Clinical Infectious Diseases

MAJOR ARTICLE

The Spectrum of Influenza in Children

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Background. Children constitute an important component of the influenza burden and community transmission, but the frequency of asymptomatic infection and post-influenza sequelae at the community level is poorly understood.

Methods. Two community-based prospective cohort studies (2011–2020, 2017–2020) and 1 case-ascertained study (2012–2017) were conducted in Managua, Nicaragua. Non-immunocompromised children aged 0–14 years with ≥1 influenza infections, determined by polymerase chain reaction and hemagglutination inhibition assay, were included.

Results. A total of 1272 influenza infections occurred in the household-based portion of the study. Influenza infection was asymptomatic in 84 (6.6%) infections, and the asymptomatic fraction increased with age (1.7%, 3.5%, and 9.1% for ages 0–1, 2–4, and 5–14, respectively; $P < .001$). Of asymptomatic children, 43 (51.2%) shed virus, compared to 1099 (92.5%) symptomatic children ($P < .001$). Also, 2140 cases of influenza occurred in the primary care portion of the study. Sequelae of influenza were rare, with the most common being pneumonia (52, 2.4%) and acute otitis media (71, 3.3%). A/H1N1 had higher age-adjusted odds of acute otitis media (odds ratio [OR] 1.99, 95% confidence interval [CI]: 1.14–3.48; $P = .015$) and hospitalization (OR 3.73, 95% CI: 1.68–8.67; $P = .002$) than A/H3N2. B/Victoria had higher age-adjusted odds of pneumonia (OR 10.99, 95% CI: 1.34–90.28; $P = .026$) than B/Yamagata.

Conclusions. Asymptomatic influenza infection is much less common in children than adults, although viral shedding still occurs in asymptomatic children. Post-influenza sequelae are rare in children in the community setting, and virus strain may be important in understanding the risk of sequelae.

Keywords. influenza; pediatrics; clinical presentation; asymptomatic influenza; global health.

Influenza is extremely common in children globally, and the youngest children are at increased risk of severe disease [1–3]. The clinical presentation of influenza in children is broad, and much of the burden of influenza in children comes from post-influenza sequelae, such as secondary bacterial pneumonia, acute otitis media, and sinusitis, which makes precise estimation of the true burden difficult, especially in low-to-middle-income countries where children are disproportionally affected [1, 4]. Much of our knowledge of the frequency of post-influenza sequelae comes from hospitalized populations, which, although important for understanding influenza severity, do not represent the true burden of influenza in the community [5–7]. In addition, there is no consensus on the impact of virus strain on the risk of sequelae [8].

Furthermore, data on asymptomatic influenza infection in children are sparse. Up to half of influenza infections in adults are thought to be asymptomatic, with a large amount of variance by type, influenza season, location, and other factors [9–11]. However, few studies have examined the frequency of asymptomatic influenza in children specifically. Substantial evidence supports the importance of children in the community spread of influenza and the possible importance of asymptomatic infection for transmission, so further understanding the dynamics of asymptomatic influenza in children, including frequency and associations with viral shedding, is critically important [12–14].

This study leverages several of the largest and longest running community studies of influenza to better understand of the full spectrum of influenza in children, ranging from asymptomatic infection to severe disease and hospitalization. We examine the frequency of asymptomatic influenza infection and post-influenza sequelae among children in a community setting and explore associations between virus strain and clinical outcomes, and between symptomatology and viral shedding.

METHODS

Study Population and Design

This study examines data from 2 household studies, the Household Influenza Transmission Study (HITS) and the Household Influenza Cohort Study (HICS), as well as the Nicaraguan Pediatric Influenza Cohort Study (NPICS) (Figure 1). All studies are based at the Health Center Sócrates

Received 29 June 2022; editorial decision 30 August 2022; published online 7 September 2022

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Clinical Infectious Diseases® 2023;76(3):e1012–e20

