Clinical Predictors of Influenza in Young Children: The Limitations of "Influenza-Like Illness"

Nicholas T. Conway,[1,2] Zoe V. Wake,[3] Peter C. Richmond,[1,3,4] David W. Smith,[5,6] Anthony D. Keil,[7] Simon Williams,[5] Heath Kelly,[8] Dale Carcione,[9] Paul V. Effler,[9] and Christopher C. Blyth[1,3,4,7] on Behalf of the Western Australia Influenza Vaccine Effectiveness (WAIVE) Team

[1]Vaccine Trials Group, Telethon Institute for Child Health Research, Perth, Western Australia; [2]Child Health, University of Dundee, Scotland; [3]Department of Paediatric and Adolescent Medicine, Princess Margaret Hospital for Children, [4]School of Paediatrics and Child Health, University of Western Australia, Perth, [5]PathWest Laboratory Medicine WA, QEII Medical Centre, Nedlands, [6]School of Pathology and Laboratory Medicine, University of Western Australia, Perth, [7]Department of Microbiology, PathWest Laboratory Medicine, Princess Margaret Hospital for Children, Perth, Western Australia, [8]Victorian Infectious Diseases Reference Laboratory, North Melbourne, Victoria, Australia, and [9]Communicable Disease Control Directorate, Department of Health, Perth, Western Australia

Corresponding Author: Dr. Nicholas Conway, Child Health, MACHS Building, Ninewells Hospital, Dundee, Scotland, UK DD1 9SY. E-mail: n.z.conway@dundee.ac.uk.

Background. Influenza-like illness (ILI) definitions have been infrequently studied in young children. Despite this, clinical definitions of ILI play an important role in influenza surveillance. This study aims to identify clinical predictors of influenza infection in children ≤5 years old from which age-specific ILI definitions are then constructed.

Methods. Children aged 6–59 months with a history of fever and acute respiratory symptoms were recruited in the Western Australia Influenza Vaccine Effectiveness (WAIVE) Study. Clinical data and per-nasal specimens were obtained from all children. Logistic regression identified significant predictors of influenza infection. Different ILI definitions were compared for diagnostic accuracy.

Results. Children were recruited from 2 winter influenza seasons (2008–2009; n = 944). Of 919 eligible children, 179 (19.5%) had laboratory-confirmed influenza infection. Predictors of infection included increasing age, lack of influenza vaccination, lower birth weight, fever, cough, and absence of wheeze. An ILI definition comprising fever ≥38°C, cough, and no wheeze had 58% sensitivity (95% confidence interval [CI], 50–66), 60% specificity (95% CI, 56–64), 26% positive predictive value (95% CI, 21–31), and 86% negative predictive value (95% CI, 82–89). The addition of other symptoms or higher fever thresholds to ILI definition had little impact. The Centers for Disease Control and Prevention definition of ILI (presence of fever [≥37.8°C] and cough and/or sore throat) was sensitive (92%; 95% CI, 86–95), yet lacked specificity (10%; 95% CI, 8–13) in this population.

Conclusions. Influenza-like illness is a poor predictor of laboratory-confirmed influenza infection in young children but can be improved using age-specific data. Incorporating age-specific ILI definitions and/or diagnostic testing into influenza surveillance systems will improve the accuracy of epidemiological data.

Key words. Influenza, Human; Child; Preschool; Population Surveillance

Population surveillance is used to guide preventative strategies for influenza such as choosing strains for seasonal influenza vaccine constitution and early identification of pandemic or epidemic antigenic drift variants [1]. Early diagnosis of influenza disease also influences clinical decision making, especially when managing those at higher risk of severe disease [2]. Influenza disease surveillance usually includes a combination of community- and hospital-based syndromic surveillance and routinely collected data concerning morbidity and mortality, with only some including laboratory confirmation of influenza infection.

Consistent with other countries, Australian children <5 years old experience the highest laboratory-confirmed influenza notification rate (3.4 times the rest of the population in 2008), the highest rate of general practice consultations with influenza-like illness (ILI) (~50 000/100 000 population in 2008), and the greatest morbidity [3]. In the United States, children <5 years comprised 28% of ILI presentations in the Centers for Disease Control and Prevention (CDC) national network during the 2007–2008 influenza season [4].

