



# Symptoms collected and definitions used in the Global Influenza Hospital Surveillance Network (GIHSN)

Joan Puig-Barberà, Md, MPH, PHD

Vaccine Research

*Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunidad Valenciana (FISABIO)*

GIHSN Coordination Centre

# Background

- It is generally not possible to distinguish infection caused by different respiratory viruses by clinical features, ...

Monto AS, Sullivan KM. Acute respiratory illness in the community. Frequency of illness and the agents involved. *Epidemiol Infect* **1993**;110:145-60

Carrat F, Tachet A, Rouzioux C, Housset B, Valleron AJ. Evaluation of clinical case definitions of influenza: detailed investigation of patients during the 1995-1996 epidemic in France. *Clin Infect Dis* **1999**;28:283-90

# Need for a case definition

- **Public health surveillance**

- **Aim:** trends and signals
  - Community cases (ILI / ARI)
  - Severe cases (SARI)

- **Clinical management**

- **Aim:** diagnosis, prognosis, to cross or not to cross a therapeutic threshold, counselling
  - Clinical symptoms (probability of influenza)
  - Laboratory (test) result (probability of influenza)

- **Research**

- **Aim:** validity, understanding, improve quality of decision making
  - Infection and disease epidemiology (virus, people, place and time)
    - Distribution or Incidence
    - Severity (description, ascertainment to adjust, main outcome)
    - Clinical course and outcomes
  - Case recruitment (influenza vaccine efficacy (RCT) effectiveness (CC or Cohort))

# Expected outcomes of the GIHSN

- Describe the pattern of the circulation of influenza viruses for different regions of the world in patients with severe disease
- Burden of severe influenza infection for different age-groups and by strain
- Vaccine effectiveness against hospitalization with influenza by strain and age-group

How to ascertain those who can provide the information *that* we need?

# GIHSN's case definition purpose

- Epidemiology of ***severe*** disease
  - Sensitivity (how much is too much?)
  - Specificity required, the higher the better
  
- Influenza vaccine effectiveness in preventing admissions with influenza, test-negative or case control study
  - Sensitivity not so critical, case definition can be narrowed as much as needed \*
  - Specificity as above \*

\* Orenstein EW, De Serres G, Haber MJ, Shay DK, Bridges CB, Gargiullo P, and Orenstein WA. Methodologic issues regarding the use of three observational study designs to assess influenza vaccine effectiveness. Int J Epidemiol; 2007;36(3):623-31..

# GIHSN strategy

MAIN FOCUS: epidemiology of influenza-related severe disease

- SENSITIVITY (first, we open): Emergency admissions for an acute process “probably” related to influenza<sup>(1-3)</sup>.
- SPECIFICITY (second, we close –minimize the number of false-negatives– in two steps):
  - Recent 7 or less days ILI (ECDC)<sup>4</sup> onset
  - rtRT-PCR (benchmark)

1. Textbook of influenza. Nicholson K, Wenster RG, Hay AJ, editors. Oxford; Malden, MA, USA: Blackwell Science; 1998.
2. Silvennoinen H, Peltola V, Vainionpää R, Ruuskanen O, Heikkinen T. Admission diagnoses of children 0-16 years of age hospitalized with influenza. Eur J Clin Microbiol Infect Dis 2011
3. Hayden FG, and de Jong MD. Human influenza: Pathogenesis, clinical features, and management. In: Webster RG, Monto AS, Braciale TJ, and Lamb RA., editors. Textbook of influenza. 2nd. Chichester, West Sussex, UK: Wiley Blackwell; 2013. p. 374-391.
4. European Influenza Surveillance Network (EISN). Influenza case definitions. Clinical criteria. Influenza-like illness (ILI). European Centre for Disease Prevention and Control (ECDC) 2005-2012; Available: [http://ecdc.europa.eu/en/activities/surveillance/EISN/surveillance/Pages/influenza\\_case\\_definitions.aspx](http://ecdc.europa.eu/en/activities/surveillance/EISN/surveillance/Pages/influenza_case_definitions.aspx). Accessed: 2 November 2012

# GIHSN: First step:

1. *Consecutive blinded (exposure or outcome) sampling* of all those who meet clinical criteria for *eligibility*