https://doi.org/10.1093/cid/ciac734

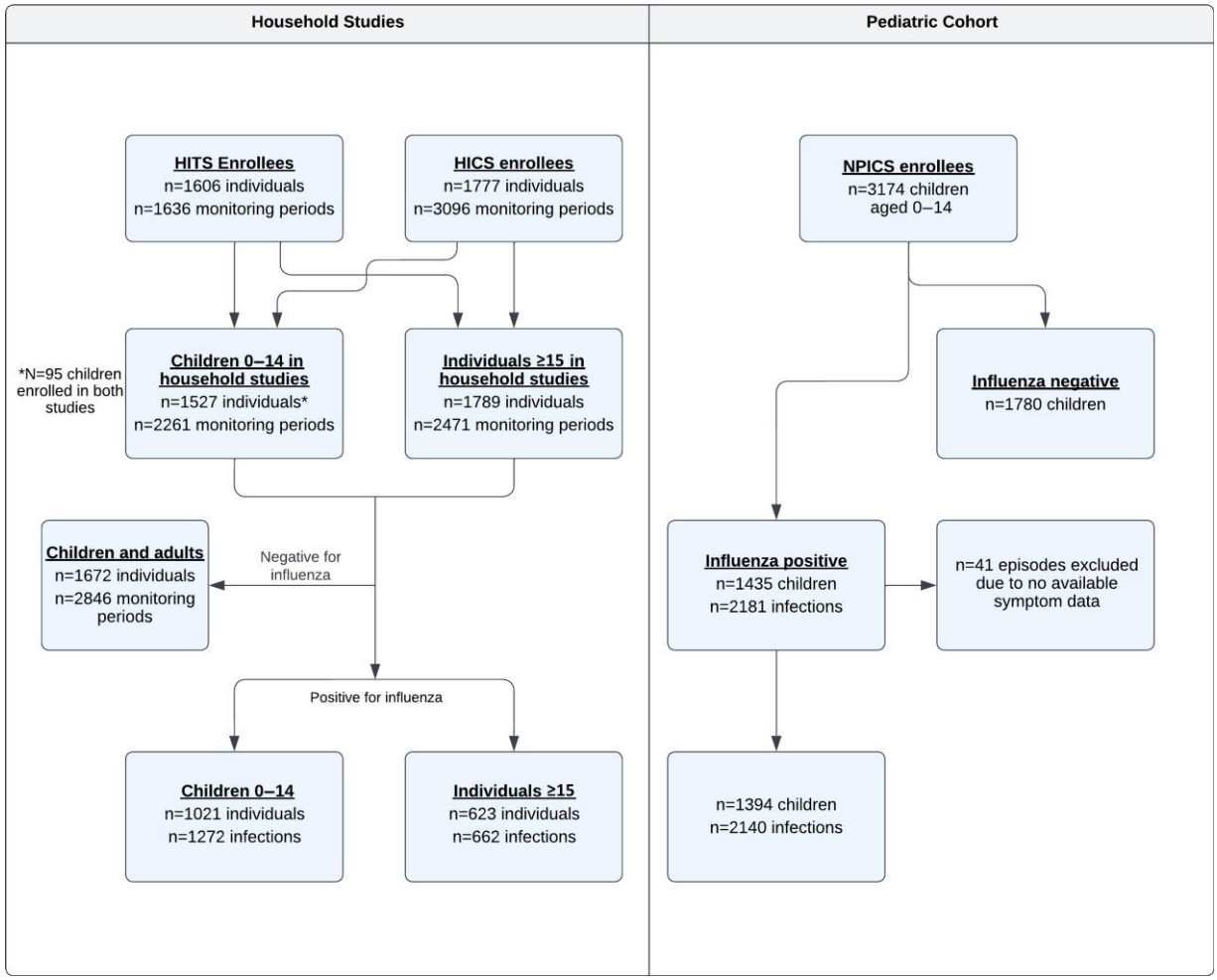

Figure 1. Flow diagram depicting HITS, HICS, and NPICS enrollees, inclusion/exclusion criteria, and final analytical subsets for the household studies and NPICS. Abbreviations: HICS, Household Influenza Cohort Study; HITS, Household Influenza Transmission Study; NPICS, Nicaraguan Pediatric Influenza Cohort Study.

Flores Vivas (HCSFV), in District II of Managua, Nicaragua. All individuals with ≥1 influenza infection were included in this study. This study was approved by the institutional review boards at the Nicaraguan Ministry of Health and the University of Michigan, and is in accordance with the Helsinki Declaration of the World Medical Association. Written consent to participate or parental permission was obtained for all participants.

Household Studies

Data from HITS (2012–2017) and HICS (2017–2020) were used to explore the full spectrum of influenza illness, including asymptomatic infection, in children. Although HITS is a case-ascertained study and HICS is an ongoing prospective cohort study, in both studies, in the event of a positive influenza test in a household member, the household is intensively monitored for ~2 weeks. During this monitoring, household members report daily symptoms and give a nasal/oropharyngeal swab specimen every 2–3 days. Blood is collected both at the start of intensive monitoring and 30–45 days later. Information on the identification of index cases in these studies has been published previously, but briefly, symptomatic individuals present to HCSFV to be tested; in the event of a positive test, household members are approached for enrollment (HITS) or previously enrolled household members are activated (HICS) [15, 16]. In these studies, testing, except for the index case, is independent of symptoms during active surveillance. Although children aged 0–14 years are the primary population of interest for this study, individuals aged ≥15 years were examined for comparison.

Nicaraguan Pediatric Influenza Cohort Study

The Nicaraguan Pediatric Influenza Cohort Study (NPICS) is a prospective pediatric cohort study that began in 2011 and is currently ongoing. A complete overview of the study design, methodology, protocols, and population is previously published [17, 18]. Briefly, healthy children aged 0–14 who reside in District II of Managua were eligible to be enrolled.

