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Review

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

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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.

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	% Coronavirus	% Influenza A	% Influenza B	% Metapneumovirus	% Parainfluenza	% Picorna virus	% Rhinovirus	% RSV	% multiple respiratory viruses	% Other viruses (not secified)	% 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] Entervoviruses and human Metapneumoviruses.