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Original Article

Validity of clinical case definitions for influenza surveillance among hospitalized patients: results from a rural community in North India

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Objective: Clinical case definitions used for influenza surveillance among hospitalized patients vary and need systematic evaluation.

Design, setting and sample: During July 2009–August 2011, we collected clinical data and specimens (nasal and throat swabs) from rural patients hospitalized for acute medical illnesses. Specimens were tested by rRT-PCR for influenza viruses.

Main outcome measures: Case definitions evaluated the following: influenza-like illness (ILI: measured fever plus cough or sore throat); severe acute respiratory illness (SARI: ILI with difficulty breathing in ≥5 years, Integrated Management of Childhood Illness–defined pneumonia or severe pneumonia, or physician diagnosed lower respiratory infection in <5 years); acute respiratory infection (ARI: ≥1 of cough, nasal discharge, difficulty breathing or sore throat); febrile acute respiratory illness (FARI: fever plus either cough, sore throat, runny nose, difficulty breathing, or earache). Variants that included ''reported fever'' and additional sign–symptom combinations were also evaluated.

Results: We enrolled 1043 hospitalized patients, including 257 children <5 years of age (range 1 day–86 years). Seventy-four patients tested influenza virus positive (including 28 A(H1N1)pdm09). Sensitivity(95% CI) and specificity (95% CI) for influenza infection were 78% (67–87) and 60% (57–63) for ILI (measured/reported fever); 37% (26–49) and 78% (75–80) for SARI (measured/reported fever); 82% (72–90) and 57% (54–60) for FARI (measured/reported fever); 88% (78–94) and 45% (42–49) for ARI; and 74% (63–84) and 61% (58–64) for measured/reported fever plus cough. Case definitions including only measured fever had lower sensitivity.

Conclusion: ILI and FARI with measured/reported fever provided good balance between sensitivity and specificity among hospitalized patients. The simpler case definition of measured/reported fever plus cough is suited for field surveillance.

Keywords Case definitions, epidemiology, FARI, ILI, India, influenza, inpatients, SARI, surveillance, validity.

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Introduction

An increasing number of countries are conducting surveillance for influenza to better understand circulating viral types and subtypes, detect influenza outbreaks, and estimate influenza disease burden. Data from these surveillance systems are improving our understanding of worldwide influenza virus circulation. However, clinical case definitions used for the detection of influenza vary substantially, depending in part on surveillance objectives, and few have been systematically evaluated for their sensitivity and specificity.[1,2] Evaluation of clinical case definitions is especially critical for influenza disease burden estimates, which should be adjusted based on the known sensitivity and specificity of surveillance case definitions in use.

Several clinical case definitions have been used for influenza surveillance including influenza-like illness (ILI)[3], severe acute respiratory illness (SARI)[4], acute respiratory infection (ARI)[5], and febrile acute respiratory illness (FARI) (Table 1). Of these, only the ILI case definition[6–8] has been systematically evaluated, although the SARI case definition has been endorsed in the past for surveillance of severe influenza-associated illness and is frequently used for influenza virologic surveillance.[9] A recent WHO consultation has discussed the merits and demerits of these commonly used case definitions and has proposed changes such as inclusion of history of fever, removing sore throat, removing shortness of

Table 1. Summary of case definitions and included symptoms used for influenza surveillance

Case definition and its source	Fever	Cough	Sore throat	Difficulty breathing (history)	Nasal discharge/ runny nose	Earache	Rapid breathing (examination)
Influenza-Like Illness (ILI): Sudden onset of a fever over 38°C, and either cough or sore throat in the absence of other diagnoses : WHO [3]	Yes	Yes	Yes	No	No	No	No
Severe Acute Respiratory Illness (SARI) in ≥5 year age: Sudden onset of Fever over 38°C and either cough or sore throat, shortness of breath or difficulty breathing, and requiring hospital admission: PAHO[4]	Yes	Yes	Yes	Yes	No	No	No
Severe Acute Respiratory Illness (SARI) in <5 year age: Any child <5 years old clinically suspected of having Pneumonia or severe/very severe pneumonia, and requiring hospital admission: WHO – IMCI.[16]	No	Yes	No	Yes	No	No	Yes
Acute Respiratory Infection (ARI): ≥1 of the following: cough (new or worsened), sore throat, difficulty breathing or nasal discharge: ECDC[5]	No	Yes	Yes	Yes	Yes	No	No
Febrile Acute Respiratory Illness: Sudden onset of fever and one or more of cough, sore throat, difficulty breathing, runny nose, or ear ache	Yes	Yes	Yes	Yes	Yes	Yes	No
≥1 respiratory symptom: ≥1 of the following signs or symptoms: cough, earache, nasal discharge, difficulty breathing (history), rapid breathing (examination), and sore throat	No	Yes	Yes	Yes	Yes	Yes	Yes

breath, etc. while developing a new set of case definitions to be used for influenza surveillance.[10]