Children who become ill are brought to HCSFV, where they are examined by study physicians. Study physicians collect clinical data on standardized forms. Children are tested for influenza if they exhibit severe respiratory illness or pneumonia or they meet the following criteria: children <2 years of age must have an illness onset ≤4 days prior and a fever or feverishness, and children ≥2 years of age must additionally have a cough, sore throat, or rhinorrhea. Data from NPICS, where children must be symptomatic to be detected as cases, were utilized to better understand the clinical presentation of influenza in children.

Laboratory Methods

Combined nasal/oropharyngeal samples were obtained. Samples were tested using real-time reverse-transcription polymerase chain reaction (RT-PCR) using validated Centers for Disease Control and Prevention (CDC) protocols [19, 20]. If positive for influenza A or influenza B, subtype or lineage was obtained following CDC protocols [21, 22].

Hemagglutination inhibition assays (HAIs) were performed using paired initial and final blood samples for household transmission participants. HAI was performed using A/H3N2 and A/H1N1pdm annual vaccine strain antigens and antigens corresponding to the dominant annual strain(s) (Supplementary Table 1). A ≥4-fold rise in HAI titer was considered evidence of an infection. HAI for influenza B was not conducted due to the poor sensitivity and specificity of HAI for influenza B [23]. Individuals who tested positive by RT-PCR or HAI were considered influenza positive.

Outcomes

The primary outcomes of this study were clinical signs, symptoms, and sequelae associated with influenza infection. Outcomes occurring up to 10 days before and 30 days after the date of the first positive test for influenza were included. An asymptomatic infection was defined as infection with no fever or cough and no more than one other minor symptom reported. The definition of asymptomatic infection used in this analysis allows for 1 minor symptom, such as a headache or rhinorrhea, across the illness period, as children often exhibit such symptoms even with no underlying infection. A sensitivity analysis was conducted to explore the results of these analyses if asymptomatic infection is defined as an infection where no symptoms occurred across the infection duration.

Statistical Analysis

Differences in age distribution were tested using Student *t* tests. Crude and age-stratified associations between influenza strain and the frequency of outcomes were tested using χ^2 or Fisher exact tests. Trends in proportions were tested using Cochran-Armitage tests for trend. Generalized linear mixed models with log-link functions and binary outcome distributions, adjusted for categorical age, were used to estimate the odds ratio of outcomes by influenza strain. A random intercept for child was included in all models to account for within-child correlation. All statistical testing was 2-sided and used a priori significance levels of .05. GLMMs adjusted for false discovery rates using the 2-stage step up method of Benjamini et al and the R package *mutoss* are presented in the Supplement [24]. Analyses were conducted using SAS 9.4 and figures were generated using R version 4.2.1.

RESULTS

Full Spectrum of Influenza in Children

Between 2012 and 2020, 1527 children participated in the household studies and a total of 1272 influenza infections occurred among 1021 children (Table 1). Few children had

Table 1. Description of Infections Among Children in the Study Population

	Household Studies (n = 1272 Infections Among 1021 Children)	NPICS (n = 2140 Cases Among 1394 Children)
Sex (no., %)		
Female	491 (48.1)	687 (49.3)
Male	530 (51.9)	707 (50.7)
Age in years at infection (mean and SD)	6.6 (4.0)	5.9 (3.9)
0–1 y	173 (13.6)	411 (19.2)
2–4 y	342 (26.9)	615 (28.7)
5–14 y	757 (59.5)	1114 (52.1)
Infection number (no., %)		
1st	1021 (80.3)	1394 (65.1)
2nd	216 (17.0)	530 (24.8)
3rd	31 (2.4)	175 (8.2)
4th	3 (0.2)	33 (1.5)
5th	1 (0.1)	8 (0.4)
Influenza vaccination status (no., %)[a]		
Vaccinated before infection	27 (2.1)	67 (3.1)
Ever vaccinated	215 (16.9)	404 (18.9)
Influenza type	…	…
Influenza A	878 (69.0)	1373 (64.2)
Influenza B	394 (31.0)	767 (35.8)
Influenza A subtype		
A/H3N2	510 (58.1)	843 (61.4)
A/H1N1pdm	349 (39.8)	529 (38.5)
A/H3N2 A/H1N1pdm coinfection	0	1 (0.1)
Unknown subtype	19 (2.2)	0 (0.0)
Influenza B lineage		
B/Yamagata	113 (28.7)	364 (45.1)
B/Victoria	133 (33.8)	357 (46.6)
No lineage	148 (37.6)	64 (8.3)

Abbreviations: NPICS, Nicaraguan Pediatric Influenza Cohort Study.

[a]Vaccinated before infection indicates the child received an influenza vaccination <180 days and >14 days before infection; ever vaccinated indicates that a child had at least 1 lifetime influenza vaccination prior to infection.

been vaccinated for influenza in the 180 days prior to infection (2.1%) or ever prior to infection (16.9%). Most infections were influenza A (69.0%), and of those, most were A/H3N2 (58.1%). Of the influenza B infections (31.0%), 33.8% were Victoria, 28.7% were Yamagata, and the remainder had no determinable lineage. Average age at infection was 6.6 years, with 13.6% of infections occurring in children under 2 years. Younger children were more likely to be infected with influenza A than influenza B (mean age 6.5 years for A and 6.9 years for B, $P = .063$). There was no association between age and influenza A subtype, as above; however, younger children were significantly more likely to be infected with B/Victoria than B/Yamagata (mean age B/6.2 years for Victoria, B/7.3 years for Yamagata, $P = .023$).

