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What are the most sensitive and specific sign and symptom combinations for influenza in patients hospitalized with acute respiratory illness? Results from western Kenya, January 2007–July 2010

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SUMMARY

Influenza causes severe illness and deaths, and global surveillance systems use different clinical case definitions to identify patients for diagnostic testing. We used data collected during January 2007–July 2010 at hospital-based influenza surveillance sites in western Kenya to calculate sensitivity, specificity, positive predictive value, and negative predictive value for eight clinical sign/symptom combinations in hospitalized patients with acute respiratory illnesses, including severe acute respiratory illness (SARI) (persons aged 2–59 months: cough or difficulty breathing with an elevated respiratory rate or a danger sign; persons aged ⩾5 years: temperature ⩾38 °C, difficulty breathing, and cough or sore throat) and influenza-like illness (ILI) (all ages: temperature ⩾38 °C and cough or sore throat). Overall, 4800 persons aged ⩾2 months were tested for influenza; 416 (9%) had laboratory-confirmed influenza infections. The symptom combination of cough with fever (subjective or measured ⩾38 °C) had high sensitivity [87·0%, 95% confidence interval (CI) 83·3–88·9], and ILI had high specificity (70·0%, 95% CI 68·6–71·3). The case definition combining cough and any fever is a simple, sensitive case definition for influenza in hospitalized persons of all age groups, whereas the ILI case definition is the most specific. The SARI case definition did not maximize sensitivity or specificity.

Key words: Influenza, predictive value of tests, respiratory infections, sensitivity and specificity, surveillance.

INTRODUCTION

Seasonal influenza virus infections cause 1–2 million cases of severe illness and approximately 28 000–111 500 deaths worldwide annually in children aged <5 years [1]. Although influenza epidemiology is well-established in temperate, high- or moderate-income countries, it is less well-characterized in tropic, low-income countries, where the burden of seasonal and pandemic influenza might be greatest [2]. Because of pandemic preparedness measures prompted by concern regarding avian influenza (H5N1), diagnostic

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capacity for influenza viruses has increased substantially in Africa and other low-income countries during recent years, allowing for improved surveillance.

Surveillance objectives vary; some influenza surveillance systems focus on estimating disease burden, and thus aim to maximize sensitivity. In other surveillance systems with more limited resources, the aim is to monitor influenza activity and collect influenza virus isolates without concern for identifying all influenza cases; in this context, a more specific clinical definition allows testing of patients most likely to have positive tests.

A proposed strategy to enhance and standardize influenza surveillance worldwide uses a severe acute respiratory illness (SARI) case definition for inpatients and the World Health Organization's (WHO) influenza-like illness (ILI) case definition for outpatients as a feasible way to monitor influenza activity in resource-limited settings [3]. The SARI case definition has been adopted by the Pan American Health Organization and the WHO European Region [4, 5] and is comprised of the case definitions for pneumonia and severe pneumonia described in the WHO Integrated Management for Childhood Illness (IMCI) guidelines for children aged 2–59 months [6] and a slightly modified WHO ILI case definition for persons aged $\geqslant 5$ years, both with an additional hospitalization requirement; however, neither of these case definitions have been fully evaluated for influenza surveillance in resource-limited settings.

There were four objectives of this study: (1) to evaluate the SARI and ILI case definitions as influenza surveillance tools in patients hospitalized with acute respiratory illnesses (ARI); (2) to identify a maximally sensitive combination of signs and symptoms in patients hospitalized with ARI; (3) to identify a maximally specific combination of signs and symptoms in patients hospitalized with ARI; and (4) to determine if testing for influenza viruses for up to 14 days after symptom onset is worthwhile.

MATERIALS AND METHODS

Surveillance sites and population

We used data from hospital-based surveillance sites located in Bondo and Siaya districts in rural western Kenya (Nyanza Province), bordering Lake Victoria. All inpatient facilities in Bondo District conducted surveillance for influenza as part of a population-based study of hospitalized influenza-associated respiratory illness, and nearby Siaya District Hospital has been part of the national sentinel surveillance system for influenza. In 1999, Bondo and Siaya districts had populations of 238 780 and 480 184 persons, respectively [7]. The population is primarily low-income and subsists on agriculture [8]. Malaria is holoendemic and human immunodeficiency virus (HIV) prevalence is 14·9 % [9].

Surveillance design

Surveillance for ARI was conducted at six Bondo District inpatient hospitals during January 2007–June 2009, one Bondo District inpatient hospital during January 2007–June 2010, and one Siaya District inpatient hospital during August 2009–June 2010. The facilities included government and non-government hospitals. Trained surveillance officers, primarily nurses, collected demographic and clinical information from patients using structured questionnaires. Data were entered on scannable forms (Cardiff Teleforms®, Cardiff Software Inc., USA).