The value of these data using ILI surveillance depends on a reliable and robust definition of ILI as well as a clear understanding of how ILI activity relates to influenza. The definition of ILI varies between countries and surveillance systems, but it usually includes the presence of fever and symptoms of acute respiratory tract infection [5–7]. Influenza-like illness is a poor predictor of actual influenza infection in adults, despite attempts to improve the accuracy of the definition [8], but there is limited data on the reliability of ILI in predicting influenza infection in children [9–12].

In this study, we have used data collected from young children recruited as part of a community and hospital influenza surveillance program to assess the clinical predictors of influenza infection in children ≤5 years old. We developed age-specific ILI definitions and tested their diagnostic accuracy against existing definitions and parental opinion.

MATERIALS AND METHODS

The Western Australia Influenza Vaccine Effectiveness (WAIVE) Study is an observational study designed to measure influenza vaccine effectiveness in children. The study design has been described elsewhere [13, 14]. In brief, children 6–59 months of age were eligible for participation if they presented with symptoms suggestive of an acute respiratory infection to selected general practices (2008 only), emergency departments (EDs; 2008 and 2009), and pediatric inpatient facilities (2008 and 2009). The recruitment period was for the duration of the winter influenza season as determined by local population surveillance. Children were eligible for enrollment in 2008 whether they had a history of fever (by parental report) or a measured temperature >37.8°C on presentation in addition to any acute respiratory symptoms within 72 hours before recruitment. To enhance recruitment in 2009, children were enrolled whether they had a history of fever or a measured temperature of >37.5°C on presentation plus the presence of any acute respiratory symptoms within 96 hours of recruitment. The study received approval from the relevant local human research ethics committees.

On enrollment by trained research staff, parents were asked to complete a questionnaire detailing demographics, medical history, and presenting symptoms. Temperature measured at enrollment was recorded by research staff. Per-nasal swabs (Copan Diagnostics Inc., Murrieta, CA) placed in viral transport medium or per-nasal aspirates were collected. Influenza testing on nasal swabs was performed by polymerase chain reaction (PCR) directed at hemagglutinin and matrix gene targets in multiplex real-time assay [14, 15], and by conventional cell cultures [14]. In addition, samples underwent PCR directed at other common respiratory viruses including respiratory syncytial virus (RSV), parainfluenza viruses 1–3, human metapneumovirus, rhinoviruses, adenoviruses, coronaviruses (other than severe acute respiratory syndrome coronavirus), and bocavirus [14].

Presence of influenza A or B detected by PCR or culture was collapsed into 1 dichotomous dependent outcome: influenza present or absent. The predictor variables of interest fell into 2 groups: (1) demographic factors (age, sex, race [indigenous or other], deprivation quintile, influenza vaccination status, prematurity [<37 completed weeks gestation], birth weight, past medical history, child care usage, household composition, and household smokers); and (2) symptomatology (recorded temperature and presence or absence of parentally reported: cough, coryza, wheeze, breathing difficulties, earache, sinusitis, sore throat, irritability, rash, diarrhoea, vomiting, lethargy, poor feeding, sleep disturbance, fever, and pallor). Vaccination status was verified via the Australian Childhood Immunisation Register (ACIR) [16]. Where ACIR conflicted with parental report, the family doctor was

contacted to establish the number of trivalent influenza vaccine (TIV) doses given previously. Because they are not normally distributed, categorical variables were created for age, household composition, and duration of fever and respiratory symptoms. Postal addresses were geo-coded before conversion to deprivation quintiles using data produced by the Australian Bureau of Statistics [17].

Statistical analysis was performed using SPSS 16.0.0 (SPSS Inc., Chicago, IL). After initial univariate analysis, variables were analyzed simultaneously within both groups (demographic factors and symptoms) by forced entry into a multivariable logistical regression model. Factors found to be significant ($P < .05$) at the group stage were then entered into a model encompassing both groups. Various definitions of ILI were then constructed based on the significant predictors of influenza infection. Sensitivity, specificity, and positive predictive value (PPV) and negative predictive value (NPV) and their respective binomial 95% confidence intervals (CIs) were then calculated. In addition, positive and negative likelihood ratios (LR+ and LR–) were also calculated. Ninety-five percent CIs for likelihood ratios were calculated in the manner described by Simel et al [18].

New ILI definitions were compared with definitions used by the CDC (presence of fever ($\geq 100^{\circ}$F [37.8° C]) and a cough and/or sore throat in the absence of a known cause other than influenza [5]) and parents' response to the questionnaire question: "Do you think your child has influenza ('flu')?"

