Factors Influencing Frequency of Pediatric Clinically Distinguishable Influenza: A 2 Season Case-Control Study

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ABSTRACT

BACKGROUND: Little is known about the individual differences in susceptibility to, or lifetime frequency of clinically distinguishable influenza in children.

METHODS: Rapid enzyme linked immunoassay-confirmed influenza pediatric cases (n = 96) in season 1 (2017-2018) were compared to age-matched (mean 7.7 years) controls (n = 171) with no evidence of influenza in season 1. The 2 cohorts were again studied in season 2 (2018-2019) for influenza outcomes and influences. Medical records, questionnaires, and interviews were used to determine past influenza disease and vaccine histories.

RESULTS: After season 2, known lifetime influenza illnesses per year of age averaged 22.6% in cases and 5.6% in controls, with 62% of controls still having never experienced known influenza. Having had prior influenza was marginally significant as a risk for season 1 influenza in cases versus controls ($P = .055$), yet a significant risk factor in controls for season 2 ($P = .018$). Influenza vaccine rates were significantly higher in controls than in cases for season 1, with a greater female vaccine benefit. Lack of previous influenza had greater calculated effectiveness (52%) than vaccination (17%-26%) in escaping season 2 influenza. Lifetime rates of vaccination did not correlate with lifetime rates of known influenza in either cohort.

CONCLUSIONS: Lifetime clinically distinguishable influenza rates varied among children, with many escaping it for years even without being immunized against it. Findings of less than expected clinical influenza, no correlation between vaccination frequency and disease frequency, sex differences, and an association between past clinical influenza and current risk, point to innate differences in individual influenza experiences.

KEYWORDS: Influenza, vaccination, sex, innate, risk factors

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Introduction

Influenza is commonly recognized as a relatively severe illness that is distinguishable from a common cold. The main distinguishing classical symptoms in children are high fever and/or body aches, early in a respiratory illness.[1] With that symptom complex, clinically distinguishable influenza (CDI) is commonly confirmed by rapid antigen testing,[2] but is reasonably presumed when classical symptoms occur within a week of contact with a confirmed case, and somewhat less reliably when classical symptoms occur during a known influenza outbreak.

Approximately 20% of unvaccinated children may be infected with influenza each year,[3,4] yet there is little data in the medical literature about how often individual children experience CDI, and how that correlates with influenza vaccination. A survey-based study involving about 500 children 2 to 12 years of age found that more than half of parents reported their child "never had the flu,"[5] yet, seroprevalence studies indicate that over 95% of children have been infected by influenza by 6 to 9 years of age.[6,7]

Seroconversion-identified influenza infections occurred frequently in both vaccinated and placebo participants in an earlier study, with up to 74% and 48% of infections respectively being asymptomatic.[8] A prospective 5 season study using a polymerase chain reaction (PCR) influenza test, found that 65% of hospitalized patients and 93% of outpatients with positive tests for influenza (results unknown to treating physicians) were not given an influenza diagnosis.[9] In another study, 624 participants were PCR-tested when they had 2 or more symptoms, including fever, cough, headache, sore throat, or nasal congestion. Only 38% of children with positive influenza PCR tests sought medical attention for their symptoms.[10] Thus, pediatric influenza infections, like coronavirus disease 2019 (COVID-19), may commonly occur with mild nonspecific symptoms. The true "burden" of influenza should not include infections that are only identified because a sensitive test was used on children with limited symptoms, who might not otherwise be considered to have influenza.[10]

The purpose of this study was to evaluate vaccination and other influences affecting CDI in children. A secondary objective was to determine the age-adjusted incidence of CDI in children. The unusual occurrence of back to back "severe" (2017-2018)[11] and "moderate" (2018-2019)[12] influenza seasons, along with a relatively controlled patient population with detailed medical information, made this study possible.

Methods

Two patient groups were recruited from a private pediatric practice in the United States according to protocol approved by the University Institutional Review Board (IRB). The first group included "cases" who had clinically suspected influenza between November 2017 and March 2018 (season 1), confirmed by a rapid antigen test (Alere BinaxNOW Influenza A & B, Abbot) on a nasal swab. The second cohort included age-matched "controls" who had no clinical evidence of influenza during season 1 by medical record and parental questioning. Parents of potential cases and controls were screened by phone for interest and eligibility. Willing participants filled out a questionnaire asking frequency of influenza vaccination and disease, and influenza exposure risk at home and/or at school. Lifetime disease and vaccine histories were corroborated with medical records. Because December 2018 through May 2019 (season 2) also had a high prevalence of influenza, follow-up data was solicited from study parents about family disease and vaccination histories.