Case definitions

An ARI was defined as onset of at least one of the following symptoms during the previous 14 days: cough, difficulty breathing, sore throat, or chest pain. The eight sign/symptom combinations evaluated were: (1) a recently proposed SARI case definition [3]; (2) the WHO's recommended case definition for ILI [10] (Table 1); (3) cough; (4) cough and measured fever $\geqslant 38\ ^{\circ}C$; (5) cough and any fever (reported or measured $\geqslant 38\ ^{\circ}C$); (6) cough or difficulty breathing; (7) cough or difficulty breathing and measured fever $\geqslant 38\ ^{\circ}C$; and (8) cough or difficulty breathing and any fever. All measured temperatures were axillary, and, when relevant, oxygen saturation levels were measured using fingertip pulse oximetry (Nonin Medical, USA).

Specimen collection and laboratory testing

All patients hospitalized for an ARI were eligible for influenza testing and had both nasopharyngeal (NP) and oropharyngeal (OP) specimens collected for influenza testing on the day of admission or the Monday following admission, if still hospitalized, when admission occurred on Saturday or Sunday. These testing eligibility criteria were broader than all of the cases definitions evaluated. NP and OP specimens

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Table 1. *World Health Organization influenza-like illness (ILI) and severe acute respiratory illness (SARI) case definitions, by age group*

	Case definition	
Age group	SARI	ILI
2–59 months	Cough or difficulty breathing *and at least one of the following*: Unable to drink or breastfeed Vomiting everything consumed Convulsions Lethargic or unconscious Chest indrawing or stridor in a calm child Elevated respiratory rate† *and* Hospitalization	Cough or sore throat* *and* Fever $\geqslant 38\ ^{\circ}C$
$\geqslant 5$ years	Cough or sore throat *and* Fever $\geqslant 38\ ^{\circ}C$ *and* Shortness of breath or difficulty breathing *and* Hospitalization	Cough or sore throat *and* Fever $\geqslant 38\ ^{\circ}C$

* Sore throat was not collected for 68% of children aged 2–59 months, but was collected for all adults.

† Elevated respiratory rate is defined as >50 breaths/minute for children aged 2–11 months and >40 breaths/minute for children aged 12–59 months [7].

were collected by trained nurses. The specimens were put into the same tube and transported (at 2–8 °C) the same day to the laboratory. Each specimen was divided into four aliquots and stored at $-70\ ^{\circ}C$ $\leqslant 8$ h after collection. Specimens that could not be transported the same day were immediately stored in liquid nitrogen tanks at $-70\ ^{\circ}C$ and divided into aliquots at the time of testing. Real-time reverse-transcriptase–polymerase chain reaction (RT–PCR) for influenza A(H3N2), seasonal A(H1N1), and B viruses was performed at the Kenya Medical Research Institute/Centers for Disease Control and Prevention laboratory in Nairobi throughout the study period. Testing for pandemic A(H1N1) (pH1N1) began in May 2009. Cycle threshold (C_T) values were used to determine sample positivity. Specimens giving C_T values $\leqslant 39{\cdot}9$ were considered positive for influenza virus, whereas those with C_T values $>39{\cdot}9$ or demonstrating no reading were considered negative [11].

Data analysis

Comparisons between patients tested and untested for influenza among those eligible were made using χ^2 tests for categorical variables and Student's t tests for continuous variables. Measures of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and 95% confidence intervals (95% CI) were calculated for the SARI and ILI case definitions and six other sign/symptom combinations against laboratory-confirmed influenza infection. χ^2 tests were performed to compare sensitivities and specificities. The SARI and ILI case definitions were analysed as met or unmet, and the other sign/symptom combinations were analysed as present or absent. Data were analysed throughout the entire surveillance period (January 2007–June 2010) and were also restricted to months when $\geqslant 10\%$ of specimens tested positive for influenza viruses.

Additionally, to determine if differences existed in the sensitivity, specificity, PPV, and NPV of the case definitions during periods when only seasonal influenza was circulating, compared to periods when pH1N1 was circulating, the surveillance period was divided into two periods: (1) pre-pandemic, which consisted of the period before isolation of the first pH1N1 virus in Kenya (January 2007–June 2009), and (2) pandemic, which consisted of the months after

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the first isolation of pH1N1 in which ⩾50% of the subtyped influenza A viruses were pH1N1 (October 2009–February 2010, April 2010, July 2010). Months in which pH1N1 was circulating but was not the predominant influenza A subtype were excluded from this part of the analysis (July 2009–September 2009, March 2010, May 2010–June 2010). We also calculated the sensitivity, specificity, PPV, and NPV of the case definitions and sign/symptom combinations stratified by malaria smear status (positive or negative) to assess the impact malaria might have on our estimates.

Cumulative sensitivity of each case definition was also calculated for different symptom durations (days 1–14 after symptom onset). Symptom duration was defined as the number of days from the earliest onset of cough, fever, or diarrhoea to specimen collection. All analyses were performed by using SAS version 9.2 (SAS Institute Inc., USA).