Early studies evaluating influenza case definitions were limited to non-hospitalized patients with fever or respiratory symptoms.[6–8,11] Recent studies have included all hospitalized adults with any acute illness but have only evaluated the performance of a limited number of clinical case definitions based on a combination of fever, cough, or sore throat.[12,13] Influenza-associated illness can also present with a range of symptoms, some of which might not be captured by commonly used clinical case definitions. As patients without obvious respiratory symptoms are not always tested for influenza, the true sensitivity and specificity of various constellations of signs and symptoms for influenza-associated illness is unknown. Therefore, using data from surveillance for hospitalizations of patients of any age for any recent-onset medical illness in a rural area of northern India, our objective was to evaluate a broad range of clinical signs and symptoms as predictors of influenza, and to estimate the sensitivity and specificity of several clinical case definitions that have been used for the detection of influenza.

Methods

Setting

The study was conducted in the Comprehensive Rural Health Services Project (CRHSP), located in Ballabgarh, approximately 40 km south of New Delhi. As of December 2009, the CRHSP include a rural Health and Demographic Surveillance Site (HDSS) comprising 28 villages with a total population of 88300 individuals. In the HDSS, two primary health centers provide primarily outpatient care and a secondary level facility provides outpatient and inpatient care (Civil Hospital Ballabgarh). In addition, the government-funded Employee State Insurance Hospital and the Badshah Khan District Hospital and a large number of private health facilities (ranging in size from 5 to 35 beds) also provide inpatient and outpatient health services. Most of these facilities have the resources to care for patients requiring supplemental oxygen but transfer patients requiring mechanical ventilation and intensive care to tertiary care facilities outside the Ballabgarh area. This study was conducted in the three mentioned government-funded hospitals and 30 private facilities in Ballabgarh and Faridabad towns where patients from CRHSP were likely to be hospitalized. Ongoing virologic surveillance have shown that influenza circulates throughout the year in the study area and peaks during the rainy season (July–September) and a winters (January–March) and average influenza virus isolation rates of 4·8% among samples collected from patients with influenza-like illness.[14] Further it was observed in 2009 that the influenza A(H1N1)pdm09 virus continued to circulate after August.[15]

Patient enrollment

Patients were eligible for enrollment if they were residents of a CRHSP village and were hospitalized overnight at a participating hospital. We prospectively enrolled inpatients (i.e., hospitalized patients) with any recent-onset medical illness or acute exacerbation of chronic illness during July 2009 through August 2011. Infants admitted with fever as the only complaint were also included. We excluded patients hospitalized because of trauma, diarrhea without fever, elective surgery, pure obstetrical or gynecological conditions, accidental poisonings, elective blood transfusions, or orthopedic or ophthalmological conditions as we assumed a priori that these conditions are unlikely to be associated with an influenza virus infection. For each enrolled inpatient, data on demographics, medical history, and clinical symptoms were obtained by interview of the patient or caregiver. Medical history was elicited specifically for presence of following symptoms within previous 7 days (from the day of interview) from all patients: fever(with duration), rash, cough, hemoptysis, sputum, difficulty breathing, nasal discharge, sore throat (patients >2 years age), earache/discharge, vomiting, diarrhea, seizures, loss of consciousness, jaundice. In addition, patients or caregivers of patients ≥5 years of age were asked about history of chills, headaches, muscle-aches, chest pain and confusion, and caregivers of patients <5 years of age were asked about history of lethargy and refusal to feed. Data on clinical signs were collected directly by trained study physicians as well as abstracted from the medical record using structured data collection forms. Clinical signs included body temperatures, pulse, respiratory rates, oxygen saturation, altered sensorium, cyanosis, dehydration, respiratory signs, hepatomegaly, splenomegaly, acute paresis and neck stiffness, and additionally among children <5 years of age, nasal flaring, chest indrawing and grunting. Age-specific cutoffs were used for defining tachypnea: respiratory rate of ≥60 breaths per minute (bpm) in children <2 months of age; ≥50 bpm in 2–12 months; ≥40 bpm in 1–4 years; ≥30 bpm among 5–13 years; and ≥20 bpm among >13 years of age.[16,17] Admitting diagnosis was noted from the case sheet. Combined nasal and oropharyngeal samples were collected from enrolled inpatients within 24 hours of admission to the hospital using polyester swabs. Only nasal swabs were collected from patients <1 year of age.