Historical influenza was based on the questionnaire definition, "having had flu symptoms (mainly fever, body aches, runny nose, and cough) along with a positive flu test, exposure within a week to someone else with a positive flu test, and/or those symptoms during a flu outbreak."

Patients were considered to have confirmed influenza if they had clinical influenza with positive tests, probable influenza if they were not tested, or had a negative test done within 1 day of symptom onset, but had classical symptoms and had a confirmed close contact within 1 week, and possible influenza if they had compatible symptoms during an influenza outbreak but were not tested and had no confirmed close contacts.

Historical influenza by questionnaire was corroborated with the medical record. Confirmed and probable CDI were each counted as 1 episode, whereas possible CDI was counted as half an episode. Vaccination histories were compiled by a combination of parental input and medical record documentation. Vaccines done at school, other offices, and pharmacies usually could not be confirmed in the medical record.

Historical influenza vaccination with inactivated (IIV) or live attenuated (LAIV) influenza vaccine was determined by parental interview plus medical record documentation, counting seasons vaccinated. All patients had been offered the influenza vaccine. The first season vaccinated usually included 2 doses. The 2009 pandemic season often included up to 4 doses. Patients were considered vaccinated for a season if at least 1 dose was given for that season. For study seasons 1 and 2, a participant was considered vaccinated only if the vaccine was completed at least 2 weeks prior to CDI onset.

Two-tailed Fisher exact testing and contingency table analyses were used for statistical comparisons in this exploratory study. $P < .050$ was considered significant.

Results

Demographics and Influenza Strains

In season 1, 102 patients aged 6 months to 17 years at time of clinical disease, had positive influenza tests either at the practice office (n=99) or at the local pediatric emergency department (n = 3). Six did not participate, leaving 96 cases. There were 60 cases with type A once, 31 with only type B, 2 with type A & B coinfection, and 3 who had 2 separate type A CDIs. Males predominated (55 vs 41, $P = .060$), but mostly at <5 years of age (13/55 vs 5/41) and at ≥ 14 years of age (10/55 vs 1/41). The majority (79%) were White, followed by 6% Black, 5% Asian, 3% Hispanic, and >6% mixed races.

Demographics of the participating 171 controls and 96 cases are shown in Table 1. Controls were reportedly exposed to influenza at home (15%) and/or at school (65%) during season 1. There were 13 potential controls that were either unable or unwilling to participate.

The same 2 cohorts (minus 2 cases unable to contact) participated for season 2. Of the influenza types confirmed that season, 27 patients had type A (2 twice in the same season), 1 type B, and 1 type A & B coinfection.

Disease Frequency

Prior to the first season, 44/72 (61%) of controls and 20/41 (49%) of cases that were $\geq$ 8 years old had no previous known history of influenza. At the end of season 2, 52/91 (57%) of controls and 52/143 (36%) of the total participants who were at least 8 years of age, still had no known CDI. After season 2, average CDI episodes per year of age in cases (22.6%) were 4 times that of controls (5.6%), (Table 1) and 62% of controls had still not had CDI. Age adjusted CDI incidence for all 265 participants was 11.7% after season 2.

Season 2 CDI attack rates (including possible and probable influenza) were 44/171 (26%) for controls and 14/94 (15%) for cases ($P = .044$). In that season, 21 controls and 10 cases had confirmed influenza, 8 controls and no case had probable influenza, while 15 controls and 4 cases had possible influenza.

Vaccination Frequency, Types, and Effectiveness

Season 1, with only IIV available, demonstrated vaccination benefit: 36/96 (38%) cases versus 91/171 (53%) controls were completely vaccinated ($P = .015$). Case males (25/55) were vaccinated against influenza for season 1 more frequently than case females (11/41) ($P = .088$). Influenza vaccination rates in controls (47/91 males vs 44/80 females for season 1, and 61/91 males vs 51/80 females for season 2) did not differ significantly

Table 1. Participant demographics and data.