Ethical considerations

Surveillance for influenza at all eight sites was approved by the Kenya Medical Research Institute (KEMRI) Ethical Review Committee and Scientific Steering Committee (SSC) and the Centers for Disease Control and Prevention's Institutional Review Board (CDC IRB) (KEMRI SSC No. 1147 and CDC IRB No. 3308.0 for the six Bondo District hospitals; KEMRI SSC No. 1899 and CDC IRB No. 4566 for Lwak Mission Hospital; and KEMRI SSC No. 1801 and CDC IRB No. 3308 for Siaya District Hospital). Written informed consent was obtained from all participants, parents, or legally authorized representatives.

RESULTS

A total of 7857 persons aged ⩾2 months were hospitalized with an ARI characterized by cough, difficulty breathing, sore throat, or chest pain at the eight surveillance sites during the study period; 4800 (61%) had influenza laboratory results available, and 416 (9%) had laboratory-confirmed influenza infections. Of the 3057 patients without laboratory results available, 211 (7%) refused testing; 61 (2%) had indeterminate results; 16 (1%) had missing results; and 2769 (90%) did not have specimens collected. Patients admitted on Saturday and Sunday, days when swabs were not collected, comprised 606 (21%) of those untested, compared to 18% of those tested ($P<0{\cdot}01$). No additional information indicative of why these patients were untested was available for the remainder of patients, who were only captured by the clinical component of the surveillance system. Two-thirds of those tested for influenza were aged 2–59 months, and approximately equal numbers of males and females were included. About one-third of the influenza specimens were collected at Siaya District Hospital (Table 2). Age and sex distributions were similar between those tested and untested for influenza (Table 3). Three percent of persons tested for influenza died from their illness, compared to 5% of those who were untested ($P<0{\cdot}01$). Of those tested for influenza who had oxygen saturation level data available ($n=4222$), 11% had oxygen saturation levels <90%, compared to 6% of those untested ($n=2583$) ($P<0{\cdot}01$).

Sensitivity was >80% overall and in both age groups for 4/8 case definitions and sign/symptom combinations investigated (Table 4). Cough or difficulty breathing had the highest sensitivity overall for laboratory-confirmed influenza infection (99·8%), followed by cough alone (94·7%), cough or difficulty breathing and any fever (subjective or measured ⩾38 °C) (91·3%), and cough and any fever (87·0%) ($P<0{\cdot}01$ for all comparisons except between cough alone and cough or difficulty breathing and any fever, $P=0{\cdot}06$). While the SARI case definition had 71·1% sensitivity for laboratory-confirmed influenza infection in children aged 2–59 months, it was only 13·2% in hospitalized persons aged ⩾5 years. PPV was low for all sign/symptom combinations evaluated over all ages, ranging from 6·6% for SARI to 9·0% for cough alone, and cough and any fever. ILI, cough and measured fever ⩾38 °C, and cough or difficulty breathing and measured fever ⩾38 °C had the lowest sensitivities, 26·9%, 26·7%, and 28·6%, respectively ($P>0{\cdot}05$ for all comparisons); however, they also had the highest specificities for laboratory-confirmed influenza infection, 70·0%, 70·4%, and 68·1%, respectively ($P>0{\cdot}05$ for all comparisons). The SARI case definition also had a high specificity in the ⩾5 years age group (85·5%) but not in children aged 2–59 months (21·4%). Specificity and PPV for laboratory-confirmed influenza were approximately 5–10% lower in malaria smear-positive patients compared to malaria smear-negative patients for the case definitions and sign/symptom combinations that included subjective or measured fever.

When the analysis period was restricted to months when ⩾10% of specimens were positive for influenza,

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Table 2. *Demographic characteristics of hospitalized patients tested for influenza infections, western Kenya, January 2007–July 2010*

Patient characteristic	Total tested, *N* (%)	Influenza negative, total (%)	Influenza positive			
			Total (%)	A (%)	B (%)	A and B (%)
Age						
2–59 months	3116 (65)	2905 (93)	211 (7)	180 (6)	30 (1)	1 (0)
⩾5 years	1684 (35)	1479 (88)	205 (12)	159 (9)	43 (3)	3 (0)
Sex						
Male	2341 (49)	2151 (92)	190 (8)	157 (7)	31 (1)	2 (0)
Female	2458 (51)	2233 (91)	225 (9)	181 (7)	42 (2)	2 (0)
Unknown	1 (0)	1 (100)	1 (100)	1 (100)	0 (0)	0 (0)
Surveillance site						
Abidha Health Centre	419 (9)	393 (94)	26 (6)	20 (5)	4 (1)	2 (0)
Bondo District Hospital	726 (15)	681 (94)	45 (6)	40 (5)	5 (1)	0 (0)
Got Agulu Health Centre	441 (9)	361 (82)	80 (18)	64 (15)	15 (3)	1 (0)
Lwak Mission Hospital	826 (17)	757 (92)	69 (8)	54 (6)	14 (2)	1 (0)
Madiany Sub-District Hospital	380 (8)	332 (87)	48 (13)	41 (11)	7 (2)	0 (0)
Matangwe Community Health Centre	200 (4)	186 (93)	14 (7)	13 (7)	1 (0)	0 (0)
Siaya District Hospital	1672 (35)	1550 (93)	122 (7)	95 (6)	27 (1)	0 (0)
Nyangoma Mission Hospital	136 (3)	124 (91)	12 (9)	12 (9)	0 (0)	0 (0)
Total	4800 (100)	4384 (91)	416 (9)	339 (7)	73 (2)	4 (0)