RESULTS

Nine hundred and forty-four subjects were recruited (315 subjects in 2008 and 629 subjects in 2009). The majority were recruited within the hospital setting (General Practice, 153 subjects; EDs, 619 subjects; inpatient wards, 172 subjects). Twenty-five subjects were withdrawn (specimens not processed, 8; invalid consent, 8; incorrect age, 3; other, 6), resulting in a total sample population of 919. Altering the eligibility criteria in 2009 did not result in any additional recruits that were ineligible by 2008 criteria: 17 subjects had a temperature recorded >37.5°C yet <37.8°C; however, all of these subjects also had a history of fever within the previous 72 hours.

Respiratory viruses were identified in 711 subjects (77.4%). Rhinovirus (n = 239), RSV (n = 210), and influenza virus (n = 179) were most frequently

detected. Of those in whom influenza was detected, 131 had influenza A (including 97 subtyped as influenza A/H1N1 2009) and 48 had influenza B. Cultures proved positive for 59% (77 of 131) of those with influenza A and 58% (28 of 48) of those with influenza B. Influenza was detected in 23.5% (74 of 315) of recruits in 2008, compared with 17.4% (105 of 604) of eligible recruits in 2009 ($P = .03$).

The median age was 22 months and 526 of 919 (57%) were male. Chronic comorbidities were uncommon: 140 children (15%) had a comorbid condition, of which asthma was the most common (89 of 919, 10%). Premature births (<37 weeks gestation) accounted for 122 of 919 (13%) subjects. Nearly one-half of all children enrolled (430 of 919, 47%) had received the recommended schedule for seasonal influenza vaccination (ie, 2 doses of TIV in the first year of vaccination followed by 1 dose in subsequent years [19]) with a further 126 of 919 (14%) having received 1 dose in total (Table 1).

The most common symptoms reported by parents were cough (794 of 919, 86%), coryza (801 of 919, 87%), poor feeding (686 of 919, 75%), sleep disturbance (657 of 919, 71%), and irritability (607 of 919, 66%), although wheeze and respiratory distress were less prevalent (410 of 919, 45% and 413 of 919, 45%, respectively) (Table 2). For those that tested positive for influenza, the average temperature at enrollment was 39.5°C (range, 37–43.0; standard deviation [SD] 0.95; n = 155) compared with 39.2°C (range, 34.3–42.0; SD, 0.84; n = 652) in those who tested negative. When comparing influenza A and influenza B, there were no significant differences noted in presence of cough (121 of 131, 92% vs 43 of 48, 90%), wheeze (42 of 131, 32% vs 17 of 48, 35%), or recorded temperature (mean temperature [SD]: 39.5°C [0.8] vs 39.5°C [1.1]). Five hundred and ninety-eight parents recorded a response to the question, "Do you think your child has influenza ('flu')?" Seventy-eight of the 333 (23%) answering "yes" proved positive for influenza, whereas 24 of the 265 (9%) answering "no" were positive for influenza ($P < .001$).

Age >2 years, lack of TIV, lower birth weight, sharing a home with 2 or more other children, and being cared for by a single adult were significant demographic predictors of influenza infection on univariate analysis (Table 3). With the exception of the number of adult household members, all of these variables were significant when entered simultaneously within this group, and so they were entered into the final model. The symptoms that were significant

Table 1. Demographic Variables Stratified by Influenza Status[a]

	Influenza Positive (n = 179)		Influenza Negative (n = 740)	
	n	%	n	%
Age (years)				
<1	20	11.2	127	17.2
1–2	45	25.1	287	38.8
>2	114	63.7	326	44.1
Sex				
Female	72	40.2	306	41.4
Race				
Non-ATSI	161	89.9	668	90.3
Deprivation quintile				
1 (most deprived)	26	14.5	94	12.7
2	31	17.3	99	13.4
3	32	17.9	168	22.7
4	40	22.3	174	23.5
5 (least deprived)	50	27.9	204	27.6
Flu vaccination				
None	97	54.2	263	35.5
1 dose	25	14.0	101	13.6
≥2 doses	57	31.8	373	50.4
Full-term birth				
Yes	145	81.0	635	85.8
Past medical history				
Asthma	22	12.3	67	9.1
Other chronic respiratory	3	1.7	12	1.6
Cardiac condition	3	1.7	14	1.9
Neuro condition	5	2.8	14	1.9
Childcare				
Attends any	109	60.9	497	67.2
Additional children in house				
0–1	105	58.7	519	70.1
2–3	55	30.7	164	22.2
>3	10	5.6	21	2.8
Adults in house				
1	20	11.2	47	6.4
2	116	64.8	564	76.2
>2	35	19.6	100	13.5
Smokers in house				
Yes	48	26.8	197	26.6

Abbreviation: ATSI, Aboriginal or Torres Strait Islander.
[a]Accumulative percentages <100% due to unknown or missing data.