Specimen handling and laboratory methods

Both nasal and oropharyngeal swabs from each inpatient were placed in a single vial containing viral transport media, immediately stored at 4°C, and transported within 24 hours (48 hours on weekends) to the Virology Laboratory at the All India Institute for Medical Sciences, New Delhi, India, for processing and testing. Nasal swabs alone were collected from inpatients <1 year of age. Respiratory specimens were tested by real time reverse-transcriptase polymerase chain reaction (rRT-PCR) for influenza A(H3N2), influenza B and for the influenza A(H1N1)pdm09 viruses using the Centers for Disease Control and Prevention protocol. All seasonal influenza A positive samples not positive for A(H1N1)pdm09 were further subtyped using primers and probes for A/H1 and A/H3.[18] Samples positive by rRT-PCR were inoculated in Madin-Darby Canine Kidney (MDCK) cells for virus isolation followed by haemagglutination inhibition for virus identification and subtyping.[19] The clinical features of the patients were unknown to the laboratory personnel.

Sample size estimation

To detect a sensitivity of ≥50% and specificity of ≥50% with a precision of ±15% for any given clinical case definition, a sample size of 50 influenza virus-positive patients and 50 influenza virus-negative patients would be sufficient for each group of patients being evaluated.

Statistical analyses

Predictors of influenza virus infection were analyzed separately for hospitalized patients <5 years of age and those 5 years of age and older. Signs and symptoms were compared between patients with and without laboratory-confirmed influenza virus infection by bivariate analysis. Chi-square (or Fisher's exact test) and odds ratios (OR) were calculated for categorical variables. Stratified analysis was used to evaluate chronic underlying conditions as potential effect modifiers. For patients 5 years of age and older, signs and symptoms associated with laboratory-confirmed influenza at $P < 0{\cdot}1$ in bivariate models, patient age in years (as a continuous variable), and interaction terms for chronic lung disease were included in a logistic regression model to calculate adjusted odds ratios for the association with influenza virus detection. Because the number of patients <5 years of age was relatively small, a logistic regression model was not developed for this age group.

The sensitivity and specificity of commonly used case definitions and sign and symptom clusters identified as predictors of influenza in the multivariate analysis were calculated using two by two tables. Case definitions that included fever were evaluated using either only measured (>38°C) fever or measured or reported fever. Reported fever was defined as a self-report of fever by the patient or caregiver regardless of whether the body temperature was measured and noted. ''Sudden onset of symptoms'' and the ''absence of other known diagnoses'' were not included as part of case definitions. Data were entered and stored using MySQL (Version 5·5·11, Oracle Corporation, Santa Clara, CA, USA) and were analyzed using STATA (Release 9, StataCorp LP, College Station, TX, USA). A *P-value* of <0·05 was considered statistically significant. The 95% confidence

intervals (CI) for odds ratios, sensitivity, and specificity were calculated.

Ethics

Written informed consent was obtained from each study participant (or parent/legal guardian for persons <18 years) prior to enrollment. The study protocol was reviewed and approved by the Institutional Review Boards of the Indian Council of Medical Research, All India Institute of Medical Sciences and US Centers for Disease Control and Prevention.

Results

During July 2009–August 2011, a total of 1089 eligible inpatients were identified. Of these, 23 (2%) refused enrollment, 13 (1%) provided clinical histories without respiratory specimens, and 10 (1%) provided inadequate specimens. Among the 1043 inpatients who completed initial evaluation and provided adequate specimens, influenza viruses were detected in specimens from 74 (7%) inpatients. Of these 74 specimens, 28 (38%) were positive for A(H1N1)pdm09; 24 (32%) for influenza A(H3N2), and 22 (30%) for influenza B viruses. A similar proportion of inpatients with influenza virus-positive respiratory specimens had specimens collected <4 days from the time of symptom onset compared to inpatients with influenza virus-negative specimens (47% versus 41%, $P = 0{\cdot}21$). Of the 1043 inpatients, 257(25%) were <5 years of age, and 673 (65%) were male. (Table 2) The prevalence of smoking, pregnancy, and all underlying medical conditions except chronic lung disease was similar among influenza virus-positive and influenza virus-negative inpatients. We enrolled 135 infants (age ≤12 months) of whom 6(3%) tested positive for influenza viruses.

