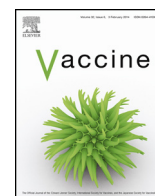




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Review

Is influenza-like illness a useful concept and an appropriate test of influenza vaccine effectiveness?



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ARTICLE INFO

Article history:

Received 28 December 2013
 Received in revised form 7 February 2014
 Accepted 12 February 2014
 Available online 28 February 2014

Keywords:

Influenza-like illness
 Vaccine effectiveness
 Outcome measure
 Sensitivity
 Specificity

ABSTRACT

Purpose: To assess the utility of “influenza-like illness” (ILI) and whether it appropriately tests influenza vaccine effectiveness.

Principal results: The WHO and CDC definitions of “influenza-like illness” are similar. However many studies use other definitions, some not specifying a temperature and requiring specific respiratory and/or systemic symptoms, making many samples non-comparable. Most ILI studies find less than 25% of cases are RT-PCR-positive, those which test for other viruses and bacteria usually find multiple other pathogens, and most identify no pathogen in about 50% of cases. ILI symptom and symptom combinations do not have high sensitivity or specificity in identifying PCR-positive influenza cases. Rapid influenza diagnostic tests are increasingly used to screen ILI cases and they have low sensitivity and high specificity when compared to RT-PCR in identifying influenza.

Main conclusions: The working diagnosis of ILI presumes influenza may be involved until proven otherwise. Health care workers would benefit by renaming the WHO and CDC ILI symptoms and signs as “acute respiratory illness” and also using the WHO acute severe respiratory illness definition if the illness is severe and meets this criterion. This renaming would shift attention to identify the viral and bacterial pathogens in cases and epidemics, identify new pathogens, implement vaccination plans appropriate to the identified pathogens, and estimate workload during the viral season. Randomised controlled trials testing the effectiveness of influenza vaccine require all participants to be assessed by a gold standard (RT-PCR). ILI has no role in measuring influenza vaccine effectiveness. ILI is well established in the literature and in the operational definition of many surveillance databases and its imprecise definition may be inhibiting progress in research and treatment. The current ILI definition could with benefit be renamed “acute respiratory illness,” with additional definitions for “severe acute respiratory illness” (SARI) with RT-PCR testing for pathogens to facilitate prevention and treatment.

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1. Introduction

Of the 10 million deaths of children <5 years in 2000, 1.9 million were estimated due to ILI. The incidence is similar in higher and lower income countries with mortality rates higher in lower income countries [1]. Severe acute respiratory illness (SARI) is an important cause of death among children in low-income countries: the WHO definition is ILI plus “cough or sore throat, plus measured fever, shortness of breath and need for hospitalization” [2]. Pathogens detected in ILI cases vary widely. The limited number of ILI studies which tested for multiple viruses and bacteria found the percentage with Influenza A usually <25% (range 8%–52%), B 0.7%–10%, and no pathogen found 20%–73% (Table 1). Pathogens

also varied over time. The French nationwide *Sentinelles* system reports ILI cases during influenza epidemics and found 1999–2012 that A(H3N2) predominated in seven epidemics (82–99% of all isolations), A(H1N1) (58–99%) in four and B in two (48–55%) [3].

2. Objectives

To assess whether influenza-like illness is: (1) a useful concept, and (2) an appropriate test of influenza vaccine effectiveness.

3. Materials and methods

Medline, Embase and the Cochrane Library were searched from inception to 22 December 2013 for “influenza-like illness” and “ILI.”

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Table 1
Laboratory investigations of cases of influenza-like illness (ILI) tested for multiple pathogens.