Of the 1272 influenza infections identified in children aged ≤14 years, 84 (6.6%) were asymptomatic, and 531 (41.8%) met criteria for an influenza-like illness (ILI), specifically cough and a measured temperature of ≥38 °C. When individuals aged ≥15 are included for comparison, 662 additional infections were identified, and 176 (26.6%) infections were asymptomatic. Children were much less likely to present asymptomatically than individuals aged ≥15 years ($P < .001$; Figure 2). The asymptomatic fraction in children increases with age, with children aged 0–1, 2–4, and 5–14 years having an asymptomatic

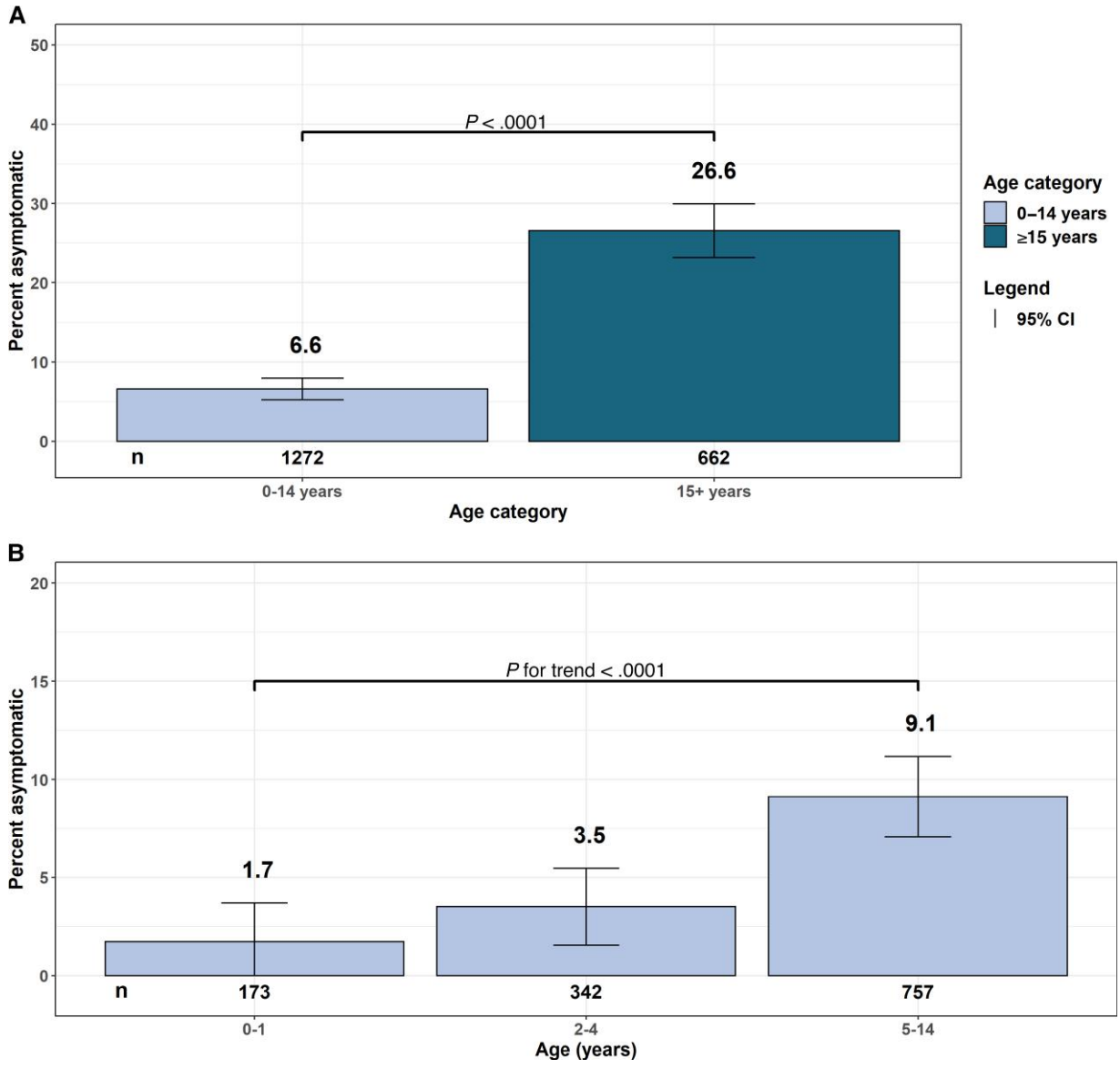

Figure 2. Point estimate and 95% CIs for the fraction of infections that were asymptomatic for (*A*) children aged 0–14 y versus individuals aged ≥15, and (*B*) children aged 0–14 y, stratified by age group. The categorical trend in asymptomatic fraction by age tested using the Cochran-Armitage test for trend. The difference in asymptomatic fraction between children and adults tested with the χ^2 test. Abbreviation: CI, confidence interval.

fraction of 1.7%, 3.5%, and 9.1%, respectively (P for trend < .001). Older individuals show no trend in the asymptomatic fraction by age (P for trend = .596, Supplementary Figure 1) nor a deviation in the asymptomatic fraction between any age group (P = .816).