Table 2. Characteristics of enrolled hospitalized patients, Ballabgarh, India, July 2009–August 2011 (n = 1043)

Characteristics	Total	Influenza virus + (n = 74) n (%)	Influenza virus − (n = 969) n (%)	P
Age group				
0–4 years	257	18 (24)	239 (25)	0·54
5–17 years	120	12 (16)	108 (11)	
18–50 years	482	30 (41)	452 (47)	
≥50 years	184	14 (19)	170 (18)	
Sex				
Female	370	24 (32)	346 (36)	0·57
Male	673	50 (68)	623 (64)	
Time from symptom onset to specimen collection*				
0–2 days	160/892**	11/72 (15)	149/820 (18)	0·21
3–4 days	212/892	24/72 (33)	188/820 (23)	
5–7 days	249/892	20/72 (28)	229/820 (28)	
8+ days	271/892	17/72 (24)	254/820 (31)	
Underlying conditions				
Asthma	26	0 (0)	26 (3)	0·15
Chronic lung disease (excluding asthma)	34	6 (8)	28 (3)	0·01
Cardiovascular disease	78	6 (8)	72 (7)	0·83
Diabetes	31	1 (1)	30 (3)	0·39
Tuberculosis	18	2 (3)	16 (2)	0·50
Neurologic condition	11	0 (0)	11 (1)	0·36
Smoking among ≥15 year old	208/696	12/47 (26)	196/649 (30)	0·50
Pregnancy among ≥15 year old females	8/272	1/19 (5)	7/253 (3)	0·54

*Time from symptom onset information was collected separately for respiratory symptoms and fever and represents the duration of symptoms with earlier onset.
**Missing information in the rest.

Clinical Predictors of Influenza virus detection

Body temperatures were measured as axillary temperatures in 1031 (99%) patients, oral temperatures in 7 (0·7%) of patients, and rectal temperatures in 5 (0·5%) of patients. Among the 257 inpatients <5 years of age, 18 (7%) had specimens positive for influenza viruses (Table 3). No sign or symptom was significantly associated with influenza virus detection in this age group. Among the 786 inpatients 5 years of age and older, 56 (7%) had specimens positive for influenza viruses (Table 4). The presence of reported fever, measured fever, chills, cough, sore throat, nasal discharge, muscle-aches and wheeze (upon examination) was significantly associated with influenza virus detection among inpatients of 5 years of age and older. The strength of association between cough and influenza virus detection was lower (OR, 1·4; CI, 0·1, 75·1) among inpatients with chronic lung disease than among inpatients without chronic lung disease (OR, 4·6; CI, 2·3, 9·7) and so in the multivariate logistic model, an interaction term for cough and chronic lung disease was included. After controlling for age, measured fever (adjusted OR, 2·5; CI, 1·3, 4·9), and cough (adjusted OR, 3·1; CI 1·5, 6·7) were significant predictors of influenza virus positivity among inpatients ≥5 years of age.

Sensitivity and specificity of clinical case definitions for influenza

One infant with influenza virus infection had a measured fever >38°C. Measured or reported fever was 83% sensitive (CI, 36–100) and 22% specific (CI, 15–30) for detection of influenza viruses in this age group. Among the case defini-

Table 3. Clinical signs and symptoms associated with laboratory-confirmed influenza in hospitalized inpatients <5 years of age, Ballabgarh, India, July 2009—August 2011(n = 257)

	No. (%) of patients		
	Influenza virus + (n = 18) n (%)	Influenza virus – (n = 239) n (%)	Crude odds ratio OR (95%CI)
Symptoms			
Fever (reported)	17 (94)	207 (79)	4·6 (0·4, 196·4)
Cough	15 (83)	143 (60)	3·4 (0·9, 18·5)
Sore throat*	0/6	3/55 (6)	–
Nasal discharge	8 (44)	65 (27)	2·1 (0.7, 6·3)
Ear pain/discharge	0 (0)	12 (5)	0
Fast breathing	7 (39)	91 (38)	1·0 (0·3–3.0)
Vomiting	10 (56)	143 (60)	0·8 (0·3, 2·5)
Diarrhea	8 (44)	133 (56)	0·6 (0·2, 1·9)
Seizures	2 (11)	9 (4)	3·2 (0·3, 17·3)
Jaundice	0 (0)	6 (3)	0
Inability/refusal to feed	5 (28)	69 (29)	1.0 (0·3, 3.0)
Lethargy	3 (17)	33 (14)	1·2 (0·2, 4·8)
Signs			
Fever (>38·0 °C)	3 (17)	40 (17)	1.0 (0·2, 3·8)
Hypoxia**	4/17 (24)	37/235 (16)	1·6 (0·4, 5·7)
Tachypnea†	4 (22)	41 (17)	1·4 (0·3, 4·7)
Stridor	0 (0)	17 (7)	0
Crepitations/ crackles	6 (33)	54 (23)	1·7 (0·5, 5·2)
Wheezing	3 (17)	45 (19)	0·9 (0·2, 3·2)
Nasal flaring, grunting, or chest indrawing	2 (11)	25 (11)	1·1 (0·1, 5·0)

*Sore throat assessed only among 2 to 5-year-old inpatients.
**Defined as oxygen saturation <90% on room air or <95% on oxygen therapy.
†Defined as a respiratory rate of ≥60 breaths per minute in children <2 months of age, ≥50 breaths per minute in children two through 12 months of age, and ≥40 breaths per minute in children 1 through 4 years of age.