Table 3. *Comparison of demographic and illness severity characteristics in patients hospitalized with a respiratory infection tested for influenza and patients hospitalized with a respiratory infection untested for influenza, western Kenya, January 2007–July 2010*

	Tested*	Untested*	*P* value
Patient characteristics			
Age	(*n*=4800)	(*n*=3057)	
2–59 months	3116 (65)	1945 (64)	0·24
⩾5 years	1684 (35)	1112 (36)	
Mean age (yr)	12·0	12·4	0·45
Sex	(*n*=4799)	(*n*=3052)	
Male	2341 (49)	1438 (47)	0·15
Female	2458 (51)	1614 (53)	
Illness severity			
Death	(*n*=4577)	(*n*=2907)	
Discharged dead	139 (3)	135 (5)	<0·01
Discharged alive	4438 (97)	2799 (95)	
Oxygen saturation	(*n*=4222)	(*n*=2583)	
<90%	454 (11)	154 (6)	<0·01
⩾90%	3768 (89)	2429 (94)	
Mean	94·3	95·8	<0·01

* Number (%) for categorical variables and mean for continuous variables.

the sensitivity and specificity patterns were similar and improvement in PPV was limited. The sensitivity of the SARI case definition during the pandemic period was significantly higher than during the pre-pandemic period in children aged 2–59 months and for all ages combined ($P<0{\cdot}01$); however, no other significant differences between the two periods were identified (Table 5). PPV was higher during the pandemic period for SARI, ILI, and the other sign/symptom combinations assessed, probably as a consequence of higher influenza prevalence during this period.

Sensitivity of the case definitions and of the sign/symptom combinations for laboratory-confirmed influenza infection increased sharply from days 1 to 7 after symptom onset; 90% of all influenza tests were performed during this period. Trends in sensitivity persisted during days 8–14 after symptom onset, but were less pronounced. Overall, sensitivity of the SARI case definition increased from 3% on day 1 to 39% by day 7 after symptom onset and to 43% by day 14 after symptom onset (Fig. 1*a*). Sensitivity of the symptom combination of cough and any fever increased from 3% on day 1 to 78% by day 7 after symptom onset and to 87% by day 14 after symptom onset (Fig. 1*b*). Although the relative gains in sensitivity decreased for days 8–14 after symptom onset, the percentage of specimens testing positive for influenza infections was similar during both periods (days 1–7 after symptom onset: 8·7%, $n=4285$; days 8–14 after symptom onset: 8·4%, $n=515$; $P=0{\cdot}79$).

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Table 4. *Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of evaluated selected signs, symptoms, and combinations of signs and symptoms for laboratory-confirmed influenza infection, western Kenya, January 2007–July 2010*