Children without influenza symptoms were less likely to shed virus detectable by RT-PCR. Among asymptomatic children aged 0–14 years, 51.2% (43/84) shed influenza virus that was detected by RT-PCR, compared to 92.5% (1099/1188) of symptomatic children (P < .001, Figure 3*A*). Among individuals aged 15 years and older, fewer asymptomatic individuals shed virus detectable by RT-PCR (46.0%, 81/176), and fewer symptomatic individuals shed virus (82.7%, 81/402). When further stratified by age, 100% (3/3) of asymptomatic children aged 0–1 shed virus, compared to 66.7% (8/12) of children aged 2–4 and 46.4% (32/69) of children aged 5–14, with a significant inverse trend between categorical age and asymptomatic viral shedding (P = .033, Figure 3*B*). In contrast, asymptomatic older children and adults show no significant trend between categorical age and asymptomatic viral shedding (P = .493).

A sensitivity analysis was conducted to test the robustness of these results to a more stringent definition of asymptomatic infection. The overall asymptomatic fraction for children 0–14 is

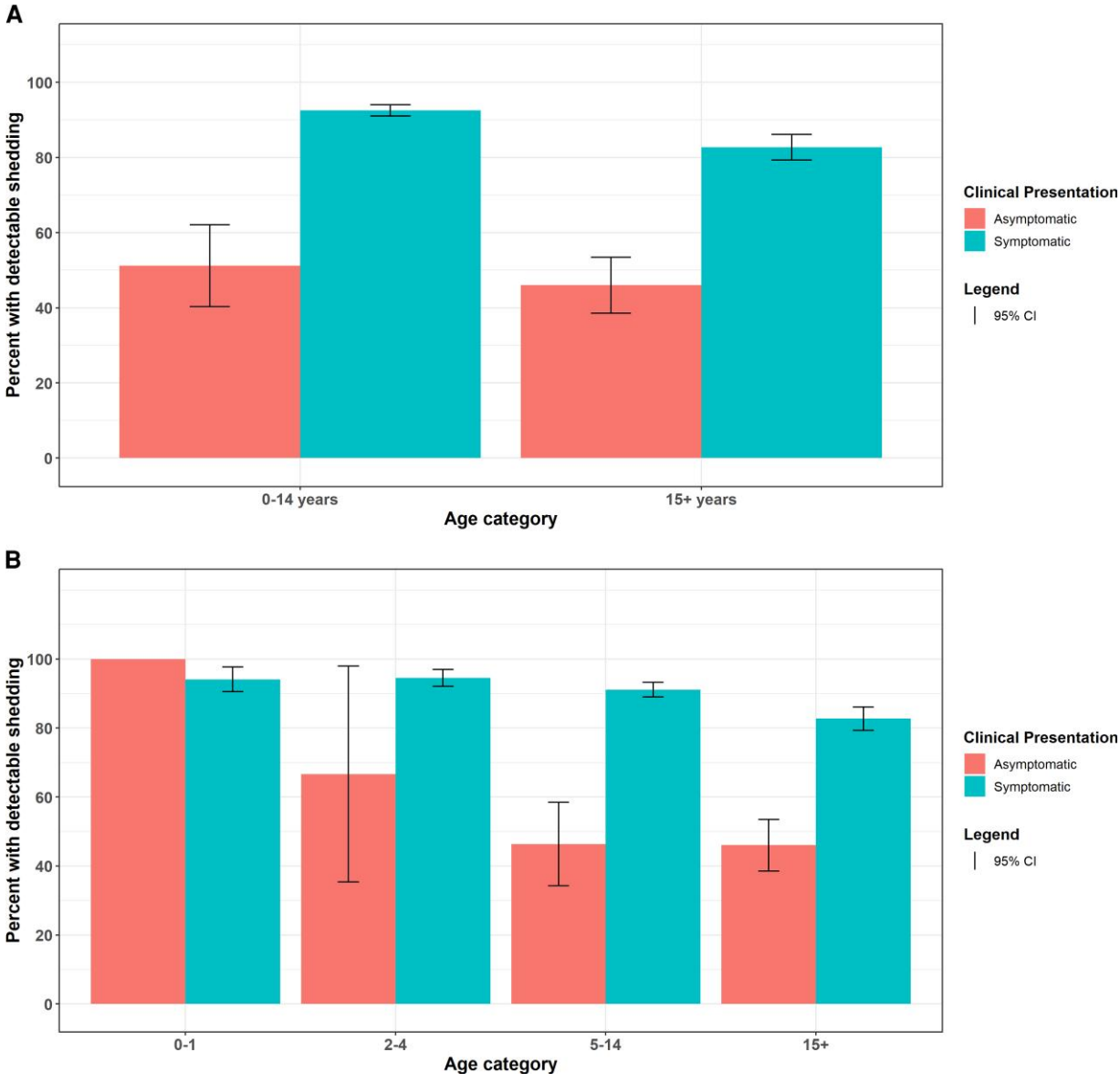

Figure 3. Point estimates and 95% CIs for the proportion of asymptomatic and symptomatic infections that exhibit viral shedding for (*A*) children aged 0–14 versus individuals aged ≥15, and (*B*) children aged 0–14 stratified by age group and individuals ≥15. The categorical trend in asymptomatic fraction by age tested using the Cochran-Armitage test for trend. Abbreviation: CI, confidence interval.

slightly smaller with 5.4% (69/1272) of children meeting this definition of asymptomatic infection, compared with 6.6% (84/1272) of children meeting the definition for the primary analysis (Supplementary Table 2). However, the trends and general results of this analysis remain the same with a more stringent definition of asymptomatic infection.

Clinical Presentation of Medically Attended Influenza

Between 2011 and 2020, 3174 children participated in NPICS, and a total of 2140 PCR-confirmed cases of influenza occurred in 1394 children (Table 1, Supplementary Table 3). The distribution of sex, age, vaccination status, and infecting strain is very similar to that found in the household studies. Younger children were more likely to be symptomatically infected with influenza A than influenza B, with an average age of cases of 5.5 years for influenza A and 6.5 years for influenza B ($P < .001$). There were no significant differences in the age distribution by subtype or lineage.