CHARACTERISTIC	CASES (N=96)†	CONTROLS (N=171)
Age range (year)/mean/SD at time of diagnosis‡	0.5-17.3/7.73/4.1	0.5-17.3/7.70/4.2
Season 2 Age (N/%)†		
1.5-4 years	18/19.1%	35/20.5%
5-7 years	24/25.5%	45/26.3%
8-13 years	41/43.6%	70/40.9%
14-18 years	11/11.7%	21/12.3%
Males (N/%)	55/57.3%	91/53.2%
White	76/79.2%	158/93.5%
Black	6/6.3%	6/3.6%
In school or daycare	83/86.4%	134/78.3%
Stays home	13/13.5%	36/21.1%
CDI§ episodes prior to season 1 (range/sum/mean/age adjusted rate)	0-3/38.5/0.41/ 0.042	0-3/41.0/0.24/ 0.028
CDI episodes in season 1 (N/%)	99/103%	0/0%
CDI episodes in season 2 (N/%)	14.5/15.0%†	37.0/20.8%
Lifetime CDI episodes after season 2 (range/sum/mean/age adjusted rate)	1-4/150/1.60/ 0.226	0-3.5/78/0.46/ 0.056
Mean age (year) established as patient	1.5	0.93
Laboratory confirmed lifetime CDI following season 2 (N/% of total lifetime CDIs)	135/90.0%	49/62.8%
Average number of seasons vaccinated per year of age through season 2	0.55	0.62
Portion of influenza season vaccinations documented in medical record	86.8%	87.8%

†Case N for second season=94.
‡Date of case influenza diagnosis used to determine age of cases and their age-matched controls.
§CDI = clinically distinguishable influenza; Confirmed and probable CDI counted as 1; Possible CDI counted as 0.5.

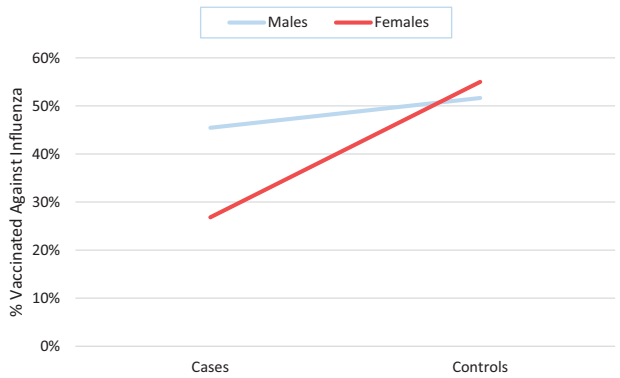

Figure 1. Sex and vaccine interaction in cases versus controls in season 1.

by sex. Females derived more benefit than males. For males, 25/55 (45%) of cases and 47/91 (52%) of controls were vaccinated ($P=.498$). For females, 11/41 (27%) of cases and 44/80 (55%) of controls were vaccinated ($P=.004$) (Figure 1).

For season 2, 60/94 (64%) cases and 112/171 (65%) controls were vaccinated, a significant increase from the first season in each group ($P<.001$ and $P=.028$ respectively). In that season, 52/60 (87%) vaccinated and 29/34 (85%) unvaccinated cases had no CDI, and 86/112 (77%) vaccinated and 41/59 (69%) unvaccinated controls had no CDI. Vaccine effectiveness for season 2 was only 18% for LAIV and 26% for IIV in controls, and 17% to 18% in all participants.

Despite the low season 2 vaccine effectiveness, control females did benefit significantly from vaccination. For control males, 19/61 (31%) of those vaccinated and 8/30 (27%) of those unvaccinated experienced CDI during season 2 ($P=.808$). For females, 7/51 (14%) of those vaccinated and 10/29 (34%) of those unvaccinated experienced CDI during season 2 ($P<.045$). Correspondingly, in season 2, vaccine failures were significantly more frequent in control males (19/61) than females (7/51) ($P=.042$).

Lifetime influenza vaccination histories (number of influenza seasons vaccinated divided by age in years) averaged 54% for cases and 62% for controls through season 2.

Disease Risk Relative to Previous Influenza Disease, Sex, and Vaccination History

CDI prior to season 1 was experienced by 31/96 (32%) cases versus 36/171 (22%) controls ($P=.055$). For cases and controls