Author, date	Country, area, date of cases	N	% Adenovirus	% Bacterial	% Coronaviruses	% Influenza A	% Influenza B	% Metapneumovirus	% Parainfluenza	% Picornavirus	% Rhinovirus	% RSV	% multiple respiratory viruses	% Other viruses (not specified)	% No pathogen identified ^a
CDC or WHO ILI definition															
Kammerer 2011 [10]	US/Mexico border 2004–2009	1855	4	7		19	4.5		1	1	4	0.6		0.4 ^b	64
Rumoro 2012 [9]	US 2009–2010	773		13.8		12.5						6.7		0.2 ^c	66.7
Thiberville 2012 [11] ^d	Marseille, France 2009	660	1.4		3	24		0.7	3	1.5	20			1.7 ^e	46.2
Yang 2012 [12]	Beijing 2010	279	1.1		0.7	23.7	0.7				1.1	0.4	2.5		61.6
Not CDC or WHO ILI definition															
Galindo-Fraga 2013 [22]	Mexico City 2010	1065	3.3	1.1	7.3	8	6	4	1.9		15.3	5.4	11.9		35.5
Hombrouck 2012 [18]	Belgium 2009 (children)	139				20	0.7	9		7	15	19	8.6		38.2
Hombrouck 2012 [18]	Belgium 2009 (adults)	810				52	0.4	0.4		1.4	5	1.6	0.4		40
Howard 2012 [25]	Australia	586	0.5		5.4	4.5	6.1	1.7	1.7	22.4		1.2			56
Laguna-Torres 2010 [21]	El Salvador, Honduras, Nicaragua	1756	3.6			7.4	2.7	0.2		3.2		6.9	1	1.7 ^f	73.3
Li 2013 [23]	Zuhai, China 2010	3747	6			8	10	5		4		7	5		55
Noh 2013 [24]	S Korea 2011–2012	1983	0.4		1.8	34.1	8.5	3	1.7		4	1.5			48
Schnepf 2011 [19]	Paris and Tours (France) 2009–2010	413	2.4	0.7	1.4	16.6			11.1		28.8	1.2	8.7		38
Smit 2011 [20]	Netherlands 2009	964			0.2	16		0.2	0.4		16				59
Thursky 2003 [26]	Australia 1998–2009	647				22.8	0.5					1		8.5	67

^a Because of co-infections the numbers in each row will not necessarily add to the same total of patients in whom any infection was detected, and hence the inverse % (no infection was detected).

^b Enteroviruses and Herpes simplex.

^c Infectious mononucleosis.

^d Thiberville based diagnoses other than H1N1 on a random sample of the 286 patients negative for H1N1, and the percentages are ascribed to the full sample of 660 as if it had been tested.

^e 1.3% Herpes viruses and 0.4% Enteroviruses.

^f Enteroviruses and human Metapneumoviruses.

4. Results

4.1. Literature search

3824 abstracts and titles in Medline, 4105 Embase, 33 Cochrane Database of Systematic Reviews: 2417 with duplicates removed, 298 read in full-text and 43 included in this review.

4.2. ILI definitions

The CDC defines ILI as: “a temperature of $\geq 100.0^{\circ}\text{F}$ ($\geq 37.8^{\circ}\text{C}$), oral or equivalent, and cough or sore throat, in the absence of a known cause other than influenza” [4]. The WHO defines ILI similarly as: “sudden onset fever ($>38^{\circ}\text{C}$) with cough or sore throat, in the absence of other diagnoses,” and severe acute respiratory illness (SARI) as ILI plus shortness of breath and/or difficulty breathing and hospital admission [5]. Many studies use other ILI definitions, some specify a fever and combinations of respiratory and constitutional symptoms (Supplemental Table 1).

Supplementary material related to this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.vaccine.2014.02.059>.

4.3. Systematic reviews of influenza and ILI

The Cochrane reviews of the effectiveness of influenza vaccine found marked differences in relative risks for laboratory-proven influenza and ILI in each age group of children under 6 years [6], 6–18, healthy adults 18–60 [7], adults >60 in nursing homes [8] and adults >60 in the community [8], implying laboratory-proven influenza and ILI measure different illnesses (Supplemental Table 2).

Supplementary material related to this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.vaccine.2014.02.059>.

4.4. Studies of ILI

The limited number of studies of ILI includes Belgium, France, the Netherlands and Portugal in Europe; Canada, Mexico, the US, and one study of El Salvador, Honduras and Nicaragua in the Americas; China, India and Vietnam in Asia, and a study of 15 African countries. They vary in using WHO or CDC definitions or their own.