Table 2. Parentally Reported Symptoms Stratified by Influenza Status[a]

	Influenza Positive (n = 179)		Influenza Negative (n = 740)	
	n	%	n	%
Fever days				
<2 days	74	41.3	338	45.7
2–3 days	62	34.6	218	29.5
>3 days	32	17.9	138	18.6
Days of respiratory symptoms				
<2 days	42	23.5	193	26.1
2–3 days	59	33.0	234	31.6
>3 days	60	33.5	238	32.2
Respiratory symptoms				
Cough	164	91.6	630	85.1
Coryza	154	86.0	647	87.4
Wheeze	59	33.0	351	47.4
Respiratory distress	61	34.1	352	47.6
Earache	61	34.1	263	35.5
Sore throat	68	38.0	322	43.5
Sinusitis	6	3.4	47	6.4
Other symptoms				
Irritability	111	62.0	496	67.0
Rash	17	9.5	118	15.9
Diarrhoea	41	22.9	185	25.0
Lethargy	71	39.7	296	40.0
Poor feeding	139	77.7	547	73.9
Sleep disturbance	123	68.7	534	72.2
Vomiting	63	35.2	292	39.5
Pallor	45	25.1	210	28.4

[a]Accumulative percentages <100% due to unknown or missing data.

univariate predictors of influenza infection were as follows: raised temperature, fever for >3 days, presence of cough, absence of wheeze, respiratory distress, and rash. Fever, presence of cough, and absence of wheeze remained significant when entered simultaneously within the symptom group, and so they were retained for the final model. With the exception of number of children in the house, all variables entered into the final model remained significant (see Table 3).

Based on the results of the regression equation, ILI was defined in this population using various combinations of the following criteria: presence of cough, absence of wheeze, and incremental thresholds of fever (See Figure 1 and Table 4). A complete data set for each of these variables was available for 798 cases, which were used for subsequent calculations of the performance of ILI definition. The presence of cough alone was highly sensitive (93%; 95% CI, 84–96) yet lacked specificity in diagnosing influenza infection (14%; 95% CI, 12–17). If the definition of ILI comprised cough and the absence of wheeze, sensitivity was reduced (60%; 95% CI, 52–68) but specificity improved (59%; 95% CI, 55–63). The addition of fever ≥38°C to this definition resulted in a small

Table 3. Significant Predictors of Influenza Infection[a]

	Univariate OR		Within Group Multivariate OR		Final Model Multivariate OR	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Group 1: Demographic factors						
Age (years)						
<1		<.001		<.001		.023
1–2	1.00 (0.56–1.75)	.988	1.15 (0.61–2.18)	.659	0.92 (0.48–1.76)	.794
>2	2.23 (1.33–3.74)	.002	2.62 (1.44–4.80)	.002	1.66 (0.91–3.05)	.100
Flu vaccination						
None		<.001		.010		<.001
1 dose	0.68 (0.41–1.11)	.125	0.71 (0.39–1.28)	.251	0.69 (0.38–1.25)	.222
≥2 doses	0.41 (0.29–0.60)	<.001	0.52 (0.35–0.80)	.002	0.41 (0.26–0.63)	<.001
Birth weight						
Per Kg	0.79 (0.62–1.00)	.048	0.65 (0.46–0.91)	.012	0.74 (0.56–0.97)	.031
Additional children in house						
0–1		.006		.006		.112
2–3	1.67 (1.15–2.42)	.007	1.63 (1.07–2.47)	.023	1.55 (1.01–2.38)	.045
>3	2.35 (1.08–5.14)	.032	3.47 (1.35–8.91)	.010	1.67 (0.51–5.44)	.397
Adults in house						
1		.005		.076	–	
2	0.48 (0.28–0.85)	.011	0.51 (0.26–0.97)	.041		
>2	0.82 (0.43–1.57)	.555	0.73 (0.33–1.58)	.419		
Group 2: Symptoms						
Fever						
Per °C	1.51 (1.23–1.85)	<.001	1.62 (1.17–2.24)	.003	1.48 (1.18–1.87)	.001
Fever days						
<2 days		<.001		.412		
2–3 days	0.88 (0.59–1.33)	.545	0.69 (0.33–1.44)	.321	–	
>3 days	2.32 (1.55–3.48)	<.001	1.19 (0.54–2.66)	.664		
Respiratory symptoms						
Cough	2.21 (1.19–4.12)	.012	4.95 (1.37–17.90)	.015	2.60 (1.27–5.33)	.009
Wheeze	0.54 (0.38–0.77)	.001	0.39 (0.20–0.74)	.004	0.55 (0.36–0.83)	.005
Respiratory distress	0.56 (0.40–0.79)	.001	0.59 (0.31–1.14)	.116	–	
Other symptoms						
Rash	0.55 (0.32–0.94)	.030	0.81 (0.36–1.79)	.601	–	