Case definition	Total admitted	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
All ages					
SARI	2674	42·5 (37·8–47·5)	43·0 (41·6–44·5)	6·6 (5·7–7·6)	88·8 (87·3–90·1)
ILI	1429	26·9 (22·8–31·5)	70·0 (68·6–71·3)	7·8 (6·5–9·4)	91·0 (90·0–91·9)
Cough	4401	94·7 (92·0–96·6)	8·6 (7·8–9·5)	9·0 (8·1–9·8)	94·5 (91·6–96·4)
Cough and measured fever $\geqslant$38 °C	1410	26·7 (22·5–31·3)	70·4 (69·0–71·7)	7·9 (6·5–9·4)	91·0 (90·0–91·9)
Cough and any fever*	4003	87·0 (83·3–88·9)	16·9 (15·8–18·1)	9·0 (8·2–10·0)	93·2 (91·2–94·8)
Cough or difficulty breathing	4768	99·8 (98·5–100·0)	0·7 (0·5–1·0)	8·7 (7·9–9·5)	96·9 (82·0–99·8)
Cough or difficulty breathing and measured fever $\geqslant$38 °C	1516	28·6 (24·4–33·3)	68·1 (66·7–69·8)	7·8 (6·6–9·3)	90·9 (89·9–91·9)
Cough or difficulty breathing and any fever*	4353	91·3 (88·1–93·8)	9·3 (8·5–10·2)	8·7 (7·9–9·6)	91·9 (88·8–94·2)
2–59 months					
SARI	2432	71·1 (64·4–77·0)	21·4 (20·0–23·0)	6·2 (5·3–7·2)	91·1 (88·6–93·1)
ILI	957	29·4 (23·4–36·1)	69·2 (67·5–70·9)	6·5 (5·0–8·3)	93·1 (91·9–94·1)
Cough	2904	94·3 (90·0–96·9)	6·9 (6·0–7·9)	6·9 (6·0–7·8)	94·3 (90·1–96·9)
Cough and measured fever $\geqslant$38 °C	955	29·4 (23·4–36·1)	69·3 (67·5–71·0)	6·5 (5·1–8·3)	93·1 (91·9–94·1)
Cough and any fever*	2712	89·6 (84·4–93·2)	13·1 (11·9–14·4)	7·0 (6·1–8·0)	94·5 (91·7–96·5)
Cough or difficulty breathing	3113	100·0 (97·8–100·0)	0·1 (0·0–0·3)	6·8 (5·9–7·7)	100·0 (31·0–100·0)
Cough or difficulty breathing and measured fever $\geqslant$38 °C	1034	31·8 (25·6–38·6)	66·7 (65·0–68·4)	6·5 (5·1–8·2)	93·1 (91·9–94·1)
Cough or difficulty breathing and any fever*	2915	94·8 (90·6–97·2)	6·5 (5·6–7·4)	6·9 (6·0–7·9)	94·5 (90·1–97·1)
$\geqslant$5 years					
SARI	242	13·2 (9·0–18·8)	85·5 (83·5–87·2)	11·2 (7·6–16·0)	87·7 (85·8–89·3)
ILI	472	24·4 (18·8–31·0)	71·5 (69·1–73·7)	10·6 (8·0–13·8)	87·2 (85·2–89·0)
Cough	1497	95·1 (91·0–97·5)	12·0 (10·4–13·8)	13·0 (11·4–14·9)	94·7 (90·1–97·3)
Cough and measured fever $\geqslant$38 °C	455	23·9 (18·4–30·4)	72·5 (70·2–74·8)	10·8 (8·1–14·1)	87·3 (85·3–89·1)
Cough and any fever*	1291	84·4 (78·5–88·9)	24·4 (22·2–26·6)	13·4 (11·6–15·4)	91·8 (88·6–94·3)
Cough or difficulty breathing	1655	99·5 (96·9–100·0)	1·9 (1·3–2·8)	12·3 (10·8–14·0)	96·6 (80·4–99·8)
Cough or difficulty breathing and measured fever $\geqslant$38 °C	482	25·4 (19·7–32·0)	70·8 (68·4–73·1)	10·8 (8·2–14·0)	87·2 (85·2–89·0)
Cough or difficulty breathing and any fever*	1438	87·8 (82·3–91·8)	14·8 (13·1–16·8)	12·5 (10·9–14·4)	89·8 (85·1–93·1)

SARI, Severe acute respiratory illness; ILI, influenza-like illness; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.
* Either a subjective or measured fever $\geqslant$38 °C.

Table 5. *Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of evaluated case definitions for laboratory-confirmed influenza infection, pre-pandemic* and pandemic† influenza A(H1N1) periods, western Kenya, January 2007–July 2010*

	Pre-pandemic period					Pandemic period				
Case definition	Total admitted	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Total admitted	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
All ages										
SARI	1336	33·6	50·1	6·3	88·3	755	53·7	32·8	7·7	87·2
ILI	881	23·6	67·2	6·7	89·8	294	31·5	74·9	11·6	91·3
Cough	2547	93·6	7·7	9·2	92·4	1040	94·4	9·5	9·8	94·3
Cough and measured fever $\geqslant$38 °C	866	23·2	67·8	6·7	89·8	292	31·5	75·1	11·6	91·3
Cough and any fever‡	2358	87·2	14·6	9·2	92·0	919	84·3	20·1	9·9	92·4
Cough or difficulty breathing	2736	99·6	0·8	9·1	95·2	1138	100·0	0·7	9·5	100·0
Cough or difficulty breathing and measured fever $\geqslant$38 °C	922	25·2	65·7	6·8	89·8	326	34·3	72·1	11·3	91·3
Cough or difficulty breathing and any fever‡	2537	92·4	8·0	9·1	91·3	1013	88·9	11·4	9·5	90·8
2–59 months										
SARI	1130	58·7	30·1	5·7	91·1	738	83·1	11·7	7·3	89·2
ILI	530	23·9	66·9	4·9	92·5	236	35·4	72·5	9·7	93·0
Cough	1543	91·7	5·3	6·5	90·0	765	95·4	9·3	8·1	96·0
Cough and measured fever $\geqslant$38 °C	528	23·9	67·1	4·9	92·5	236	35·4	72·5	9·7	93·0
Cough and any fever‡	1444	87·2	11·5	6·6	92·6	713	89·2	15·4	8·1	94·4
Cough or difficulty breathing	1630	100·0	0·2	6·7	100·0	840	100·0	0·0	7·7	UD
Cough or difficulty breathing and measured fever $\geqslant$38 °C	563	26·6	65·0	5·2	92·5	267	38·5	68·8	9·4	93·0
Cough or difficulty breathing and any fever‡	1526	94·5	6·6	6·7	94·4	787	93·8	6·1	7·8	92·2
$\geqslant$5 years										
SARI	206	14·2	81·1	9·7	86·8	17	9·3	95·0	23·5	86·5
ILI	351	23·4	67·7	9·4	86·0	58	25·6	82·1	19·0	87·0
Cough	1004	95·0	11·5	13·3	94·2	275	93·0	10·3	14·5	90·0
Cough and measured fever $\geqslant$38 °C	338	22·7	68·8	9·5	86·1	56	25·6	82·8	19·6	87·1
Cough and any fever‡	914	87·2	19·5	13·5	91·4	206	76·7	34·0	16·0	89·9
Cough or difficulty breathing	1106	99·3	1·7	12·7	94·4	298	100·0	2·7	14·4	100·0
Cough or difficulty breathing and measured fever $\geqslant$38 °C	359	24·1	66·9	9·5	86·0	59	27·9	82·0	20·3	87·3
Cough or difficulty breathing and any fever‡	1011	90·8	10·1	12·7	88·4	226	81·4	27·1	15·5	89·9