4.4.1. Studies which used CDC or WHO ILI definitions

4.4.1.1. Studies which tested for influenza and other pathogens. Studies of ILI patients found influenza and a variety of viruses and other pathogens (Table 1). Two were in the US. In a retrospective study of 32,922 patients seen for acute respiratory problems in a US emergency department 2009–2010 1233 were tested for respiratory viruses by RT-PCR, 773 met the CDC ILI definition and 12.5% were positive for A H1N1, and the sensitivity of the CDC ILI definition was 79.2% and specificity 57.5%. The CDC definition excludes proven other causes and when patients were tested for four common alternative diagnoses 13.5% had a chest X-ray positive for acute bacterial pneumonia, 6.7% a positive rapid RSV antigen, 0.3% a rapid streptococcal throat culture and 0.2% a positive Mononucleosis spot test and the sensitivity of the CDC definition increased to 86.4% and specificity declined to 40.7% [9]. A study of 1855 persons who crossed the US/Mexico border 2004–2009 who met the CDC ILI definition and were tested by viral culture or PCR found that 19% were Influenza A positive, 4.5% Influenza B, 4% Adenovirus, 1% Parainfluenzavirus, 1% Picornavirus, 0.6% RSV, 0.4% Enterovirus or HSV, and 7% bacterial pathogens (*Streptococcus pneumoniae*, *S. pyogenes*, *Haemophilus influenzae*, β -hemolytic streptococcus, group C streptococcus or *Moraxella catarrhalis*) [10]. One study was in

Europe. In Marseille during the 2009 H1N1p pandemic a GP network assessed 660 patients as CDC ILI cases and by RT-PCR 24% were A/H1N1p positive. Of the 502 RT-PCR influenza-negative patients a random sample of 296 were tested for 18 viruses: 82 were positive for ≥ 1 other virus (20% Rhinovirus, 3% Parainfluenza viruses, 3% Coronaviruses, 1.4% Adenovirus, 1.3% Herpes viruses, 0.7% human Metapneumovirus, 0.4% Enterovirus) and 46.2% were negative for all 18 [11]. Two studies were in China. At Peking University People's Hospital all patients ≥ 16 years at the fever outpatient service during 2010 were screened for WHO ILI, 279 were tested by RT-PCR and 23.7% were positive for Influenza A, 0.7% Influenza B, 1.1% Rhinoviruses, 1.1% Adenovirus, 0.7% Coronaviruses, 0.4% RSV, and 2.5% multiple viruses [12]. A study assessed whether China's national ILI sentinel surveillance system (554 sentinel hospitals across China, 2.5% of all hospitals) could identify new strains. In 2013 laboratory systems reported 130 cases of A/H7N9 but only five were first identified by the sentinel system [13].

4.4.1.2. Studies which tested only for influenza (Table 2). Four studies were in Asia. In India trained investigators assessed all 10,080 patients admitted to hospitals over two years: of the 3179 ILI cases, 13% <5 years and 22% ≥ 5 years were Influenza A PCR positive and 6% Influenza B. For children <5 years the SARI definition had a very low sensitivity of 11% and a high specificity of 87%. If shortness of breath was omitted sensitivity increased to 69% and specificity decreased to 43%, if reported fever was allowed sensitivity increased to 87% and specificity decreased to 5%, and if cough was added sensitivity decreased to 77% but specificity increased to 33% [14]. A study of the H1N1 epidemic in Singapore June–October 2009 found paired samples from 727 ILI cases yielded an influenza estimate of 17% (Bayesian CIs 14–20%) and an average of baseline and final samples a rate of 15% (BCI 10 to 25%) [15]. A study in Vietnam 2006–2010 of 15 sites in the National Influenza Sentinel System identified 29,804 ILI cases: 14.5% were Influenza A and 7.3% B, and there were 12 peaks during the five year period [16]. A study of 15 African countries 2006–2010 reported 69,860 WHO ILI cases: 21.7% tested RT-PCR positive for influenza (range Angola 6.9%–40.4% Madagascar) but there was a low adult consultation rate [17]. Thus in studies with WHO or CDC ILI definitions there was a wide range of viruses, some bacteria, and influenza rates were usually $<25\%$.