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

[a]Results presented for all variables with univariate significance of *P* < .05. All variables in Tables 1 and 2 entered within demographic and symptom groups, irrespective of univariate significance. All variables with significance of *P* < .05 at the group stage were retained for the final model.

improvement in specificity (60%; 95% CI, 56–64) and an insignificant decrease in sensitivity (58%; 95% CI, 50–66). The PPV, NPV, LR+ and LR– for this definition were as follows: 26% (95% CI, 21–31), 86% (95% CI, 82–89), 1.46 (95% CI, 1.24–1.72), and 0.69 (95% CI, 0.57–0.84), respectively. There was a significant drop in sensitivity and rise in specificity if the ILI definition included a temperature threshold >38.5°C.

The CDC definition of ILI (presence of fever (≥100°F [37.8°C]) and a cough and/or sore throat was highly sensitive yet poorly specific for influenza in this population: sensitivity 92% (95% CI, 86–95), specificity of 10% (95% CI, 8–13), PPV of 20% (95% CI, 17–23), NPV of 83% (95% CI, 73–91), LR+ of 1.02 (95% CI, 0.96–1.07), and LR– of 0.85 (95% CI, 0.48–1.50). There was no significant difference between presence of cough alone and the CDC definition of ILI. Asking parents whether they think that their child has influenza had a sensitivity of 77% (95% CI, 67–84), specificity of 47% (95% CI, 40–54), PPV of 29% (95% CI, 22–37), NPV of 86%
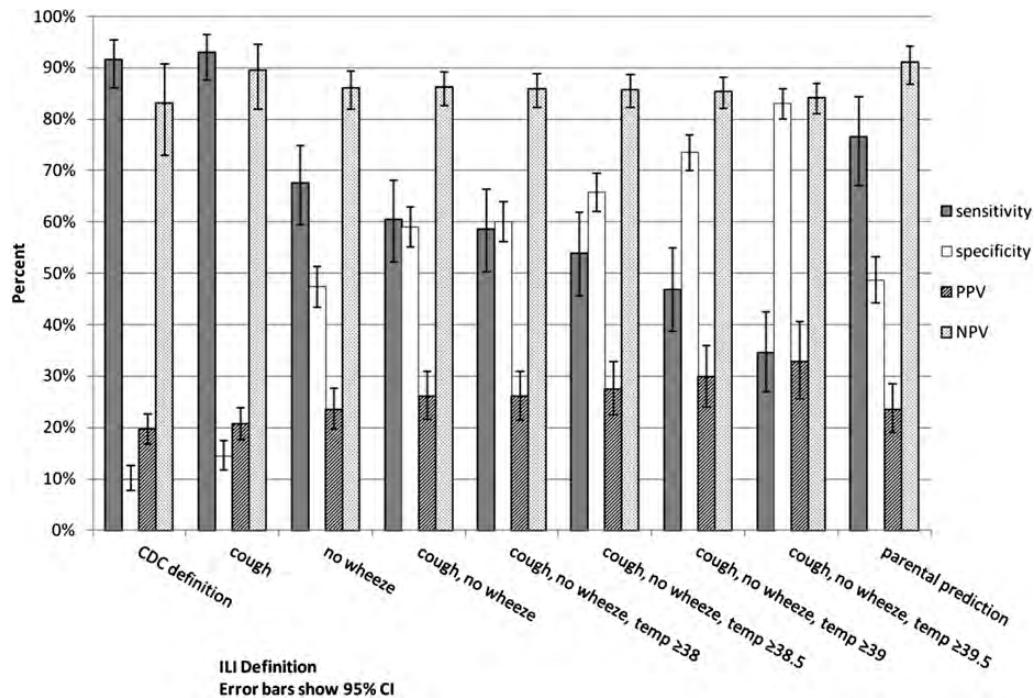
Figure 1. Diagnostic accuracy of different influenza-like illness definitions. Abbreviations: CI, confidence interval; ILI, influenza-like illness; NPV, negative predictive value; PPV, positive predictive value.