ILI, Influenza-like illness; SARI, severe acute respiratory illness; PPV, positive predictive value; NPV, negative predictive value; UD, undefined.

* Period before isolation of the first pH1N1 virus in Kenya (January 2007–June 2009).

† Months after the first isolation of pH1N1 in which $\geqslant$50% of the subtyped influenza A viruses were pH1N1 (October 2009–February 2010, April 2010, and July 2010).

‡ Either a subjective or measured fever $\geqslant$38 °C.

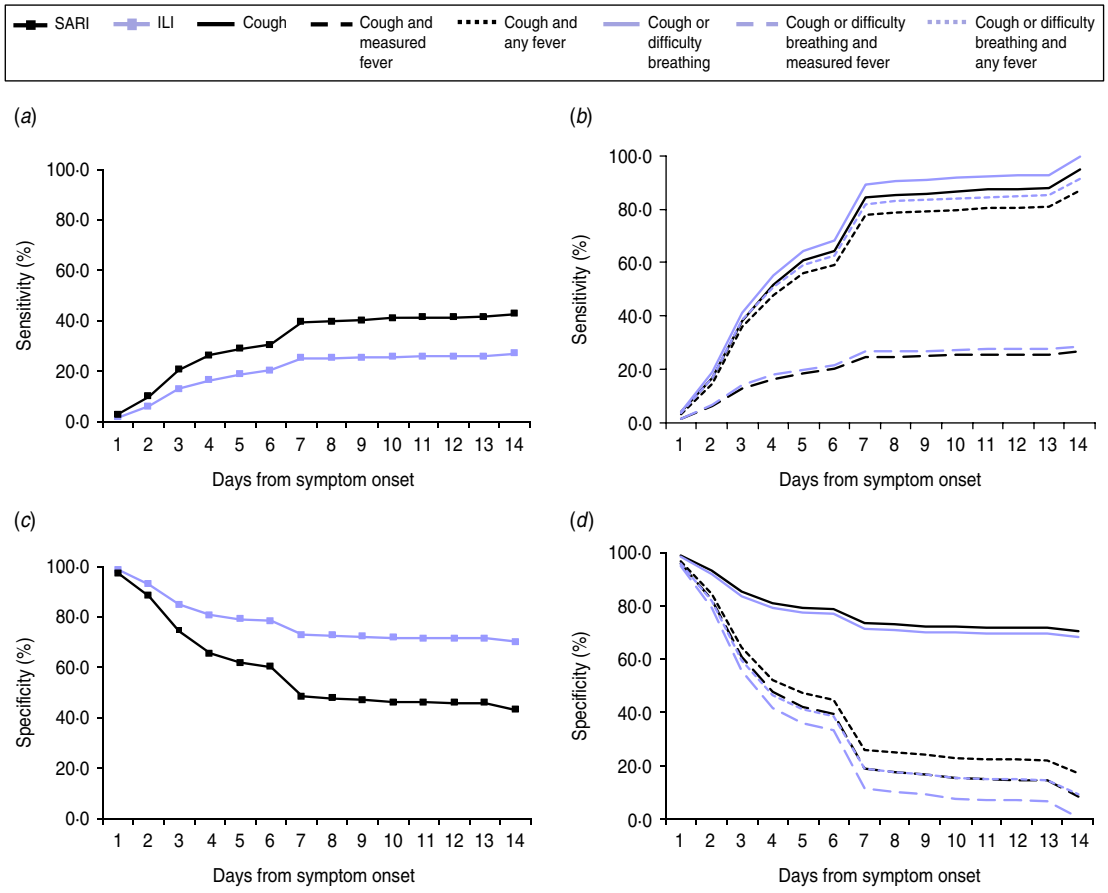

Fig. 1. [*colour online*]. Cumulative sensitivity and specificity of case definitions (*a*, *c*) and sign/symptom combinations (*b*, *d*) for laboratory-confirmed influenza infection by length of symptom duration, western Kenya, January 2007–July 2010.

Conversely, the specificity of the case definitions and the sign/symptom combinations decreased most rapidly during days 1–7 after symptom onset. The rate of decline in specificity decreased substantially during days 8–14 after symptom onset relative to days 1–7 after symptom onset (Fig. 1*c*, *d*).