4.4.2. Studies which did not use CDC or WHO ILI definitions

4.4.2.1. Studies which tested for both influenza and other viruses. Three studies were in Europe. A Belgian network screened respiratory illnesses during the A(H1N1) 2009 pandemic: 949 nasopharyngeal samples were tested by RT-PCR. Adults tested 52% positive for Influenza A (children 20%), 0.4% Influenza B (0.7%), 5% Rhinovirus (15%), 1.6% RSV (19%), 1.4% Picornavirus (7%), and 0.4% Metapneumovirus (9%) [18]. ILI patients at two French University hospitals early in the 2009–2010 H1N1 epidemic were tested by RT-PCR and multiplex assay RespiFinder19: 28.8% were positive for rhinoviruses, 16.6% Influenza A, 11.1% Parainfluenza viruses, 8.7% mixed viral infections, 2.4% Adenoviruses, 1.4% Coronaviruses, 1.2% RSV and 0.7% bacteria [19]. An Amsterdam study of 964 ILI patients found 16% had Influenza A, 16% Rhinovirus, 0.4% Parainfluenza virus, 0.2% Coronaviruses, 0.2% Metapneumoviruses and 3% other viruses not specified [20]. Two studies were in the Americas. All ILI outpatients at five health centres in El Salvador, Honduras and Nicaragua 2006–2009 were tested by RT-PCR: Influenza A was identified in 7.4% of ILI cases, Influenza B 2.7%, RSV 6.9%, Adenoviruses 3.6%, Picornaviruses 3.2%, and Metapneumoviruses 0.2% [21]. In Mexico City in five hospitals in 2010 1065 ILI patients were tested by RT-PCR: 8% Influenza A, 6% Influenza B, 15.3% Rhinovirus, 7.3% Coronaviruses, 5.4% RSV, 4% Metapneumovirus, 1.9% Parainfluenzavirus, and 11.9% mixed viral infections [22]. Three studies were in Asia. Of the 337,272 outpatients at Zhuhai

Table 2
Laboratory investigations of cases of Influenza-like illness (ILI) tested only for influenza.

Author, date	Country, area, date of cases	N	% Influenza A	% Influenza B
CDC or WHO ILI definition				
Hirve 2012 [14]	Western India, 2012	3167	13% <5 years; 22% ≥5 years	6
Lee 2011 [15]	Singapore 2009	Not stated	17% ^a	
Nguyen 2013 [16]	Vietnam 2006–2010	29,804	14.5	7.3
Radin 2012 [17]	15 African countries 2006–2010	69860	21.7 ^b	^b
Not CDC or WHO ILI definition				
Barbara 2012 [27]	Canada 2008/9	176	11	10
Chadha 2011 [32]	India 2004–2008	13928	2.5	1.9
Chuang 2012 [33]	Taiwan 2009–2011	26601	21	3.9
Fowlkes 2012 [29]	US 2009–2010	8747	23	0
Mulpuru 2013 [28]	Canada 2009	391	12 ^c	
Portuguese Laboratory 2011 [31]	Portugal 2009–11	62,089 (2009–10) 1512 (2010–11)	42 (2009–10) 38 (2010–11)	0.05 (2009–10)
Wei 2012 [34]	China 2009–2011	6143	20	6
Woolpert [30]	US 2007–8	789	19	8

^a Only an influenza rate was stated, with Bayesian credible 95% confidence intervals 14–20% based on paired samples.

^b Only an influenza rate is reported. B was the predominant strain in 2006 and 2007 except South/Central Africa

^c Only an influenza rate is reported. The study was during the A(H1N1) epidemic.