Table 4. Positive and Negative Likelihood Ratios for Different Influenza-Like Illness Definitions

	Likelihood Ratios	
	LR+ (95% CI)	LR– (95% CI)
CDC definition	1.02 (0.96-1.07)	0.85 (0.48–1.5)
Cough	1.09 (1.03–1.15)	0.49 (0.27–0.9)
No wheeze	1.28 (1.12–1.46)	0.69 (0.54–0.87)
Cough, no wheeze	1.47 (1.26–1.73)	0.67 (0.55–0.82)
Cough, no wheeze, temp ≥38	1.46 (1.24–1.72)	0.69 (0.57–0.84)
Cough, no wheeze, temp ≥38.5	1.58 (1.32–1.89)	0.7 (0.59–0.84)
Cough, no wheeze, temp ≥39	1.77 (1.43–2.19)	0.72 (0.62–0.84)
Cough, no wheeze, temp ≥39.5	2.03 (1.54–2.68)	0.79 (0.7–0.89)
Parental prediction	1.49 (1.3–1.71)	0.48 (0.34–0.69)

Abbreviations: CDC, Centers for Disease Control and Prevention; CI, confidence interval; LR +, positive likelihood ratio; LR–, negative likelihood ratio; temp, temperature.

(95% CI, 79–92), LR+ of 1.49 (95% CI, 1.30–1.71), and LR– of 0.48 (95% CI, 0.34–0.69).

The above analyses were repeated with data stratified according to vaccination status (no TIV vs any TIV) and age group (≤2 years vs >2 years) (see supplementary digital content). The observed PPVs in the unvaccinated group were significantly greater than the vaccinated group. Subgroup analysis of each vaccination group stratum by year of illness was undertaken with no appreciable difference noted (data not shown). For those ≤2 years, an ILI definition that included fever ≥38°C, cough, and the absence of wheeze had a significantly lower sensitivity and PPV and a higher specificity compared with those >2 years. The reliability of parental opinion was unaffected by vaccination status or age group of child.

DISCUSSION

Young children and infants with seasonal influenza can present with a wide variety of symptoms and may not yet be developmentally capable of verbalizing symptoms to their caregivers [20]. Current definitions of ILI are largely derived from adult studies and lack validation within the pediatric setting [5–7]. Fever is a common presenting symptom for young children with influenza. When all children with acute respiratory illness (irrespective of presence or absence of fever) are tested, 95% of those who test positive for influenza had a history of fever [21, 22]. Systematic review of the literature has failed to find any particular combination of additional symptoms that can reliably predict influenza infection [8]. Only 2 studies in this systematic review enrolled preschool children: in 1 study, 18 of 610 cases with fever and respiratory illness were <5 years old [9], whereas the other did not stratify by age [10]. Later, Ohmit and Monto [11]

reported a PPV of 64% in a subset of 221 children <5 years old presenting with cough and fever (>38.2°C). The generalizability of these figures is limited, however, because the study design excluded children with RSV infection, which would have falsely elevated the incidence of influenza infection in the study population [11]. A further prospective pediatric study assessing the predictive nature of an ILI diagnosis in children with fever and symptoms suggestive of respiratory infection (n = 128; age <17 years) did not stratify results by age, making it less generalizable to younger children [12].

This study recruited young children presenting with acute respiratory symptoms during 2 successive winter influenza seasons, which included the first wave of pandemic influenza A/H1N1 2009. In this population, we have found that an existing ILI definition in common usage (CDC definition) proved highly sensitive yet lacked specificity in identifying those with influenza infection. A surveillance system that uses this ILI definition in isolation would therefore grossly overestimate influenza prevalence by virtue of the large number of false positives generated. In contrast, we found that an ILI definition comprising fever ≥38°C, cough, and absence of wheeze achieved a greater balance between sensitivity and specificity in the study population.