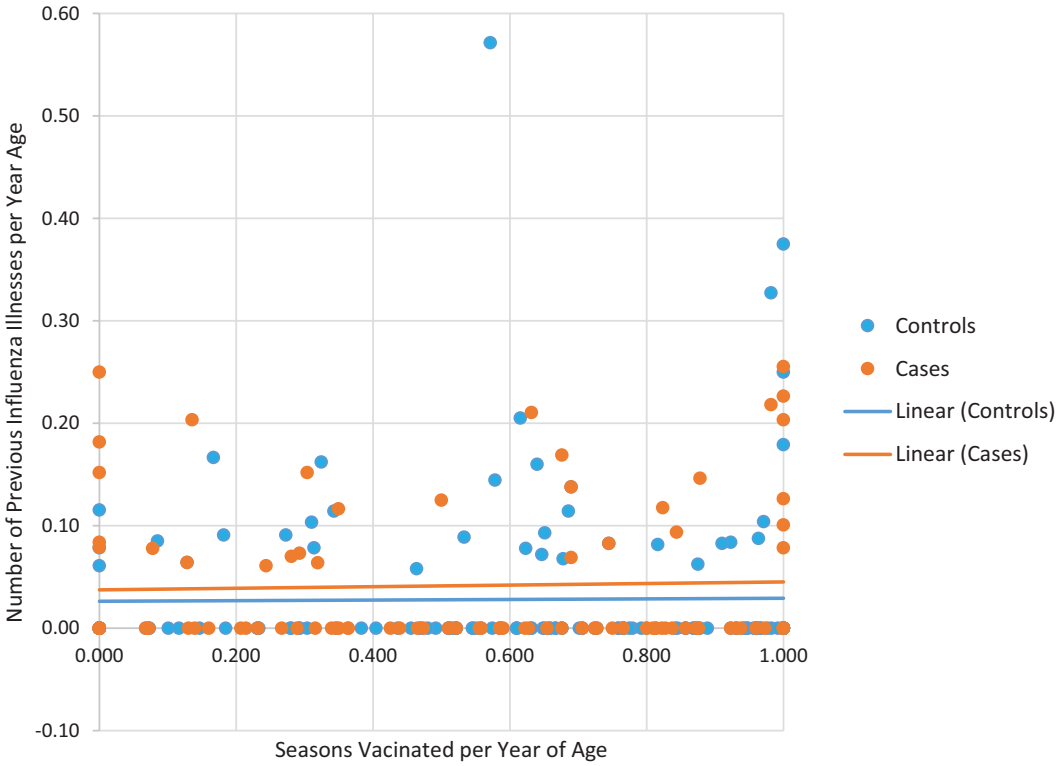

Figure 2. Pre-season 1 lifetime influenza and vaccination history normalized by age.

combined, 19/67 (28%) with CDI prior to season 1 experienced CDI during season 2, compared to 39/198 (20%) without CDI prior to season 1 ($P = .171$). However, 11/42 (26%) males with CDI and 25/103 (23%) without CDI prior to season 1 experienced CDI during season 2 ($P = .834$), while 8/25 (32%) females with CDI and 14/95 (15%) without CDI prior to season 1 experienced CDI during season 2 ($P = .077$).

In season 2, of the 36 controls with previous influenza, 7 had confirmed, 2 probable, and 6 possible influenza (42%). Of the 135 controls with no known previous CDI, 9 that were vaccinated and 5 unvaccinated had confirmed influenza, 5 vaccinated and 1 unvaccinated had probable influenza, and 4 vaccinated and 5 unvaccinated had possible influenza in season 2, for a total rate of 29/135 (21%) ($P = .018$). Effectiveness of no previous CDI compared to previous CDI for controls in season 2 ($100\% \times (1 - (29/135)/(15/36))$) was 52%.

Of the 33 case participants who had type B influenza in the first season, 6 had type A influenza (2 twice) and 1 had an unknown type in season 2 for a total of 7/33 (21%). That compares to 4 confirmed (type A) and 1 probable case in season 2, or 5/65 (7.7%), among the case participants who had type A influenza in the first season ($P = .099$).

Of 10 case patients who had confirmed influenza again in season 2, two had type A twice, both of whom had type B the previous year, and both were rarely ever vaccinated. Five (50%) of the confirmed cases in season 2 were IIV failures in both seasons.

Figures 2 and 3 show the relationship in individual cases and controls between vaccine frequency and disease frequency going into season 1, and after season 2. Children who had been vaccinated for every possible season had as much or more CDI than those who had never been vaccinated. Historical seasons vaccinated against influenza had over 85% documentation in the medical records of both cases and controls. The practice had seen 62.5% of cases and 72.5% of controls since birth, and only 6% of case and 3.9% of control vaccine doses were reportedly given at school. A high portion of lifetime CDI episodes were laboratory confirmed (Table 1).