We used symptomatic cases from NPICS to establish the frequency of influenza-related symptoms, signs, and sequelae (Table 2). These cases represent medically attended influenza, or influenza of sufficient severity to be picked up by the medical system without necessarily requiring hospitalization. The most reported symptoms were subjective fever (98.8%), cough (88.4%), and rhinorrhea (85.0%). Approximately 20% of children aged 0–14 experienced at least 1 gastrointestinal symptom, including vomiting, nausea, and diarrhea. Pharyngeal erythema was appreciable in 67.2% of cases, and cervical lymphadenopathy in 29.1% of cases.

Sequelae of influenza in children aged 0–14 were rare, with pneumonia (2.4%) and acute otitis media (3.3%) being the most common. However, children aged 0–1 were at increased risk of sequelae, with pneumonia occurring in 7.3% of cases, and acute otitis media occurring in 4.6%. Febrile seizures were exceedingly rare, occurring in 0.6% of cases among children 0–1 years of age and in no reported cases among children aged

Table 2. Clinical Spectrum of Medically Attended Influenza in NPICS, by Age

	0–1 y[a] (n = 411)	2–4 y (n = 615)	5–14 y (n = 1114)	Total (n = 2140)
Symptom, no. (%)	…	…	…	…
Fever[b]	403 (98.1)	608 (98.9)	1104 (99.1)	2115 (98.8)
Cough[c]	358 (87.1)	538 (87.5)	996 (89.4)	1892 (88.4)
Rhinorrhea[c]	358 (87.1)	541 (88.0)	920 (82.6)	1819 (85.0)
Congestion	195 (47.4)	240 (39.0)	430 (38.6)	865 (40.4)
Sore throat	n/a	186 (30.2)	515 (46.2)	701 (40.5)
Headache	n/a	81 (13.2)	354 (31.8)	435 (25.2)
Malaise	n/a	49 (8.0)	74 (6.6)	123 (7.1)
Myalgia	n/a	6 (1.0)	60 (5.4)	66 (3.8)
Any GI symptom	82 (20.0)	125 (20.3)	190 (17.1)	397 (18.6)
Vomiting	36 (8.8)	53 (8.6)	95 (8.5)	184 (8.6)
Nausea	n/a	4 (0.7)	36 (3.2)	40 (2.3)
Diarrhea	57 (13.9)	58 (9.4)	27 (2.4)	142 (6.6)
Abdominal pain	n/a	49 (8.0)	82 (7.4)	131 (7.6)
Clinical sign, no. (%)				
Temp ≥ 37.8 °C	291 (70.8)	395 (64.2)	694 (62.3)	1380 (64.5)
Pharyngeal erythema	257 (62.5)	439 (71.4)	742 (66.6)	1438 (67.2)
Pharyngeal exudate	62 (15.1)	71 (11.5)	120 (10.8)	253 (11.8)
Conjunctival injection	7 (1.7)	12 (2.0)	40 (3.6)	59 (2.8)
Cervical lymphadenopathy	69 (16.8)	196 (31.9)	357 (32.0)	622 (29.1)
Wheezing	31 (7.5)	31 (5.0)	29 (2.6)	91 (4.3)
Ronchi	58 (14.1)	33 (5.4)	31 (2.8)	122 (5.7)
Crepitus	20 (4.9)	12 (2.0)	5 (0.4)	37 (1.7)
Stridor at rest	1 (0.2)	0	0	1 (0.1)
Sequela, no. (%)				
Pneumonia	30 (7.3)	16 (2.6)	6 (0.5)	52 (2.4)
Acute otitis media	19 (4.6)	24 (3.9)	28 (2.5)	71 (3.3)
Sinusitis	2 (0.5)	4 (0.7)	4 (0.4)	10 (0.5)
Febrile seizure[d]	2 (0.6)	0	n/a	2 (0.2)
Hospitalization	13 (3.2)	5 (0.8)	22 (2.0)	40 (1.9)

