted $\lambda_0(t)$, where $\lambda_0(t)$is a function mapping days to the baseline log-hazard of pneumonia for the month containing day $t$. To represent the log-hazard ratio of pneumonia risk on each day postinfluenza, we defined a second smoothed term, $f(t-\zeta_i,\ s_i)$, where $\zeta_i$ is the day of influenza onset for individual $i$, and $s_i$ indicates the infecting influenza subtype (H3N2, H1N1pdm09, or B). This allowed for the modeling of time-varying log-hazard of pneumonia by influenza subtype. Finally, we defined $\beta$ to be a vector of hazard ratios, corresponding to their respective combination of age and sex, $x_i$. We then defined the rate of pneumonia for individual $i$ on day $t$ as:

Model 3:

$$\log(\lambda_i(t)) = \lambda_0(t) + x_i'\beta + I(s_i > 0)\, f(t-\zeta_i,\ s_i)$$

where $I(s_i > 0)$ is an indicator variable evaluating to 1 if the individual was infected by any influenza subtype in the last 30 days, and 0 otherwise. We can then express this rate as the probability of pneumonia on any given day using the conditional log-log link function, ie, $\Pr(y_{it}=1) = 1-\exp(-\lambda_i(t))$, which allows the values of $\lambda_0(t)$ and $\beta$ to be interpreted as a baseline hazard and hazard ratios, respectively [28].

## RESULTS

Between 1 January 2011 and 31 December 2018, 3234 children participated in the study (Table 1). The mean age at enrollment was 3.2 years (standard deviation [SD], 3.8 years), and mean follow-up time was 3.7 years (SD, 2.5 years). The proportion of study participants withdrawn or lost to follow-up was low at 3.1% per year. The most common reasons for early withdrawal/removal from the study were not meeting the requirements of the annual sampling routine (54.8%) and inability to locate the participant's home (23.2%). A total of 12 (0.4%) participants died during the study. Pneumonia was listed on the death certificate as a cause of death for 8 (66.7%). While seasonal influenza vaccination in the cohort was low, averaging 3.2% (range, 0.7%–7.7%) of participants per year, oseltamivir was relatively common, being used in 41.0% of influenza episodes. Antibiotics were provided in 27.1% of total clinic visits and 26.1% of clinic visits associated with an influenza episode.

There were 1199 cases of clinical pneumonia (Table 1 and Figure 2), of which 226 (18.9%) required hospitalization. Pneumonia cases were more likely to occur in children who were younger and male, with nearly 60% of pneumonia cases in boys and >70% in children aged <2 years (Table 1). Pneumonia cases among infants (<1 year) more frequently required

**Table 1. Characteristics of Participants and Pneumonia Cases**

| Participants | All Participants (N = 3234) | Clinical Pneumonia Cases (n = 1199; 683 Participants) | Influenza-associated Pneumonia Cases (n = 62; 59 Participants) |
|---|---|---|---|
| Age at enrollment, y, mean (SD) | 3.6 (3.6) | 0.5 (1.7) | 0.6 (2.1) |
| Person-years contributed, mean (SD) | 3.7 (2.5) | 4.5 (2.6) | 4.8 (2.6) |
| Male sex | 1602 (49.5) | 702 (58.5)[a] | 34 (54.8)[a] |
| Smoking in household | 998 (31.3) | 239 (35.0)[a] | 25 (42.4)[a] |
| Share a bed | 1964 (63.2) | 475 (71.6)[a] | 44 (74.6)[a] |
| Mother with secondary or tertiary education | 2312 (76.5) | 506 (74.1)[a] | 46 (91.5)[a] |
| Father with secondary or tertiary education | 2082 (73.1) | 464 (67.9)[a] | 38 (64.4)[a] |
| Age, mo | | | |
| <12 | … | 496 (41.4) | 22 (35.5) |
| 12–23 | … | 389 (32.4) | 20 (32.2) |
| 24–59 | … | 224 (18.7) | 14 (22.6) |
| ≥60 | … | 90 (7.5) | 6 (9.7) |
| Required hospitalization | … | 226 (18.9) | 8 (12.9) |
| Deemed severe pneumonia | … | 176 (14.7) | 6 (9.7) |
| Primary pneumonia (0–6 d following influenza) | … | … | 40 (64.5) |
| Secondary pneumonia (7–30 d following influenza) | … | … | 22 (35.5) |
| Influenza type | | | |
| A(H3N2) | … | … | 21 (33.9) |
| A(H1N1)pdm09 | … | … | 24 (38.7) |
| Influenza B | … | … | 17 (27.4) |

Data reflect no. (column %) unless otherwise specified.