Municipal People's Hospital in China in 2010 3747 (1.11%) with assessed as ILI. Of these 924 were tested by RT-PCR: 8% were Influenza A, 10% Influenza B, 5% RSV, 6% Adenoviruses, 5% Metapneumoviruses, 4% Picornaviruses and 5% co-infections. The most common co-infection pattern was H3N2 and RSV. sFluA(H3N2) peaked July–September, sFluB March–May, H1N1pdm09 January, HMPV January, RSN January–March and October–December, and PIV and ADV throughout the year [23]. Seven South Korean teaching hospitals in the Hospital-based Influenza Morbidity and Mortality surveillance Scheme 2011–2012 tested 1983 ILI patients by RT-PCR: 34.1% had Influenza A, 8.5% Influenza B, 4% Rhinovirus, 3% Metapneumovirus, 1.8% Coronavirus, 1.7% Parainfluenzavirus, 1.5% RSV and 0.4% Adenoviruses [24]. Two studies were in Australia. During an influenza vaccine trial, of the 7544 participants 586 were asked to report ILI symptoms weekly and by RT-PCR 4.5% were positive for Influenza A, 6.1% Influenza B, 22.4% Picornavirus, 5.4% Coronaviruses, 1.7% Metapneumovirus, 1.7% Parainfluenzavirus, 1.2% RSV and 0.5% Adenovirus. Picornaviruses were most common in May, coronaviruses in June–August and Influenza in August–September. Those who received influenza vaccine had a lower influenza risk (OR 0.52; 0.31, 0.87), $p = 0.01$ [25]. A study used different definitions for two states and different definitions for two years for Western Australia. Of 647 samples tested by viral culture and RT-PCR 22.8% were Influenza A positive, 0.5% Influenza B, 8.5% other viruses (not specified) and 1% RSV [26].

4.4.2.2. Studies which tested only for influenza. Four studies were in the Americas. Children 36 months to 15 years ($n = 947$) in 46 Hutterite colonies in Canada were randomised to seasonal influenza vaccine to assess influenza incidence would decrease in children and adults. The residents ($n = 2326$) were asked to record ILI symptoms and 142 were tested by RT-PCR: 11% were positive for Influenza A and 10% for B [27]. In Canada at the Ottawa Hospital in 2009 391 admitted emergency patients were retrospectively assessed. For 200 tested by PCR 12% were Influenza A or B, and the sensitivity of the ILI definition was 75.6% (95% CI 61.3–85.8) and specificity 46.3% (38.2–54.7) [28]. A study of 38 practices with 450,484 patients in six US states had 272,642 visits October 2009–July 2010, of which 3.2% were for ILI (13% in the peak activity week of 24 October 2009), and tested 68% of the 8747 ILI visits with the Quidel QuickVue test: 23% were positive for influenza, of which >99% were A(H1N1)pdm09. The sensitivity compared to RT-PCR was 59% and specificity 97% [29]. In San Diego in 2007–2008 789 ILI military patients were tested with RT-PCR: 19% were Influenza A and 8% Influenza B [30]. One study was in Europe. In Portugal during the 2009/2010 pandemic 2089 cases were tested by

RT-PCR and 42% were A(H1N1)pdm09; and in the 2010/11 1512, of which 38% were A(H1N1)pdm09 [31]. Three studies were in Asia. In India 13,928 patients in the Indian Council of Medical Research influenza surveillance network 2004–2008 were tested by hemagglutination tests US CDC performed genetic characterisation. ILI and SARI results were reported together: 2.5% were Influenza A and 1.9% B [32]. The Taiwan Influenza Laboratory Surveillance Network of 275 sentinel physicians Of identified 26,601 ILI cases 2009–2011 and by viral culture and/or RT-PCR 21% were Influenza A and 3.9% Influenza B [33]. In eight influenza sentinel hospitals in China 6143 ILI patients 20% had Influenza A and 6% B [34]. CDC China ILI definition is in reference [35]. Thus in these studies which did not use WHO or CDC ILI definitions, PCR-positive rates for influenza were usually <20%.

4.5. Symptoms assessed in ILI surveys, and ability to discriminate pathogens

Using ILI symptoms to predict culture or RT-PCR positivity for influenza is difficult:

“Symptoms do not occur in 30–50% of influenza infections. Asymptomatically infected persons can shed detectable influenza virus and may transmit influenza to others, although data supporting the frequency of transmission prior to symptoms is limited” and “In most instances, individual cases of influenza are difficult to identify reliably by clinical examination and routine clinical laboratory findings alone, and the appropriate use of influenza diagnostic tests is helpful.” [36]

ILI can be caused by more than 200 viral species, and patients “exhibit widely overlapping symptoms, rendering clinical diagnosis unreliable. . .” [23]