# GIHSN clinical criteria for “eligibility”, admissions in patients $\geq 5$ years of age (i)\*

Criteria	Valencia	St. Petersburg	Moscow	Turkey	China	ICD 9 Codes	ICD 10 Codes
Acute respiratory infection	X	X	X	X	X	382.9; 460-466	J00-J06, J20-J22, H66.90
Pneumonia and influenza	X	X	X	X	X	480-488	J09-J18
Acute myocardial infarction or acute coronary syndrome	X			X	X	410-411 and 413-414	I20-I25.9
Asthma	X			X	X	493-493.92	J45.2-J45.22, J45.9-J45.998, J44-J44.9
Heart failure	X			X	X	428-429.0	I50-I50.9; I51.4
Chronic obstructive pulmonary disease	X			X	X	490, 491, 492, 496	J40-J44.9
Myalgia	X			X	X	729.1	M79.1
Metabolic failure (diabetic coma, renal dysfunction, acid-base disturbances, alterations to the water balance)	X			X	X	250.1- 250.3; 584-586; 276-277	E11.9, E10.9, E11.65, E10.65, E10.11, E11.01, E10.641, E11.641, E10.69, E11.00, E10.10, E11.69, N17.0, N17.1, N17.2, N17.8, N17.9, N18.1, N18.2, N18.3, N18.4, N18.5, N18.6M N18.9, N19, E87.0, E87.1, E87.2, E87.3, E87.4, E87.5, E87.6, E87.70, E87.71, E87.79, E86.0, E86.1

\* GIHSN. Hospitalizations with influenza in the Northern Hemisphere during the 2013–2014 influenza season: Preliminary results from the Global Influenza Hospital Surveillance Network. Manuscript draft for discussion.

## GIHSN clinical criteria for “eligibility”, admissions in patients $\geq 5$ years of age (ii)\*

Criteria	Valencia	St. Petersburg	Moscow	Turkey	China	ICD 9 Codes	ICD 10 Codes
Altered consciousness, convulsions, febrile-convulsions	X			X	X	780.01-780.02; 780.09; 780.31-780.32	R40.20, R40.4, R40.0, R40.1, R56.00, R56.01
Dyspnea/respiratory abnormality	X			X	X	786.0	R06.0, R06-R06.9
Respiratory abnormality	X			X	X	786.00	R06.9
Shortness of breath	X			X	X	786.05	R06.02
Respiratory abnormality nec	X			X	X	786.09	R06.3, R06.00, R06.09, R06.83
Respiratory symptoms/chest symptoms	X			X	X	786.9	R06.89
Fever or fever unknown origin or non-specified	X			X	X	780.6-780.60	R50, R50.9
Cough	X			X	X	786.2	R05
Sepsis, Systemic inflammatory response syndrome	X			X	X	995.90-995.94	R65.10, R65.11, R65.20, A41.9

X indicates that the diagnosis code was used at the indicated coordinating site.

\* GIHSN. Hospitalizations with influenza in the Northern Hemisphere during the 2013–2014 influenza season: Preliminary results from the Global Influenza Hospital Surveillance Network. Manuscript draft for discussion.

# GIHSN: Second step

2. ILI\*  
symptoms  
onset  
within 7  
days ( $\geq 5$  y  
old)  
previous to  
admission

(\*)

## Clinical Criteria

Any person with at least one of the following clinical forms:

### Influenza-like illness (ILI) Not required

- Sudden onset of symptoms

at least one of the following four systemic symptoms:

- Fever or feverishness
- Malaise
- Headache
- Myalgia

*And* at least one of the following three respiratory symptoms:

- Cough
- Sore throat
- Shortness of breath

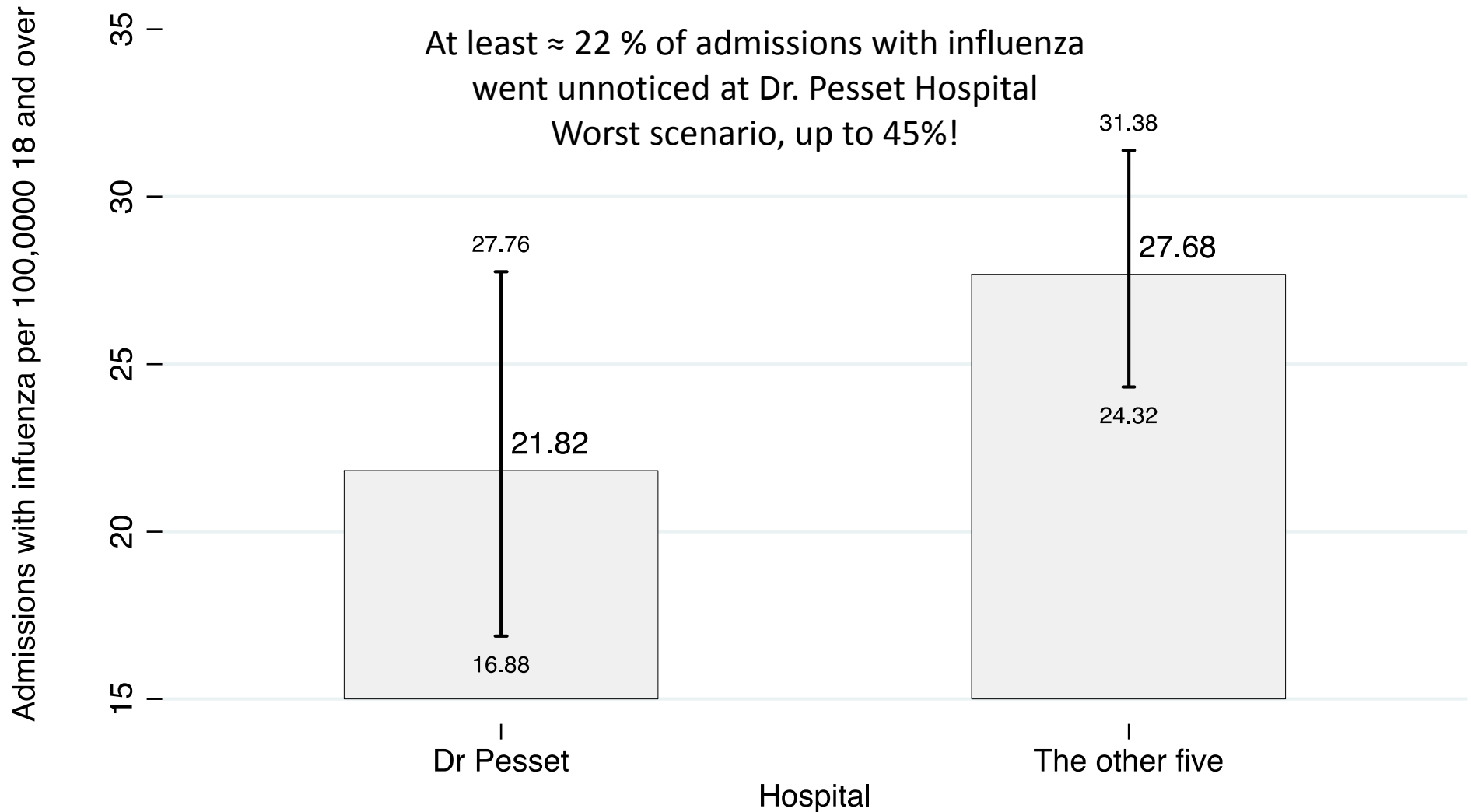
\* European Influenza Surveillance Network (EISN). Influenza case definitions. Clinical criteria. Influenza-like illness (ILI). European Centre for Disease Prevention and Control (ECDC) 2005-2012; Available: [http://ecdc.europa.eu/en/activities/surveillance/EISN/surveillance/Pages/influenza\\_case\\_definitions.aspx](http://ecdc.europa.eu/en/activities/surveillance/EISN/surveillance/Pages/influenza_case_definitions.aspx). Accessed: 2 November 2012

The Hospital Dr. Pesset experience  
applying a narrow set of eligibility criteria.  
2013-2014 season

Criteria	ICD 9 Codes
Acute respiratory infection	382.9; 460-466
Pneumonia and influenza	480-488
Asthma	493-493.92
Chronic obstructive pulmonary disease	490, 491, 492, 496
Dyspnea / Shortness of breath / respiratory abnormality	786.0; 786.00; 786.05-786.07; 786.09
Fever or fever unknown origin or non-specified	780.6-780.60
Cough	786.2