Abbreviation: SD, standard deviation.

[a]Column % reflects the number of participants.

hospitalization than those among participants aged 5–14 years (28.6% vs 4.4%).

Among clinical pneumonia cases, 62 (5.2%) had RT-PCR–confirmed influenza infection in the 30 days preceding pneumonia diagnosis. Of these, 21 (33.9%) were A/H3N2, 24 were A/H1N1pdm09 (38.7%), and 17 (27.4%) were influenza B. Pneumonia episodes following A/H1N1pdm09 were more often severe, with 25.0% requiring hospitalization compared with 4.8% and 5.9% for H3N2 and influenza B, respectively ($P$ = .08). Primary pneumonia was more common than secondary pneumonia following influenza, with 40 (64.5%) pneumonia cases occurring within 0–6 days following influenza

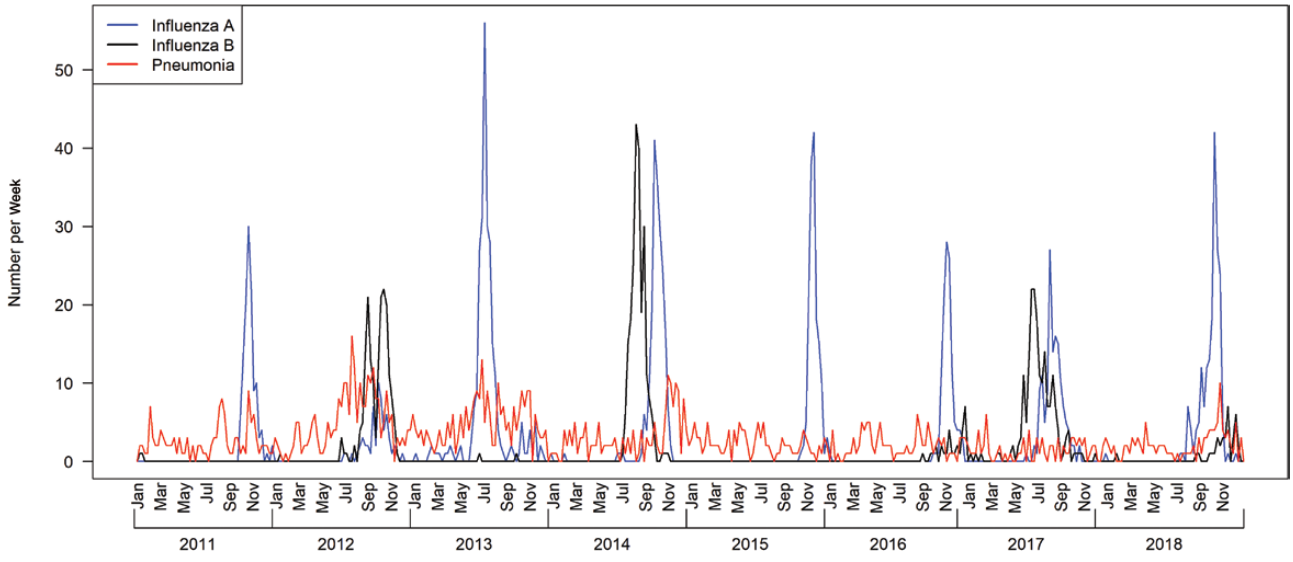


**Figure 2.** Influenza and clinical pneumonia among cohort members aged 0–14 years, Nicaragua, 2011–2018. The lines represent the number of cases of influenza A, influenza B, and clinical pneumonia per week over the course of the study.

vs 22 (35.5%) cases occurring ≥7 days following influenza ($P$ = .01). Primary pneumonia occurred an average of 2.1 days (SD, 1.5 days) after influenza symptom onset compared to 18.8 days (SD, 7.4 days) for secondary pneumonia. We observed no difference in the severity of primary and secondary pneumonias with 12.8% and 13.0% of each group, respectively ($P$ = .98), being hospitalized.