ILI patients tended to have rates of the three key ILI symptoms of fever, cough and sore throat above 70%, but there were several studies which reported symptoms at the 40% level (Table 3), which could be due to differences in the illness of the patients or questioning by the health care professionals. The Marseille 2009 H1N1 pandemic study demonstrated the remarkable similarity of influenza A/H1N1p and human rhinovirus symptoms: 75% had ILI symptoms (89% of H1N1p cases, 74% HRV) and similar percentages of other symptoms [11]. Some studies assessed up to 14 other symptoms, which showed a wide range of variation (Table 3). Several studies assessed which symptoms predicted a positive laboratory test for influenza. Schnepf's study of French ILI patients found that patients with no virus detected were less likely to have a cough (77.8%)

Table 3
ILI symptoms (percentages).

Study	Country and date	N	Fever	Cough	Sore throat	Arthralgia	Asthenia	Body ache	Chills/rigours	Coryza
Barbara 2012 [27]	Canada	2008/9	176	35.9	78.2	62.7			15.5	
Chadha 2011 [32]	India	2004–2008	13,928	96.3	91.8	18.7		29.8	13.6	
Fowlkes 2012 [29]	US	2009–2010	8747		89	69				
Howard 2012 [25]	Australia		586	40.4	69.4	77.4			59.1	
Noh 2013 [24]	S Korea		1983		86.9	53.8				
Portuguese Laboratory 2011 [31]	Portugal	2009–2011	62,089 (2009–2010)	44.1	47.4	42.1				
Rumoro 2012 [9]	US	2009–2010	773	80.8	73.6	16.0				
Schnepf 2011 [19]	Paris and Tours (France)	2009–2010	413	93.9	86.1	24.1	57.6			
Thiberville 2012 [11]	Marseille, France	2009	660	84.9	83.2	64.7	39.7	93.3		65.2
Thiberville 2012 [11]	Marseille, France	2009	660	79	86	69	31	96		52
Yang 2012 [12]	Beijing	2010–2011	279	30	59.6	62.8				
Study	Expectoration	Fatigue	Headache	Muscle aches/myalgia	Nasal discharge/rhinorrhea/runny nose	Nausea	Respiratory difficulty	Shivers	Sudden onset	
Barbara 2012 [27]		20.4	22.5	14.1	52.8					
Chadha 2011 [32]	12	11.4	32.8		78.4					
Fowlkes 2012 [29]										
Howard 2012 [25]			75.1	80.7	71.5					
Noh 2013 [24]					55.1					
Portuguese Laboratory 2011 [31]			50.4	47.2			29.4			
Rumoro 2012 [9]										
Schnepf 2011 [19]			40.8	58.4	42.9			32		59
Thiberville 2012 [11]			77.4	79.7	63.2	35.2				
Thiberville 2012 [11]			69	74	81	23				
Yang 2012 [12]			62.8	65.5						

than those with H1N1v (89.5%, $p=0.01$) and more likely to have pharyngitis (21%) compared to those with H1N1v (10%, $p=0.003$), but Schnepf was not able to predict PCR-positivity [19]. The Hutterite colony study found that combinations of fever, cough, sore throat and muscle aches predicted PCR influenza positivity, but the confidence intervals were wide [27]. The Indian Council of Medical Research influenza surveillance network study found that only three symptoms correlated with influenza PCR-positivity: cough ($p<0.0034$), fatigue ($p<0.001$) and chills/rigours ($p<0.001$). The 2068 with SARI also had wide variation in symptoms and only body ache correlated with influenza PCR-positivity [32]. The Belgian general practitioner network ILI study enquired about 16 symptoms (but did not report fever) and noted that the most frequent symptoms for the 426 with confirmed influenza were similar to those for RSV [18]. The Portuguese study found that only fever $\geq 38^\circ\text{C}$ correlated with laboratory-proven influenza [31]. The San Diego military study 2007–2008 found for that acute onset ≤ 3 days, $T > 38^\circ\text{C}$, cough, and body aches all correlated $p \leq 0.001$ with PCR proven influenza [30]. In Australia different definitions were used for two states and different definitions for two years for Western Australia. For the combination cough, fever, fatigue and myalgia sensitivity ranged from 34.8 to 72.1% and specificity from 46.6% to 86.9%, and for cough and fever sensitivity ranged from 56.5 to 88.5% and specificity from 27.6 to 61.7% [26]. A systematic review in 2005 identified seven studies of influenza symptoms and no symptom or sign had a summary likelihood ratio high >2 , and cough, nasal congestion or no