Discussion

Many influenza studies use potentially minimal non-distinguishing criteria such as "at least 2 symptoms, including fever, cough, headache, sore throat, or nasal congestion" plus PCR testing, to define influenza cases.[10] Such loose clinical criteria for "influenza-like illness"[12] apply to most non-influenza respiratory viral illnesses. Despite rapid antigen tests not being as sensitive as PCR tests, both clinicians and patients should be able to identify with the definition used in our study. Our definition also better reflects the true burden of influenza. PCR confirmation provides optimal sensitivity, but for CDI, should be limited to patients at least suspected as having influenza because of their symptoms and circumstances.

Symptoms with influenza infections, as with COVID-19, range from none to severe. Asymptomatic influenza infections were demonstrated in experimentally inoculated adults, 80% to 93% of whom shed common strains inoculated, yet only 62% to 69% experienced any symptoms.[13] Asymptomatic influenza is also supported by data in children.[8-10] At the end of season 2,

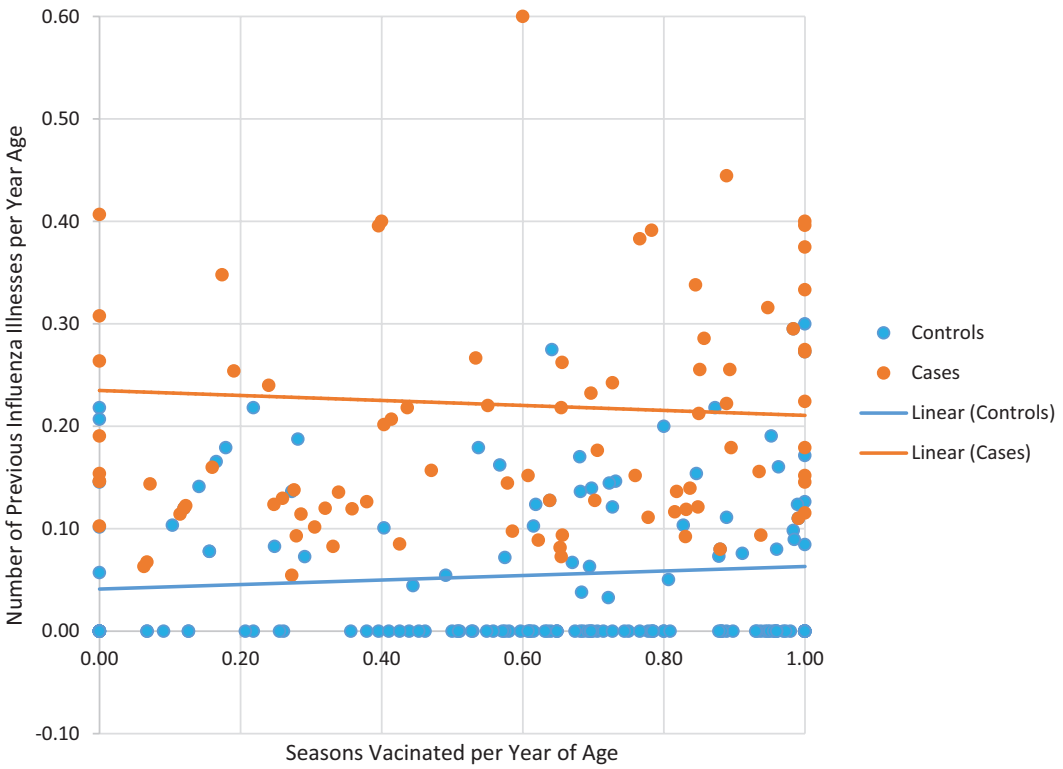

Figure 3. Post-season 2 influenza and vaccination history normalized by age.

57% of controls who were at least 8 years old still had no known influenza disease, when almost all of them would have been expected to have been infected based on serological data in the literature.[6,7] Asymptomatic infections might account for that discrepancy.

Our study indicates that CDI is not frequently experienced by the majority of children. Some individuals never vaccinated against influenza haven't experienced clinical influenza. Others, including some regularly vaccinated against the disease, experience multiple episodes, pointing to the need for improved vaccines. The case cohort averaged 22.6% lifetime CDI per year of age versus 5.6% for controls after Season 2, with all participants having experienced an average of 11.7% *known* age-adjusted influenza infections per year. That is comparable to a meta-analysis estimate of 12.7% average yearly symptomatic attack rates in unvaccinated children.[3]

We found previous influenza to be associated with a marginally ($P = .055$) significant difference between cases and controls for season 1. An earlier case control study found previous influenza to be significantly ($P < .001$) associated with influenza.[14] More in line with that previous study, controls with CDI before season 1 had significantly ($P = .018$) higher season 2 CDI rates than those with no prior CDI. Prior history of clinical influenza may possibly predict both higher risk for disease and greater benefit from yearly influenza vaccination.