DISCUSSION

Our analysis indicates that multiple sign/symptom combinations involving cough, difficulty breathing, and any fever (subjective or measured fever $\geqslant$38 °C) maximized sensitivity in both children aged 2–59 months and persons aged $\geqslant$5 years. In contrast, the ILI case definition and the sign/symptom combination of cough and measured fever $\geqslant$38 °C maximized specificity in both age groups. The goals of the surveillance system will ultimately determine the relative importance of sensitivity *vs*. specificity. If the goal of the surveillance system is to identify all hospitalized cases of influenza in order to estimate the total burden of influenza in hospitalized patients with respiratory illnesses or in a specific population, then a highly sensitive case definition is preferable. However, if the goal of the surveillance system is to maximize the yield of influenza isolates in hospitalized patients with respiratory illnesses in a resource-limited setting in order to monitor influenza activity at a minimal level, a highly specific group of signs and symptoms is preferable.

The combination of cough and any fever is highly sensitive and requires less testing of samples, and thus costs less, since fewer people meet this case definition relative to the other three sign/symptom combinations that had slightly higher sensitivity (cough alone, cough or difficulty breathing, and cough or difficulty breathing and any fever). In addition, the combination of cough and any fever was more sensitive for laboratory-confirmed influenza than both SARI and ILI in both the 2–59 months and $\geqslant$5 years age groups. Of the children aged 2–59 months, the SARI case definition requires the presence of an

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IMCI danger sign or elevated respiratory rate in addition to cough or difficulty breathing; however, the original intent of the IMCI case definition was pneumonia diagnosis and case management, not influenza surveillance [6]. While the use of a well-recognized case definition seems like a logical first step for influenza surveillance, our results indicate that it is not the best case definition to use for this purpose. In persons aged $\geqslant 5$ years, neither the SARI case definition nor the ILI case definition performed well with respect to sensitivity.

As a well-recognized case definition for influenza surveillance, ILI might be the ideal choice for influenza surveillance in hospitalized patients with ARI for maximizing specificity; however, the inclusion of sore throat has little impact since no significant difference was found between the specificities of ILI, and cough and measured fever $\geqslant 38\ ^{\circ}C$. The specificity of the SARI case definition in children aged 2–59 months was poor relative to ILI; however, SARI had the highest specificity in persons aged $\geqslant 5$ years. Using the same case definition across all age groups allows for the comparison of rates across age groups. None of the case definitions or sign/symptom combinations evaluated had high PPVs; thus, their utility for healthcare providers for clinical case management is limited.

Evaluations of the SARI case definition for laboratory-confirmed influenza infections have been conducted recently in Guatemala and Egypt [12, 13]. The overall sensitivity of the SARI case definition in rural Kenya (42%) falls between the reported sensitivities in Guatemala (64%) and Egypt (30%). Similar to what was found in rural Kenya, the Guatemala study found that the SARI case definition had a higher sensitivity and lower specificity in children aged <5 years compared to persons aged $\geqslant 5$ years. Studies evaluating the ILI case definition have found a wide range of sensitivities (43–73%) and specificities (43–87%); however, differences in study designs, inclusion criteria, and study populations between these studies and ours make direct comparison difficult [14–17]. Cough alone has routinely been found to have relatively high sensitivity (69–98%), as it was in our study, but given that cough is a nonspecific symptom with respect to respiratory illness, this is not surprising [14, 16–20]. Our analysis of sensitivity by symptom duration demonstrated that the largest gains in sensitivity are achieved during days 1–7 after symptom onset, with only limited gains during days 8–14. However, we also determined that the percentage of specimens testing positive for influenza was consistent between the two periods and that only 10% of all persons meeting our testing criteria who were tested had symptom duration of 8–14 days. Therefore, testing for influenza throughout the 14-day period after symptom onset can provide additional sensitivity to the surveillance system without a loss in the proportion of influenza positivity or substantial increases in testing. However, these gains in sensitivity are relatively minor.

Our analysis had certain limitations. A substantial percentage of inpatients meeting the influenza testing criteria were not tested for influenza. Although we did not identify differences in demographic characteristics between those tested and untested, we did find limited but statistically significant differences in the percentage of deaths and the percentage of patients with oxygen saturation levels $<90\%$ in the tested and untested groups. However, because the absolute differences were $\leqslant 7\%$ for all comparisons and our sample size was large, giving us the power to detect minor differences, our estimates probably would not have changed substantially had everyone been tested. This study was conducted within a relatively homogeneous, hospitalized population in rural western Kenya, an area with a high rate of malaria and a high prevalence of HIV; thus, the results might not be generalizable to outpatients, urban areas, other hospitals where admitting practices vary, or regions with a lower burden of malaria and HIV [21]. We were unable to assess differences in sensitivity, specificity, PPV, and NPV between HIV-positive and HIV-negative individuals because this information was not available in the surveillance system. Finally, RT–PCR was the only influenza testing mechanism used in our surveillance system, and axillary temperatures were used in every healthcare facility. Sensitivities could vary in surveillance systems or studies where other tests (e.g. culture and serology) and other temperature sites are used.