Abbreviations: GI, gastrointestinal; NPICS, Nicaraguan Pediatric Influenza Cohort Study.

[a]Children under 2 years of age were not assessed for sore throat, headache, malaise, myalgia, or abdominal pain (total n = 1729 for these symptoms).

[b]Part of the testing definition for children 0–14 years.

[c]Part of the testing definition for children 2–14 years.

[d]Febrile seizures are only formally diagnosed in children under 5 years of age (total n = 1026).

Table 3. Age-Adjusted Odds Ratios of Influenza Sequelae by Type, Subtype, and Lineage

	Type, Subtype, or Lineage		
	Influenza A (n = 1373)	Influenza B (n = 767)	*P* value
Sequela (OR, 95% CI)			
Pneumonia	0.96 (.51–1.79)	Ref	.888
Acute otitis media	1.54 (.89–2.68)	Ref	.124
Sinusitis	0.78 (.22–2.83)	Ref	.705
Febrile seizure	0.39 (.02–6.30)	Ref	.504
Hospitalization	1.01 (.52–1.96)	Ref	.988
	A/H1N1pdm (n = 529)	A/H3N2 (n = 844)	
Pneumonia	1.77 (.91–3.46)	Ref	.092
Acute otitis media	1.99 (1.14–3.48)	Ref	.015*
Sinusitis	0.32 (0.04–2.77)	Ref	.299
Febrile seizure	Not run due to insufficient number of events		
Hospitalization	3.73 (1.60–8.67)	Ref	.002*
	B/Victoria (n = 357)	B/Yamagata (n = 346)	
Pneumonia	10.99 (1.34–90.28)	Ref	.026*
Acute otitis media	1.25 (.45–3.47)	Ref	.664
Sinusitis	2.94 (.29–30.22)	Ref	.356
Febrile seizure	Not run due to insufficient number of events		
Hospitalization	2.28 (.68–7.68)	Ref	.179

Odds ratios estimated from generalized linear mixed models with a random intercept for child, adjusted for categorical age (* $P < .05$).

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

2–4. Finally, hospitalization occurred in just under 2% of cases (1.9%) among children 0–14 years of age, although hospitalization was also more common in the children younger than 2 (3.2%).

Next, we explored associations between clinical presentation and virus type, subtype, and lineage. Odds ratios of influenza sequelae were calculated for influenza A compared to influenza B, A/H1N1pdm compared to A/H3N2, and B/Yamagata compared to B/Victoria, adjusted for categorical age, or in the case of febrile seizures, unadjusted because all cases occur in the 0–1 year age group (Table 3). There were no differences in the odds of sequelae between influenza A and influenza B. However, acute otitis media (odds ratio [OR] 1.99, 95% confidence interval [CI]: 1.14–3.48) and hospitalization (OR 3.73, 95% CI: 1.60–8.67) were more likely to occur from A/H1N1pdm when compared to A/H3N2. Pneumonia was more likely to occur from B/Victoria than B/Yamagata (OR 10.99, 95% CI: 1.34–90.28). Clinical signs and symptoms were largely similar between strain, with a few notable differences: both influenza A and A/H1N1pdm were more likely to present with cough and rhinorrhea than influenza B and A/H3N2, respectively (Supplementary Table 5). Furthermore, A/H1N1pdm was more likely than A/H3N2 to present with pharyngeal exudate, and B/Victoria was more likely to present with pharyngeal erythema, exudate, conjunctival injection, and cervical lymphadenopathy than B/Yamagata (Supplementary Table 6). Results adjusted for multiple comparisons are presented in the Supplement (Supplementary Tables 4–6).

DISCUSSION

To the best of our knowledge, this is the largest prospective, community-based analysis of the clinical presentation of influenza in children. Our findings suggest that children are far less likely to be asymptomatic with influenza than adults, and that asymptomatic fraction increases in an age-dependent manner until about age 15 years. However, when compared to older individuals, young children are more likely to still shed virus when asymptomatic. These phenomena may be due to the relatively naive immune response that children have to influenza, suggesting that as children grow older and are exposed to more influenza strains, they gain relatively more protection against symptomatic influenza than influenza infection in general. There is evidence that asymptomatic infections are an important component of influenza transmission, and children are known to be drivers of community spread of influenza [10, 13, 14, 25, 26]. Given our findings, any contribution of asymptomatic children to community transmission may be driven by an increased propensity for asymptomatic children to actively shed virus, rather than by the existence of large numbers of asymptomatic children. However, viral shedding detectable by RT-PCR does not necessarily correspond to infectivity, so further work on the relationship between asymptomatic infection and transmission in children is needed [27].