For participants with a laboratory-confirmed influenza infection, the matched odds ratio (mOR) of developing clinical pneumonia in the 30 days after influenza onset was 2.7 (95% confidence interval [CI], 1.9–3.9) times that of children without influenza (Table 2). Sex-specific effects were also observed, with male participants' odds of developing pneumonia 1.6 (95% CI, 1.4–1.8) times that of females. For every 1000 infants with symptomatic influenza, there were 36.3 (95% CI, 17.9–60.0) excess pneumonia cases among males, and 26.2 (95% CI, 11.9–43.8) excess cases among females (Supplementary Table 2). The overall number of excess cases per 1000 symptomatic influenza infections among children <5 years of age was 17.4 (95% CI, 8.4–28.7) for males, and 12.7 (95% CI, 6.0–21.4) for females.

#### Influenza Subtype and Subsequent Pneumonia

Examined by subtype (model 1), those with symptomatic H1N1pdm09 infections had the highest odds of developing clinical pneumonia in the subsequent 30 days—3.7 (95% CI, 2.0–6.9) times that of participants without influenza illness. Those with symptomatic H3N2 or influenza B infection also had greater odds of developing pneumonia, specifically 2.1 (95% CI, 1.2–3.7) and 2.7 (95% CI, 1.5–5.2) times, respectively, that of participants without influenza.

Similarly, the time-to-event model (model 3) indicated an increased hazard of clinical pneumonia in the 30 days following symptomatic influenza infection (Figure 3). Hazard ratios were highest for H1N1pdm09, followed by influenza B, and then H3N2 (Figure 3). The relationship between symptomatic influenza and clinical pneumonia was largely consistent across participants aged 0–5 years (regardless of subtype) but became difficult to distinguish among older participants (>7 years) because of sparse data. As such, results reported from model 3 are limited to those aged ≤7 years (Supplementary Figures 1 and 2). While the HRs remained relatively consistent from age 0–5 years, incidence decreased sharply as age increased, particularly beyond 2 years (Supplementary Figures 1 and 3).

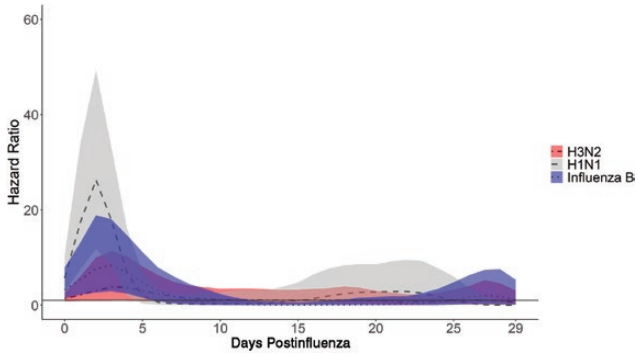


**Figure 3.** Hazard ratios for pneumonia in the 30 days following influenza infection among participants aged <5 years. The lines represent the relative hazard of pneumonia (model 3) in the 30 days following an influenza infection compared to those who had no influenza infection. The relative hazard of pneumonia for each influenza subtype can be distinguished by line type provided in the legend. The shaded areas reflect the 95% confidence intervals, with those that are overlapping being indicative of differences that were not statistically significant at $\alpha$ = .05.