tions for influenza virus infection that were evaluated, presence of ≥1 respiratory symptom had the highest sensitivity (95%, CI, 87–99%) but the poorest specificity (13%; CI, 11,15%) (Table 5). Of the 130 patients without any respiratory symptoms, 4 (3%) had specimens positive for influenza viruses: two patients with fever and body aches, one with fever, diarrhea and vomiting, and one with abdominal pains. The conventional ILI and SARI case definitions had sensitivity of 45% and 28% respectively and specificity of 85% and 84%, respectively. Modified definitions that included reported fever had relatively higher sensitivities and lower specificities. While the ILI case definition with measured or reported fever (sensitivity 78%, specificity 60%) and the FARI case definition with measured or reported fever (sensitivity 82%, specificity 57%) provided a balance between sensitivity and specificity for influenza virus infection, the more parsimonious combination of measured or reported fever and cough performed similarly (sensitivity 74% and specificity 61%). All case definitions had high negative predictive values (over 90%) while having relatively poor positive predictive values (under 20%). When comparing across age groups, definitions that include reported fever (FARI, ILI, fever with cough, fever with cough or nasal discharge) and ARI had comparable sensitivity among children under 5 years age (78–83%) and those 5-years and older (73–82%). The sensitivity of the same case definitions when including measure fever only, were lower among children under-5 years of age (17%) as compared to inpatients 5 year and older (48–54%). (For details, please view the online supplementary table)

Discussion

Using broad enrollment criteria that included all acute illnesses that might be associated with influenza virus infection, we evaluated the sensitivity and specificity of four commonly used case definitions (ILI, ARI, FARI, SARI) and additional combinations of symptoms and signs for the detection of laboratory-confirmed influenza virus infections among rural inpatients. We found that the modified ILI and FARI case definitions that included either measured or reported fever provided the best balance between sensitivity and specificity of all the evaluated case definitions, but the more parsimonious case definition of measured or reported fever and cough performed similarly. Limiting case definitions to include only measured fever substantially decreased their sensitivity, especially among infants (age ≤12 months). We were unable to identify any individual symptom or sign as a significant predictor of influenza virus infection among inpatients <5 years of age. However, among inpatients 5 years of age and older, measured fever, cough, and nasal discharge were associated with influenza virus infection.

Prior studies from the United States, Canada, and the Netherlands have evaluated a limited number of case definitions for influenza virus infection among hospitalized adults but have varied in their enrollment criteria.[12,13,20] Among inpatients with measured fever and at least two other respiratory symptoms, cough and measured fever was 87% sensitive and 39% specific to influenza virus infection,[20] whereas among all adults hospitalized in certain clinical wards, documented fever and cough were only 35–43% sensitive and 86% specific.[12,13] We observed that ILI with measured fever was 45% sensitive and 85% specific, which is consistent with studies that had broad enrollment criteria. The sensitivity of the ILI case definition improved

Table 4. Clinical signs and symptoms associated with laboratory-confirmed influenza in hospitalized patients 5 years of age and older, Ballabgarh, India, July 2009–August 2011 (*n* = 786)

	No. (%) of patients		Crude odds ratio	Adjusted odds ratio
	Influenza virus + (*n* = 56) *n* (%)	Influenza virus − (*n* = 730) *n* (%)	OR (95%CI)	OR (95%CI)†
Symptoms				
Fever (reported)	50 (89)	518 (71)	3·4 (1·4, 9·9)	1·3 (0·5, 3·6)
Chills/rigors	27 (48)	224 (31)	2·1 (1·2, 3·8)	1·1 (0·6, 2·1)
Cough	43 (77)	314 (43)	4·4 (2·3, 9·0)	3·1 (1·5, 6·7)
Sore throat	18 (32)	97 (13)	3·1 (1·6, 5·8)	1·5 (0·7, 3·1)
Nasal discharge	15 (27)	73 (10)	3·3 (1·6, 6·4)	1·5 (0·7, 3·4)
Ear pain/discharge	2 (4)	15 (2)	1·8 (0·2, 7·9)	–
Fast breathing	19 (34)	153 (21)	1·9 (1·0, 3·6)	1·2 (0·5, 2·6)
Headache	34 (61)	371 (51)	1·5 (0·8, 2·7)	–
Muscle-aches	35 (63)	320 (44)	2·1 (1·2, 3·9)	1·5 (0·8, 3·0)
Chest pain	10 (18)	177 (24)	0·7 (0·3, 1·4)	–
Vomiting	19 (34)	340 (47)	0·6 (0·3, 1·1)	0·8 (0·4, 1·4)
Diarrhea	7 (13)	143 (20)	0·6 (0·2, 1·3)	–
Seizures	1 (2)	9 (1)	1·5 (0, 10·8)	1·8 (0·2, 16·9)
Confusion	0 (0)	18 (3)	–	–
Jaundice	0 (0)	12 (2)	–	–
Signs				
Fever (>38·0°C)	32 (57)	251 (34)	2·5 (1·4, 4·6)	2·5 (1·3, 4·9)
Hypoxia*	2/51 (4)	28 (4)	1·0 (0·1, 4·2)	0·7 (0·1, 3·7)
Tachypnea**	46 (82)	628 (86)	0·7 (0·4, 1·7)	–
Stridor	0 (0)	8 (1)	–	–
Crepitations/crackles	9 (16)	93 (13)	1·3 (0·5, 2·8)	–
Wheezing	11 (20)	71 (10)	2·3 (1·0, 4·7)	1·5 (0·6, 3·5)