However, ILI was a poor predictor of influenza infection regardless of which definition was tested. Children with ILI had a 20%–30% probability of actually having influenza infection, whereas those without ILI (regardless of definition tested) had a 10%–15% probability of testing positive for influenza. Each definition tested had positive and negative likelihood ratios approaching 1, indicative of little appreciable change in the odds of an individual having disease if they met ILI definition criteria or not. Furthermore, parental prediction of influenza infection in their children compared favorably with use of an ILI definition, underlining the poor diagnostic accuracy of ILI overall. Decisions regarding the investigation and management of children suspected of having influenza take into account a number of factors, including the known incidence of influenza at that time, the likelihood of severe disease, and the availability of antiviral medication [2]. However our findings would suggest that, due to the inaccuracy of syndromic definitions, clinicians should maintain a low threshold for influenza testing in children with possible influenza. This is especially important for children with moderate to severe illness and/or those requiring hospitalization. Similarly, diagnostic testing is required to obtain accurate influenza surveillance in young children. Ideally, this should include testing by highly sensitive and specific methods such as PCR, although immunofluorescent antigen detection tests are sufficiently sensitive for use on nasopharyngeal aspirates. The rapid antigen tests have been used in some studies [23, 24], but they are less sensitive than laboratory-based tests (especially for influenza A/H1N1 2009); their performance is influenced by specimen type, test brand used, and the virus type and subtype; and they do not identify influenza A subtypes. These tests have been successfully incorporated into public health influenza surveillance systems in the past [25]; however, they need to be reassessed now that influenza A/H1N1 2009 is circulating.

The eligibility criteria for our study included a history of fever. This methodology is similar to a number of previous studies [9–12] and highlights the need for external validation of any clinical predictor tool that is intended to be used in unselected populations. However, our findings remain relevant to the general pediatric population given that the vast majority of children with influenza present with fever [21, 22]. The diagnostic accuracy of ILI differed between those vaccinated and those unvaccinated (reflecting the lower prevalence of influenza in those who were vaccinated). The pediatric population studied had high vaccination rates with TIV as a result of a state-wide campaign introduced in 2008 that provides free seasonal influenza vaccination to this age group. The high prevalence of influenza vaccination in our study population contributes to the generalizability of our findings to other countries where influenza vaccination is readily available to children <5 years of age. The reliability of ILI as defined by fever (≥38°C), cough, and absence of wheeze was age dependent, with less sensitivity and greater specificity in those 2 years of age or younger. This is a reflection of proportionally higher numbers of children ≤2 years old with wheeze irrespective of influenza status (data not shown), presumably as a result of a bronchiolitic-type illness. This age-dependent manifestation of influenza infection further highlights the problems inherent in applying adult-derived ILI definitions to the pediatric population. Because the presence of wheeze was determined by the parents, the calculated prevalence is likely to be different from one based on a clinical definition [26]. However, because this bias is constant between those who tested positive for influenza and those who were negative, it is not expected to have affected the results.

Also, in practice, assessing children with an ILI usually relies on parental history as well as clinical findings, making our findings relevant to real-life circumstances.

CONCLUSION

To our knowledge, this is the first study attempting to construct a definition of ILI for children aged 5 years and under using prospectively gathered data from a general pediatric population presenting with symptoms suggestive of acute respiratory tract infection. We have demonstrated that when predicting influenza infection in younger children, an ILI definition constructed using age-specific data and comprising presence of fever ($\geq$38°C), cough, and absence of wheeze results in a greater balance between sensitivity and specificity compared with a definition of ILI used by current surveillance systems. The diagnostic accuracy of influenza virus surveillance systems would be enhanced by developing age-specific ILI definitions aimed at the pediatric age group and/or by incorporating diagnostic testing into the system.