In conclusion, if the surveillance goals are to determine disease burden and thus maximize sensitivity, the combination of cough and any fever (subjective or measured fever $\geqslant 38\ ^{\circ}C$) can provide a simple, sensitive case definition for surveillance for hospitalized laboratory-confirmed influenza for all age groups. However, using a maximally sensitive case definition would require large resources because of the large number of specimens collected and tested; however, developing a sampling scheme for specimen testing could alleviate some of the resource burden while still

providing a representative and highly sensitive case definition. In resource-limited settings where a priority might be to ensure identification of a minimum number of positive specimens, the ILI case definition is well-recognized and maximizes specificity for all age groups. Surveillance systems that have mixed objectives could choose a case definition that provides more of a balance between sensitivity and specificity. Given funding availability, continuing testing for influenza up to day 14 after symptom onset can provide additional gains in sensitivity without a reduction in specimen positivity.

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DECLARATION OF INTEREST

None.

REFERENCES

1. **Nair H, *et al.*** Global burden of repiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. *Lancet* 2011; **375**: 1545–1555.
2. **Murray CJ, *et al.*** Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918–20 pandemic: a quantitative analysis. *Lancet* 2006; **368**: 2211–2218.
3. **Ortiz JR, *et al.*** Strategy to enhance influenza surveillance worldwide. *Emerging Infectious Diseases* 2009; **15**: 1271–1278.
4. **WHO Regional Office for Europe.** WHO Regional Office for Europe guidance for influenza surveillance in humans, 2009.
5. **Pan American Health Organization.** Prevention CfDCa. PAHO-CDC generic protocol for influenza surveillance. Washington, DC: Pan American Health Organization and US Centers for Disease Control and Prevention, 2006.
6. **WHO.** *Handbook: IMCI Integrated Management of Childhood Illness*. Geneva: World Health Organization, 2005.
7. **Central Bureau of Statistics.** Population distribution by administrative areas and urban centres. Kenya 1999 population and housing census. Nairobi: Central Bureau of Statistics, Ministry of Planning and National Development, 2001.
8. **Central Bureau of Statistics.** Kenya Demographic and Health Survey 2003. Nairobi, Kenya: Central Bureau of Statistics, Ministry of Planning and National Development, 2004.
9. **National AIDS and STD Control Program.** Kenya AIDS indicator survey 2007: Final report. Nairobi: Ministry of Health, Kenya, 2009.
10. **WHO.** *WHO Recommended Surveillance Standards*. Geneva: WHO, 1999.
11. **WHO Collaborating Center for Influenza at CDC-Atlanta.** CDC protocol for realtime RT-PCR for influenza A(H1N1). Atlanta: CDC, 2009.
12. **McCracken J, *et al.*** Performance of a CDC-WHO classification of severe acute respiratory infections for influenza infection surveillance among Guatemalan hospital admissions. In: *International Conference on Emerging Infectious Diseases*. Atlanta, GA: Centers for Disease Control and Prevention, 2010, p. 80.
13. **Peters L, *et al.*** Sensitivity of various case definitions in identifying influenza cases in acute respiratory infection (ARI) surveillance in the Eastern Mediterranean Region (EMR). In: *International Conference on Emerging Infectious Diseases*. Atlanta, GA: Centers for Disease Control and Prevention, 2010, pp. 194–195.
14. **Babcock HM, *et al.*** Case-control study of clinical features of influenza in hospitalized patients. *Infection Control and Hospital Epidemiology* 2008; **29**: 921–926.
15. **Kasper MR, *et al.*** Evaluation of an influenza-like illness case defintion in the diagnosis of influenza among patients with acute febrile illness in Cambodia. *BMC Infectious Diseases* 2010; **10**: 1–5.
16. **Monto AS, *et al.*** Clinical signs and symptoms predicting influenza infection. *Archives of Internal Medicine* 2000; **160**: 3243–3247.
17. **Ong AK, *et al.*** Improving the clinical diagnosis of influenza – a comparative analysis of new influenza A(H1N1) cases. *PLoS One* 2009; **4**: e8453.
18. **Carrat F, *et al.*** Evaluation of clinical case definitions of influenza: detailed investigation of patients during the 1995–1996 epidemic in France. *Clinical Infectious Diseases* 1999; **28**: 283–290.
19. **Hulson TD, *et al.*** Diagnosing influenza: the value of clinical clues and laboratory tests. *Journal of Family Practice* 2001; **50**: 1051–1056.

20. **van Elson LJ, *et al.*** Clinical diagnosis of influenza virus infection: evaluation of diagnostic tools in general practice. *British Journal of General Practice* 2001; **51**: 630–634.

21. **Reyburn H, *et al.*** Over diagnosis of malaria in patients with severe febrile illness in Tanzania: a prospective study. *British Medical Journal* 2004; **329**: 1212–1218.

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