fever were the only signs with a likelihood ratio <0.5 that decreased the likelihood of influenza [36]. A study of 964 Amsterdam patients used the Netherlands Medical Assistance for Accidents and Disasters ILI definition and tested them by RT-PCR. The CDC, WHO, and UK Health Protection Agency ILI definitions were also tested and the average sensitivity was 66% and specificity 70%. The authors concluded that all four case definitions "seemed comparable but rather useless." [20] A review of 15 studies 1997–2007 found the sensitivity of clinical diagnosis compared to viral culture or RT-PCR was 65% (55%–74%) and the specificity 67% (57%–76%), but the studies showed marked heterogeneity ($I^2 = 95.4$) [37]. ILI cases thus show wide variation in symptom frequency. Although fever and cough correlate positively with PCR-proven influenza in many studies, there is a ceiling effect as fever and cough are often $>70\%$ or even 90%, and the predictive value is not strong enough to rely on them to discriminate from PCR negative cases. Symptoms and symptom combinations vary between studies and do not provide statistically stable patterns to predict which ILI patients have influenza or other pathogens.

4.6. Factors affecting influenza diagnostic test accuracy

Several factors improve diagnostic test accuracy. Nasopharyngeal aspirates and washes followed by nasopharyngeal swabs and mid-turbinate swabs from each nostril provide higher yields than throat swabs. Flocked swabs release samples into transport media

better than mattress swabs. Samples obtained within 2–4 days of symptom onset provide higher yields than those in the first 12 h. RT-PCR is more sensitive than culture because it does not require infectious virus, and remains positive longer in transport. Results in experienced laboratories which monitor test performance are better [38]. Rapid influenza diagnostic tests (RIDTs) are increasingly used for ILI screening. Sixteen studies 2002–2009 of the QuickVue Rapid Flu test found marked heterogeneity ($I^2 = 92.5\%$). Compared to viral culture or RT-PCR random-effects sensitivity was 72% (62%, 81%) and specificity 96% (93%, 97%) [37]. A study of the patients in six US states found the Quidel QuickVue A+B test had 59% sensitivity and 97% specificity compared to RT-PCR [29]. A meta-analysis of 159 studies (35% during the H1N1 pandemic) of 26 RIDTs found many methodological defects: only 33% defined recruitment criteria, 41% were blinded, and 13% provided information on symptom duration. The RIDT was compared to RT-PCR in 54% of studies, to viral culture in 43% and to both in 3%. RT-PCR is more sensitive than culture, and RIDT pooled sensitivities compared to RT-PCR were lower (53.9%; 48.2%, 59.6%) than compared to viral culture (72.3%; 66.8%, 7.9%). RIDT specificity was high (98.8%; 98.3%, 99.3%) compared to RT-PCR and (96.7%; 95.2%, 98.3%) compared to viral culture. Sensitivity was higher in children (66.6%; 61.6%, 71.7%) than adults (53.9%; 47.9%, 59.8%) because they have higher viral loads and shed longer. Sensitivity was also higher in Influenza A (64.6%; 59.0%, 70.1%) compared to Influenza B (52.2%; 45.0%, 59.3%) [39]. There are few head-to-head comparisons of RIDTs. Directigen Flu A had the highest pooled sensitivity (76.7%; 63.8%, 86%) but it was not statistically better than the next best test (QuickVue Influenza Test), and Directigen Flu A+B ($p=0.011$), QuickVue Influenza A+B ($p<0.001$) and BinaxNOW ($p=0.028$) were statistically inferior to the other RIDTs combined [39]. Seven FDA-approved RIDTs were tested for their ability to detect variant Influenza A viruses, and all detected the seasonal A/Georgia/01/2011 and six of the seven detected H1N1pdm09 A/California/04/2009, but only four detected all A(H3N2)v viruses and at different concentrations [40]. Thus RIDTs have high specificities but very variable and modest sensitivities, and if used to assess the effectiveness of influenza vaccines inaccuracy will be introduced.