#### Risk Period for Clinical Pneumonia Following Influenza

Model 2 assessed the risk period for clinical pneumonia following any symptomatic influenza infection in the matched case-control study. Participants with symptomatic influenza infection had substantially higher odds of developing pneumonia in the 30 days postinfluenza compared with participants without symptomatic influenza. Specifically, the relative odds of pneumonia were highest in the first (0–6 days) and third weeks (14–20 days) following symptomatic influenza infection. Participants with symptomatic influenza had 8.3 (95% CI, 4.8–14.5) times higher odds of developing pneumonia in the week following infection, and 2.5 (95% CI, 1.1–5.5) times higher odds of developing pneumonia in the third week following infection (Table 3) compared to participants without symptomatic influenza, a pattern similar to that observed in the survival model (model 3). For each subtype, an initial peak in relative hazard of clinical pneumonia was observed during the first week following influenza illness, though its magnitude varied by subtype. Additionally, H1N1pdm09 displayed

**Table 2. Odds Ratios of Developing Clinical Pneumonia Within 30 Days Following Symptomatic Influenza Infection, by Sex and Influenza Subtype**

| Characteristic | Matched OR | (95% CI) | *P* Value |
|---|---|---|---|
| Male sex | 1.6 | (1.4–1.8) | <.001 |
| Influenza (overall) | 2.7 | (1.9–3.9) | <.001 |
| Influenza A | 2.7 | (1.8–4.1) | <.001 |
| A(H3N2) | 2.1 | (1.2–3.7) | .008 |
| A(H1N1)pdm09 | 3.7 | (2.0–6.9) | <.001 |
| Influenza B | 2.7 | (1.5–5.2) | .0018 |

Results obtained from model 1.

Abbreviations: CI, confidence interval; OR, odds ratio.

**Table 3. Odds Ratios of Developing Pneumonia in the 30 Days Following Influenza Infection, by Week**

| Characteristic | Matched OR | (95% CI) | *P* Value |
|---|---|---|---|
| Male sex | 1.6 | (1.4–1.8) | <.001 |
| Influenza 0–6 d prior | 8.3 | (4.8–14.5) | <.001 |
| Influenza 7–13 d prior | 0.9 | (.4–2.3) | .8 |
| Influenza 14–20 d prior | 2.5 | (1.1–5.5) | .03 |
| Influenza 21–30 d prior | 0.9 | (.4–2.0) | .7 |

Results obtained from model 2.

Abbreviations: CI, confidence interval; OR, odds ratio.

a secondary peak of pneumonia hazard beginning around the third week postinfection. While the confidence region did include the null value, the magnitude closely matches the OR for the corresponding period in model 2 (Figure 3 and Table 3).

## DISCUSSION

We show that among children, symptomatic influenza infection is associated at the individual level with increased risk of pneumonia in the 30 days following illness onset. This association was observed across influenza subtypes (H1N1pdm09, H3N2, and B) and was stronger among young children. We also observed that pneumonia risk was not constant throughout the 30 days following symptomatic influenza infection, with distinct periods of elevated pneumonia risk 0–6 and 14–20 days following influenza illness onset. This suggests differing pathologies causing pneumonia, with primary pneumonias nearly concurrent with influenza, and secondary pneumonias after a 2- to 3-week lag.

Multiple studies have suggested that secondary bacterial pneumonia was a primary driver of mortality in influenza pandemics, including those in 1918 [8, 29] and 2009 [4, 6, 30]. However, it is unclear whether this extends to interpandemic periods or nonfatal secondary bacterial pneumonia. A 2000 matched case-control study found that cases of pneumococcal pneumonia were more likely to have reported influenza-like illness in the 7–28 days preceding hospital admission (mOR, 12.4 [95% CI, 1.7–306]) than age-matched controls [17]. The magnitude of this association decreased when influenza infection was determined using H1N1 serology, but remained substantial (mOR, 3.7 [95% CI, 1.0–18.1]). This is similar to our estimate for H1N1pdm09 over a comparable timeframe of 30 days (mOR, 3.7 [95% CI, 2.0–6.9]). A South African study from 2016 reported prevalence of influenza-associated severe pneumonia and influenza-associated pneumonia requiring hospitalization as 20% and 33%, respectively, among children aged ≤2 years [31]. While our estimates for this age group were lower (14% severe, 19% hospitalized), this difference reflects a small variation in the absolute number of cases.

The proportion of Nicaraguan children who are age-appropriately vaccinated with PCV13 is nearly 100% [21]. The burden of influenza-associated pneumonia observed in our study may be different from populations with lower PCV coverage where a greater number of secondary bacterial pneumonias would be expected. Additionally, pneumococcus is not the only cause of secondary bacterial pneumonias and, given our use of clinical pneumonia, we cannot therefore exclude the possibility that some secondary pneumonia cases resulted from other bacteria or even (noninfluenza) viral infections.