*Defined as oxygen saturation <90% on room air or <95% on oxygen therapy.
**Defined as a respiratory rate of ≥30 breaths per minute in patients five through 12 years of age, and ≥20 breaths per minute in respondents 13 years and older.
†Adjusted for patient age (in years), chronic lung disease (excluding asthma) and interaction of chronic lung disease (excluding asthma) with cough. The odds ratio for independent effects of chronic lung disease (excl. asthma) was 10·9 (1·0, 116·8) and for the interaction term of cough with chronic lung disease (excl. asthma) was 0·3 (0·0, 3·3).

substantially (accompanied by a fall in specificity) if it included reported fever. To our knowledge, no previously published study has evaluated influenza clinical case definitions that include reported fever.

Clinical case definitions for influenza virus infections have been designed to meet different goals such as to identify circulating influenza strains, facilitate diagnosis and treatment, monitor seasonal trends and identify outbreaks, and quantify influenza-associated disease burden.[2,8,21,22] The relative importance of the sensitivity and specificity of case definitions varies according to which of these goals is of highest priority. Case definitions that maximize specificity may be most efficient for obtaining influenza virus-positive specimens to identify circulating influenza strains while minimizing unnecessary testing, whereas for diagnosis and treatment and to identify outbreaks, case definitions that provide a balance between sensitivity and specificity are preferred. Similarly, for studies quantifying influenza-associated disease burden, both sensitivity and specificity of case definitions need to be high. Given the relative importance of clinical case definition attributes for each of these goals, our findings suggest that the ILI and FARI case definitions including only measured fever are suitable for virologic surveillance in hospitalized patients. The same case definitions (ILI, FARI) modified to include reported fever are suited for diagnosis and treatment decisions among hospitalized patients, and identifying influenza outbreaks. For surveillance systems where the ILI and FARI clinical case definitions may be too cumbersome for surveillance staff, the simpler combination of measured or reported fever with cough may provide adequate sensitivity and specificity. A systematic review of twelve studies that evaluated clinical decision rules for the diagnosis of influenza similarly concluded that fever and cough, and fever, cough, and a history of acute onset of symptoms have modest accuracy.[21] Studies designed to estimate the burden of hospitalized influenza should consider that use of any of these clinical case definitions will result in an underestimate of

Table 5. Sensitivity, specificity and predictive values of different case definitions for detection of influenza among hospitalized patients of all ages, Ballabgarh, India, July 2009–August 2011

	No. (%) of patients						
	All patients (*n* = 1043)	Influenza virus + (*n* = 74)	Influenza virus – (*n* = 969)	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive predictive value % (95% CI)	Negative predictive value % (95% CI)
≥1 respiratory symptom	913 (88)	70	843	95 (87, 99)	13 (11, 15)	7 (6, 7)	97 (92, 99)
Acute respiratory infection	594 (57)	65	529	88 (78, 94)	45 (42, 49)	11 (8, 14)	98 (96, 99)
Influenza-like illness	180 (17)	33	147	45 (33, 57)	85 (82, 87)	18 (13, 25)	95 (94, 97)
Severe acute respiratory illness*	179 (17)	21	158	28 (19, 40)	84 (81, 86)	12 (7, 17)	94 (92, 95)
Febrile acute respiratory illness	185 (18)	33	152	45 (33,57)	84 (82, 87)	18 (13, 24)	95 (94, 96)
Additional Case Definitions that include reported fever and case definitions based on symptom complexes							
Influenza-like illness: measured or reported fever	448 (43)	58	390	78 (67, 87)	60 (57, 63)	13 (10, 16)	97 (96, 99)
Severe acute respiratory illness: measured or reported fever*	243 (23)	27	216	37 (26, 49)	78 (75, 80)	11 (8, 16)	94 (92, 96)
Febrile acute respiratory illness: measured or reported fever	478 (46)	61	417	82 (72, 90)	57 (54, 60)	13 (10, 16)	98 (96, 99)
Measured fever plus cough	169 (16)	30	139	41 (29, 53)	86 (83, 88)	18 (12, 24)	95 (93, 96)
Measured or reported fever plus cough	430 (41)	55	375	74 (63, 84)	61 (58, 64)	13 (10, 16)	97 (95,98)
Measured fever plus either cough or nasal discharge	173 (17)	30	143	41 (29, 53)	85 (83, 87)	17 (12, 24)	95 (93, 93)
Measured or reported fever plus either cough or nasal discharge	446 (43)	57	389	77 (66, 86)	60 (57, 63)	13 (10, 16)	97 (96, 98)