More males than females made up the case cohort, yet more case males than females were vaccinated for season 1. Likewise, control males had more vaccine failures than females in season 2, and vaccination of females, more than males, was associated with less influenza for both seasons. CDI experienced prior to season 1 for cases and controls combined was also associated with season 2 CDI risk in females more than in males. Other studies have found a young male predominance in influenza infection and greater innate and adaptive immune responses in females.[15-18] Females with COVID-19 may have better antibody responses than males.[19] Potential influence of hormones and/or sex on both innate and adaptive immune responses deserves more study.

The control group had significantly greater rates of influenza vaccination than the case group for season 1, in which the vaccine was well matched to circulating strains.[11] Due to the emergence of a drifted H3N2 strain in early 2019,[12] season 2 vaccine effectiveness was poor. Despite higher rates (64%-65%) of vaccination in both cohorts going into the second season, controls had a greater attack rate than cases in season 2, possibly due to natural immunity in cases, having had recent influenza. Cross protection against drifted A strains has been demonstrated,[20] and a previous study of back-to-back H3N2 epidemics showed some cross protection and very high levels of seroprevalence after each epidemic.[21] Having had influenza B may not have been as protective against the new strain as having had influenza A in season 1, although the difference did not reach statistical significance. A study examining multiple seasons found lower rates of preceding season influenza in cases than in controls for both A and B types.[22]

The present findings of less than expected lifetime clinical influenza, poor correlation of vaccination frequency and disease frequency, sex frequency difference, and association

between past clinical influenza and current risk, provide evidence for innate differences in individual clinical responses to influenza exposure. Marked differences in individual responses to influenza infection were demonstrated by a study examining detailed gene and immunological activity in 17 adults voluntarily inoculated with influenza A.[23] The virus quickly triggered an inflammatory response in 9 subjects who developed mild to severe symptoms. In contrast, the subjects with no symptoms upregulated genes involving anti-oxidation, which reduced inflammation. Both symptomatic and asymptomatic subjects shed the virus and seroconverted. Assuming that children may have similar responses to influenza exposure, a significant number of them, vaccinated or not, may experience asymptomatic or mildly symptomatic disease that boosts immunity without experiencing the clinical pathology normally attributed to influenza. That could explain why our CDI was observed less often than would have been expected from available seroprevalence data.

Individual differences in severity of influenza can be influenced by gene variants affecting interferon response,[24,25] and HLA presentation to cytotoxic T lymphocytes.[26] Identifying individuals with these genetic variants, and determining modifiable factors that could affect severity, such as diet,[27,28] vaccines, and the microbiome,[29,30] is ripe for further investigation for both influenza and COVID-19.

Limitations of the present study include limited numbers of subjects and using a rapid influenza enzyme-linked immunoassay rather than PCR (reduced sensitivity for season 2). Even though good medical records were used in corroboration with participant historical accounts, parents sometimes forgot CDI noted in the medical record and sometimes reported episodes that were clearly not CDI upon further questioning. Multiple statistical comparisons were made in this exploratory study. Findings need to be validated by independent investigators. Limited racial diversity and location limits generalizability. Strengths include individual lifetime vaccine and disease data in a controlled population with most data verified by reliable medical records. The disease definition used is more practical for pediatric patients and their clinicians than previously used definitions. To our knowledge, this is the first study to explore individual differences in frequency of CDI and factors, including vaccines, associated with those differences.

In conclusion, children studied experienced CDI at an average lifetime rate of 12% per year of age at the end of 2 successive heavy influenza seasons. More than half of participants had never been known to have had influenza prior to the first season, and over half of controls still had not had the disease after these 2 seasons. Some individuals are affected by CDI more than others, regardless of influenza vaccine status. Asymptomatic influenza infections are probably common but understudied. Potential markers of influenza resistance are female sex and paucity of past CDI. More research is needed to find more effective vaccines as well as to better understand individual differences in resistance to CDI.

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Author Contributions

Both authors contributed significantly to the conception, design, data analysis, literature review, and drafting of this manuscript.

Data Availability

Databases utilize Protected Health Information, so cannot be openly shared. Any available data desired outside the manuscript can be accessed and provided upon request.

Patient Consent

Parents of participating patients were given full disclosure of the study and their rights by forms approved by the University of Alabama at Birmingham (UAB) School of Medicine Institutional Review Board prior to their enrollment. No materials from other sources are contained in this manuscript.

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