The frequency of signs and symptoms of influenza that we found largely support the results of previous work, but the frequencies of acute otitis media and pneumonia in this study are lower than the frequencies often reported in the literature [2, 5, 6, 28, 29]. This is partially because this study primarily examines non-hospitalized children, a population expected to be less severely ill than children in hospitalized cohorts [5–7]. However, several pre-2010 outpatient studies also report a post-influenza frequency of AOM of 10% or greater and a post-influenza frequency of pneumonia of up to 6% [28, 29]. The release of the 13-valent pneumococcal conjugate vaccine in 2010 drastically changed the landscape of both pneumonia and AOM, and more stringent diagnostic criteria for AOM have also been adopted [28–33]. Thus, our estimate of the frequency of post-influenza AOM and pneumonia in children is likely more representative of current dynamics than estimates from previous studies. Febrile seizures were very rare; though previous reports have demonstrated that up to 20% of children hospitalized with influenza experience febrile seizures, we found much lower risk in outpatient settings [34, 35].

Our results support earlier work that suggests that influenza A and influenza B lead to similar clinical presentations, as we found no difference in the age-adjusted odds of sequelae and few differences in the clinical presentation [5, 8, 36]. However, we found important differences in the age-adjusted odds of certain sequelae by influenza subtype and lineage. Many studies have examined the relevance of virus strain on influenza presentation, but diverse settings, small sample sizes, and lack of adjustment for important covariates such as age have made identifying these associations difficult [8]. Our findings suggest that virus strain may impact the severity of infection in children. An increased risk of pneumonia for B/Victoria when compared to B/Yamagata is of particular importance with the global absence of B/Yamagata reported during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, as B/Victoria may constitute a higher proportion of influenza B infections in the future, leading to a proportional increase in pneumonia secondary to influenza B relative to influenza A [37]. Heterogeneous results across studies for the importance of subtype and lineage in infection severity may be partially driven by temporal and spatial differences in influenza exposure history and subsequent immunologic imprinting [38, 39]. Further work that better characterizes the precise immunologic history and resulting responses to certain types, subtypes, and lineages of influenza is needed.

Limitations

This work should be interpreted considering several limitations. First, although this is one of the largest prospective studies of influenza in children, this study is not sufficiently powered to detect important but rare outcomes of influenza in children, such as encephalitis, acute myositis, myocarditis/pericarditis, and death. Second, differential reporting of symptoms by age is a possible source of bias in the associations between age and asymptomatic infections. Some subjective symptoms, such as sore throat, headache, and abdominal pain, were not ascertained in children under 2 years due to the inability of young children to precisely verbalize symptoms. If young children experienced these symptoms but were not able to verbalize them, then the true asymptomatic fraction in the youngest age group would be smaller. Because of the direction of bias, however, hypothetically correcting that bias would further strengthen, rather than weaken, our findings. Low influenza vaccine uptake in this population may make the results less generalizable to highly vaccinated populations. However, influenza vaccine coverage is suboptimal even in high-resource settings, so this study provides much-needed understanding of the natural history of influenza among the unvaccinated [40]. Finally, the index cases were more likely to be children (Supplementary Table 7), which could bias the asymptomatic fraction downward. An analysis of only the non-index household members is presented for comparison (Supplementary Table 8), though the asymptomatic fraction from this analysis is likely biased upwards due to systematic exclusion of symptomatic infections.

CONCLUSIONS

Using data from several large community studies of influenza in children, we found that asymptomatic influenza in children is rare and age-dependent, and that asymptomatic young children are still very likely to actively shed virus. Furthermore, we established the frequency of influenza signs, symptoms, and sequelae in a community setting. Finally, we found evidence that A/H1N1pdm and B/Victoria have higher odds of important post-influenza outcomes.

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

Acknowledgments. The authors thank all of the participants and the many dedicated study personnel in Nicaragua at the Centro Nacional de Diagnóstico y Referencia and the Sócrates Flores Vivas Health Center.

Financial support. This work was supported by the National Institute of Allergy and Infectious Disease (NIAID) (grant numbers U01 AI088654, R01 AI120997, and U01 AI144616; and contract numbers HHSN272201400006C and 75N93021C00016) and the National Institutes of Health (grant number T32GM007863 to G. H.). The funding agencies had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Potential conflicts of interest. A. G. serves on a scientific advisory board for Janssen Pharmaceuticals and has consulted for Gilead Sciences. G. H.

reports support for attending meeting and/or travel from NIAID contract number HHSN272201400006. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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