*Age-specific definitions as noted in Table 1 were used. The requirement of fever (measured or measured/reported) was included only for persons 5 years of age and older.

influenza hospitalizations as even the ILI and FARI definitions miss up to one-fifth of patients hospitalized with influenza.

Our study was subject to several limitations. First, the definitions for ILI and SARI used in our analysis did not require ''absence of another diagnosis,'' which is frequently included in these case definitions as specific diagnoses were not available at the time of admission for the majority inpatients enrolled in our study. Second, we enrolled a relatively small number of children younger than 5 years of age which limited our ability to identify symptoms and signs that might be significantly associated with influenza virus infection and to evaluate clinical case definitions separately in this age group. The clinical presentation of influenza varies across age groups, and additional studies are needed to evaluate clinical case definitions for the detection of influenza in young children and to comprehensively assess the performance of case definitions across a wider range of age groups. Third, the prevalence of lung disease and asthma was relatively low in our inpatient population, so we were unable to evaluate case definitions separately in this group. A study conducted in the United States in which 13% of enrolled hospitalized patients had asthma, documented differences in case definition performance in patients with asthma compared to other hospitalized patients.[12] Fourth, our study includes a substantial number of inpatients who had respiratory specimens collected five or more days after symptom onset and rates of detection of influenza virus from respiratory specimens decrease as the time from symptom onset to collection increases.[23] The distribution of time from symptom onset to specimen collection was similar among influenza virus-positive and influenza virus-negative inpatients, making it unlikely that this would have influenced our findings. The mean gap (days) between symptom onset and swab collection was also similar among inpatients with only reported fever (2·2 ± 0·1), only measured fever (2·3 ± 0·81), both reported and measured fever (2·1 ± 0·1) and no fever (2·2 ± 0·21). Lastly, we assumed that influenza virus detection in patients' upper respiratory specimens was an influenza virus infection associated with that hospitalization..

On the basis of the prospectively collected data over a 2 year period from hospitalized rural patients, we documented that measured fever, nasal discharge, and cough were associated with rRT-PCR confirmed influenza virus infection among persons ≥5 years of age. Among the commonly used clinical case definitions for influenza surveillance, the modified FARI and ILI case definitions that include both reported

and/or measured fever provide a good balance between sensitivity and specificity for influenza virus infection, although the more parsimonious combination of measured or reported fever and cough also performs well Department of Communicable Disease Surveillance and Response. WHO recommended surveillance standards, 2nd edition. [Internet] Geneva (CH): World Health Organization. 126 p. Available at: http://www.who.int/entity/csr/resources/publications/surveillance/whocdscsrisr992.pdf (Accessed 25 June 2012). Our findings support the recent WHO review of case definitions used for influenza surveillance and contribute evidence to inform these discussions.[10]

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention, USA.

Addendum

SB, SKR, ACM, JAM, MAW, RBL, and AK were involved in protocol development of the study. SB, RW, and VG were involved in data collection from patients and laboratory testing. VG, FSD, KL, and RW conducted statistical analysis. FD, KL, and VG did literature search. All authors were involved in manuscript drafting, reviewing, and finalization.