4.7. Correlations between ILI community surveys and influenza tracking programmes

In the Australian Flutracking programme in 2008 4827 community members recorded symptoms on-line and 10,773 in 2010 (no statement of survey questions) and those who reported fever and cough were defined as ILI. There was minimal correlation with national laboratory influenza notifications [41]. A study of “influenza activity” in Hong Kong for January 2004–May 2009 (excluding the subsequent pandemic) defined ILI as $T > 38.5$ plus cough and/or sore throat and found diagnoses by 50 GPs ILI correlated 0.67 and by 62 outpatient clinics correlated 0.70 with the influenza rate for all samples reported by the public laboratory, but no data were provided on numbers of cases or testing for other pathogens. The authors commented that: “laboratory data alone which suffer from denominator dilution during periods of non-influenza epidemics, and the GP ILI data alone which suffer from numerator dilution because not all ILI episodes are associated with influenza.” [42] Google Flu Trends (GFT) collates Internet searches in the US by the public for information about influenza and ILI. GFT for 2003–2008 (excluding the 2009 H1N1 pandemic) correlated 0.72 (0.64, 0.79) with the CDC Influenza Virologic Surveillance System of 140 laboratories data. GFT correlated 0.94 (0.92, 0.96) with the CDC Outpatient ILI Surveillance Network data. The two CDC databases correlated 0.85 (0.81–0.89). Correlations varied by influenza season and by region [43]. A study 2003–2013 (which

included the updated Google algorithm) assessed GFT as: “completely missing the first wave of the 2009 A/H1N1 pandemic, and greatly overestimating the intensity of the A/H3N2 epidemic during the 2012/2013 season. . . Current Internet search query data are no substitute for timely local clinical and laboratory surveillance” [44].

5. Discussion

“Influenza-like illness” is a broad definition and RT-PCR or viral culture testing shows in many ILI studies 25% or fewer patients have influenza, many other viruses and some bacteria are found and no pathogen is identified in the majority of patients. Thus hearing “influenza” as the only pathogen in the ILI definition may cause inappropriate certainty in the public, politicians, decision-makers and health professionals that influenza is the cause of far more acute respiratory illnesses than is true. The use of the ILI concept reduces the focus of the public and health professionals’ attention on proven measures to reduce the transmission of all acute respiratory pathogens. Because influenza vaccines and anti-viral medications have no effect on the other 200+ viruses and pathogens involved in acute respiratory illness there is a diversion of societal, medical and financial resources away from interrupting the transmission cycles of other pathogens and suggests to patients, health care workers, organisers and funders that anticipation of influenza pandemics, the prevention of influenza by vaccines and treatment by influenza-specific anti-virals are the key activities for health systems. Attention also needs to be given to detecting which pathogens are circulating and using proven barrier and hygiene methods to prevent transmission of as many pathogens as possible, which would also reduce the overall workload of the medical system.

6. Conclusions

Health officials would benefit by renaming the symptoms and signs labelled “ILI” as “acute respiratory illness” and using the WHO definition of severe acute respiratory illness (SARI) of “cough or sore throat, plus measured fever, shortness of breath and hospitalisation” [2], (and for areas without hospitals “need for hospitalisation” could serve as a descriptor of severity). Renaming would focus on funding the identification of all viral and bacterial epidemics. Randomised controlled trials testing the effectiveness of influenza vaccines require all participants to be assessed by a gold standard (RT-PCR) and follow patients for long enough to measure influenza-specific mortality. ILI has no role in measuring influenza vaccine effectiveness. ILI is well established in the literature and the operational definition of many surveillance databases. However, would tuberculosis specialists accept a definition that included many unrelated pathogens? Imprecise definitions inhibit progress in research and treatment. Should ILI be added to the list of 146 once recommended but now contradicted medical practices we should stop using and rename it? [45].

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