Our observation that H1N1pdm09 was associated with greater risk of subsequent pneumonia compared to H3N2 may seem to contradict the widely accepted convention of more severe disease during H3N2-predominant seasons. However, the differences that we found were not statistically significant beyond the first 3 days following infection. Also, our models assessed the expected severity of illness given infection, which is different from disease frequency.

Exploring the relationship between viral respiratory infections and subsequent pneumonia is notoriously difficult to do at a participant level. A recent review of studies examining the relationship between viral respiratory infection and subsequent pneumococcal disease found that nearly 90% of relevant studies were ecologic, substantially limiting causal inference [15]. Among the 2 participant-level studies of influenza and pneumonia, 1 was limited by seasonal confounding [18], while the other [17] was hampered by its small sample size (13 cases). Several large-scale studies exploring pneumonia etiology have recently published their results including Pneumonia Etiology Research for Child Health (PERCH) [32], Global Approach to Biological Research, Infectious Diseases and Epidemics in Low-Income Countries (GABRIEL) [33], Etiology of Pneumonia in the Community (EPIC) [34], and the Drakenstein cohort [31]. These studies have focused on assessing pathogens that are detectable upon diagnosis with pneumonia compared to nonpneumonia controls. However, none of these studies have yet examined the temporal dynamics of pneumonia following influenza.

This study has several strengths. First, data were obtained from a community-based prospective cohort, limiting the potential for reverse causation bias. Second, this study was conducted on a participant level, allowing us to calculate individual-level hazard rather than population-level correlation. Third, this analysis involved a larger sample size than previous studies, improving power and precision of effect estimates. Fourth, seasonality of the exposure and outcome were accounted for in both the matched case-control cohort and the prospective cohort. The consistency of trends observed in both the conditional logistic regression and survival models lends further support to the primary conclusions of this analysis.

This analysis did have some limitations. Influenza-associated pneumonia is a rare outcome, and categorization by subtype and lag time between influenza and pneumonia only resulted in fewer

cases per strata. This limited statistical power to assess variation in risk period for pneumonia by influenza subtype, as well as the number of covariates included in the model. As such, the existence of residual confounding is a possibility. However, we would not expect such residual confounding to affect the temporal relationship between pneumonia and influenza as confounders would likely be constant over such a short time scale (30 days). While we did not examine other respiratory pathogens as potential causes of pneumonia, by accounting for calendar time the model captures such associations. This does not account for coinfections between influenza and other respiratory pathogens (particularly respiratory syncytial virus [RSV]), but we would anticipate the effect of coinfections to be minimal as previous analyses have shown that influenza/RSV coinfections are rare in this population [20]. Perhaps the biggest limitation of this study is our use of clinical pneumonia to define cases rather than imaging and molecular diagnostics. While we were unable to definitively state whether a pneumonia case was viral or bacterial in origin, the importance of clinical pneumonia diagnosis should not be forgotten. Pneumonia diagnosis using Integrated Management for Childhood Illness criteria remains a widely utilized approach, particularly in low- and middle-income countries. Even with more sophisticated diagnostics such as RT-PCR, bacterial culture, and chest radiography, distinguishing between primary viral and secondary bacterial pneumonias is challenging [3]. Last, we were unable to determine exact date of pneumonia onset and instead used diagnosis date; however, as this corresponds with when the symptoms were severe enough to seek treatment, it is a reasonable measure of pneumonia.

Many important questions remain regarding the biological, social, and environmental factors that affect the relationship between influenza and pneumonia. We hope the results of this study highlight the importance of understanding the temporal dynamics between influenza and pneumonia. Furthermore, we hope that increased collaboration and data sharing may facilitate the exploration of aspects of this relationship, which studies to date have been underpowered to address. Regardless, it is clear that influenza remains an important driver of the global pneumonia burden, through both primary and secondary pneumonias. More effective tools to prevent and treat influenza present promising mechanisms by which the burden of pneumonia can be reduced.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

## Notes

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