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References

1 Aguilera JF, Paget WJ, Mosnier A *et al.* Heterogeneous case definitions used for the surveillance of influenza in Europe. Eur J Epidemiol 2003; 18:751–754.
2 Nichol KL. Heterogeneity of influenza case definitions and implications for interpreting and comparing study results. Vaccine 2006; 24:6726–6728.
3 Department of Communicable Disease Surveillance and Response. WHO recommended surveillance standards, 2nd edition [Internet] Geneva (CH): World Health Organization; 126 p. Available at: http://www.who.int/entity/csr/resources/publications/surveillance/whocdscsrisr992.pdf (Accessed 25 June 2012).
4 PAHO Health Surveillance and Disease Management Area, Communicable Disease Unit, Viral Disease Team. PAHO-CDC generic protocol for influenza surveillance (Draft). [Internet]. Washington DC (WA): PAHO, 2006; 43p. Available at http://www.paho.org/English/AD/DPC/CD/flu-snl-gpis.pdf (Accessed 25 June 2012).
5 ECDC [Internet]. Solna, (SE): European Centre for Disease Prevention and Control (ECDC); c2005–2012. Influenza case definitions. Available at http://ecdc.europa.eu/en/activities/surveillance/EISN/surveillance/Pages/influenza_case_definitions.aspx (Accessed 25 June 2012).
6 Smit PM, Limper M, van Gorp ECM *et al.* Adult outpatient experience of the 2009 H1N1 pandemic: clinical course, pathogens, and evaluation of case definitions. J Infect 2011; 62:371–378.
7 Monto AS, Gravenstein S, Elliott M, Colopy M, Schweinle J. Clinical signs and symptoms predicting influenza infection. Arch Intern Med 2000; 160:3243–3247.
8 Thursky K, Cordova SP, Smith D, Kelly H. Working towards a simple case definition for influenza surveillance. J Clin Virol 2003; 27: 170–179.
9 Ortiz JR, Sotomayor V, Uez OC *et al.* Strategy to enhance influenza surveillance worldwide. Emerg Infect Dis 2009; 15:1271–1278.
10 WHO global technical consultation: global standards and tools for influenza surveillance. [Internet] Geneva (CH): World Health Organization, 2011; 38p. Available at http://whqlibdoc.who.int/hq/2011/WHO_HSE_GIP_2011.1_eng.pdf (Accessed 25 June 2012).
11 Carrat F, Tachet A, Rouzioux C, Housset B, Valleron A-J. Evaluation of clinical case definitions of influenza: detailed investigation of patients during the 1995–1996 epidemic in France. Clin Infect Dis 1999; 28:283–290.
12 Babcock HM, Merz LR, Dubberke ER, Fraser VJ. Case-control study of clinical features of influenza in hospitalized patients. Infect Control Hosp Epidemiol 2008; 29:921–926.
13 van den Dool C, Hak E, Wallinga J, van Loon AM, Lammers JWJ, Bonten MJM. Symptoms of influenza virus infection in hospitalized patients. Infect Control Hosp Epidemiol 2008; 29:314–319.
14 Chadha MS, Broor S, Gunasekaran P *et al.* Multisite virological influenza surveillance in India: 2004-2008. Influenza Other Respi Viruses 2012; 6:196–203.
15 Broor S, Krishnan A, Roy DS *et al.* Dynamic patterns of circulating seasonal and pandemic A(H1N1)pdm09 influenza viruses from 2007 to 2010 in and around Delhi, India. PLoS ONE 2012; 7:e29129.
16 World Health Organization, UNICEF. Integrated Management of Childhood Illness chart booklet [Internet]. Geneva (CH): World Health Organization, 2008; 42p. Available at http://whqlibdoc.who.int/publications/2008/9789241597289_eng.pdf (Accessed 25 June 2012).
17 World Health Organization. Integrated Management of Adolescent and Adult Illness: Guidelines for first-Level facility health workers at health centre and district outpatient clinic: acute care. 3rd ed. [Internet]. Geneva, (CH): World Health Organization, 2009; 136p. Available at http://www.who.int/hiv/pub/imai/acute_care.pdf (Accessed 25 June 2012).
18 WHO Collaborating Centre for Influenza at at CDC Atlanta, (US). CDC protocol of realtime RTPCR for influenza A(H1N1) [Internet]. Geneva, (CH): World Health Organization, 2009; 7p. Available at http://www.who.int/csr/resources/publications/swineflu/CDCRealtimeRTPCR_SwineH1Assay-2009_20090430.pdf (Accessed 25 June 2012).
19 Broor S, Gupta S, Mohapatra S *et al.* Emergence of 2009A/H1N1 cases in a tertiary care hospital in New Delhi, India. Influenza Other Respi Viruses 2011; 5:e552–e557.
20 Boivin G, Hardy I, Tellier G, Maziade J. Predicting influenza infections during epidemics with use of a clinical case definition. Clin Infect Dis 2000; 31:1166–1169.

21 Ebell MH, Afonso A. A systematic review of clinical decision rules for the diagnosis of influenza. Ann Fam Med 2011; 9:69–77.
22 Leitmeyer K, Buchholz U, Kramer M, Schweiger B. Enhancing the predictive value of throat swabs in virological influenza surveillance. Euro Surveill 2002; 7:180–183.
23 Carrat F, Vergu E, Ferguson NM *et al.* Time lines of infection and disease in human influenza: a review of volunteer challenge studies. Am J Epidemiol 2008; 167:775–785.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Sensitivity and specificity (with 95% Confidence Intervals) of different case definitions for detection of influenza among under-5 year and older hospitalized patients, Ballabgarh, India, July 2009—August 2011.