References

1. WHO global influenza surveillance network [homepage on the Internet]. **2010**. Available at: http://www.who.int/csr/disease/influenza/surveillance/en/index.html. Accessed December 30, 2010.
2. 2010–11 influenza antiviral medications: summary for clinicians [homepage on the Internet]. **2010**. Updated 15 Dec 2010; Available at: http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. Accessed December 30, 2010.
3. Kaczmarek M, Owen R, Barr IG. Annual report of the national influenza surveillance scheme, 2008. Commun Dis Intell **2010**; 34:8–22.
4. Centers for Disease Control and Prevention. 2007–8 influenza season, week 20 ending May 17, 2010 [homepage on the Internet]. **2008**. Updated 4 Sep 2008; Available at: http://www.cdc.gov/flu/weekly/weeklyarchives2007-2008/weekly20.htm. Accessed December 3, 2010.
5. Centers for Disease Control and Prevention. Overview of influenza surveillance in the United States [homepage on the Internet]. **2010**. Updated 15 Oct 2010; Available at: http://www.cdc.gov/flu/weekly/overview.htm. Accessed November 29, 2010.
6. Aguilera JF, Paget WJ, Mosnier A, et al. Heterogeneous case definitions used for the surveillance of influenza in Europe. Eur J Epidemiol **2003**; 18:751–4.
7. Thursky K, Cordova SP, Smith D, Kelly H. Working towards a simple case definition for influenza surveillance. J Clin Virol **2003**; 27:170–9.
8. Call SA, Vollenweider MA, Hornung CA, et al. Does this patient have influenza? JAMA **2005**; 293:987–97.
9. Carrat F, Tachet A, Rouzioux C, et al. Evaluation of clinical case definitions of influenza: detailed investigation of patients during the 1995–1996 epidemic in France. Clin Infect Dis **1999**; 28:283–90.
10. Hulson TD, Mold JW, Scheid D, et al. Diagnosing influenza: the value of clinical clues and laboratory tests. J Fam Pract **2001**; 50:1051–6.
11. Ohmit SE, Monto AS. Symptomatic predictors of influenza virus positivity in children during the influenza season. Clin Infect Dis **2006**; 43:564–8.
12. Friedman MJ, Attia MW. Clinical predictors of influenza in children. Arch Pediatr Adolesc Med **2004**; 158:391–4.
13. Dixon GA, Moore HC, Kelly H, et al. Lessons from the first year of the WAIVE study investigating the protective effect of influenza vaccine against laboratory-confirmed influenza in hospitalised children aged 6–59 months. Influenza Other Respi Viruses **2010**; 4:231–4.
14. Kelly H, Jacoby P, Dixon GA, et al. Vaccine effectiveness against laboratory-confirmed influenza in healthy young children. A case-control study. Pediatr Infect Dis J **2011**; 30:107–11.

15. Chidlow G, Harnett G, Williams S, et al. Duplex real-time reverse transcriptase PCR assays for rapid detection identification of pandemic (H1N1) 2009 and seasonal influenza A/H1, A/H3, and B viruses. J Clin Microbiol 2010; 48:862–6.

16. Australian childhood immunisation register [homepage on the Internet]. 2012. Updated 16 May 2012; Available at: http://www.humanservices.gov.au/customer/services/medicare/australian-childhood-immunisation-register. Accessed May 29, 2012.

17. SEIFA: Socio-economic indexes for areas [homepage on the Internet]. 2008. Updated 3 Jul 2008; Available at: http://www.abs.gov.au/websitedbs/D3310114.nsf/home/Seifa_entry_page. Accessed December 22, 2010.

18. Simel DL, Samsa GP, Matchar DB. Likelihood ratios with confidence: sample size estimation for diagnostic test studies. J Clin Epidemiol 1991; 44:763–70.

19. The Australian immunisation handbook 9th edition 2008 [homepage on the Internet]. 2008. Updated 26 Mar 2008; Available at: http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook-influenza. Accessed June 14, 2010.

20. Cox NJ, Subbarao K. Influenza. Lancet 1999; 354: 1277–82.

21. Silvennoinen H, Peltola V, Lehtinen P, et al. Clinical presentation of influenza in unselected children treated as outpatients. Pediatr Infect Dis J 2009; 28:372–5.

22. Poehling KA, Edwards KM, Weinberg GA, et al. The underrecognized burden of influenza in young children. N Engl J Med 2006; 355:31–40.

23. Hurt AC, Alexander R, Hibbert J, et al. Performance of six influenza rapid tests in detecting human influenza in clinical specimens. J Clin Virol 2007; 39:132–5.

24. Grijalva CG, Poehling KA, Edwards KM, et al. Accuracy and interpretation of rapid influenza tests in children. Pediatrics 2007; 119:e6–11.

25. Effler PV, Ieong MC, Tom T, et al. Enhancing public health surveillance for influenza virus by incorporating newly available rapid diagnostic tests. Emerg Infect Dis 2002; 8:23–8.

26. Cane RS, Ranganathan SC, McKenzie SA. What do parents of wheezy children understand by "wheeze"? [see comment]. Arch Dis Child 2000; 82: 327–32.