Admissions per 100,000 according to restricted or per protocol eligibility criteria

Dr Pesset hospital applied a reduced set, the other 5 hospitals followed the protocol

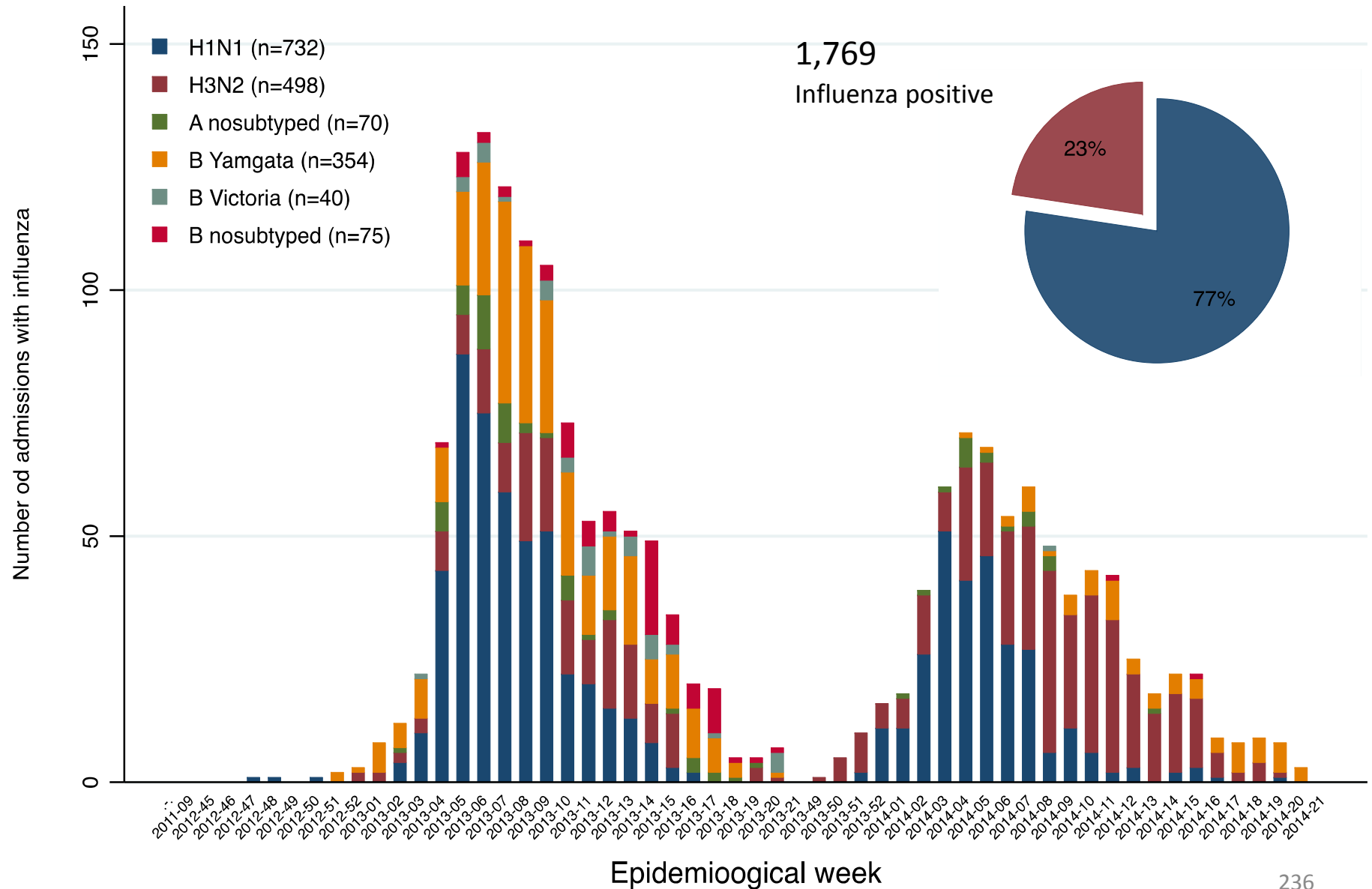


Valencia Hospital Network; 2013-2014 season

Numbers are admissions with influenza per 100,000

# Admissions with influenza by type subtype and epidemiological week patients 18 years old and over

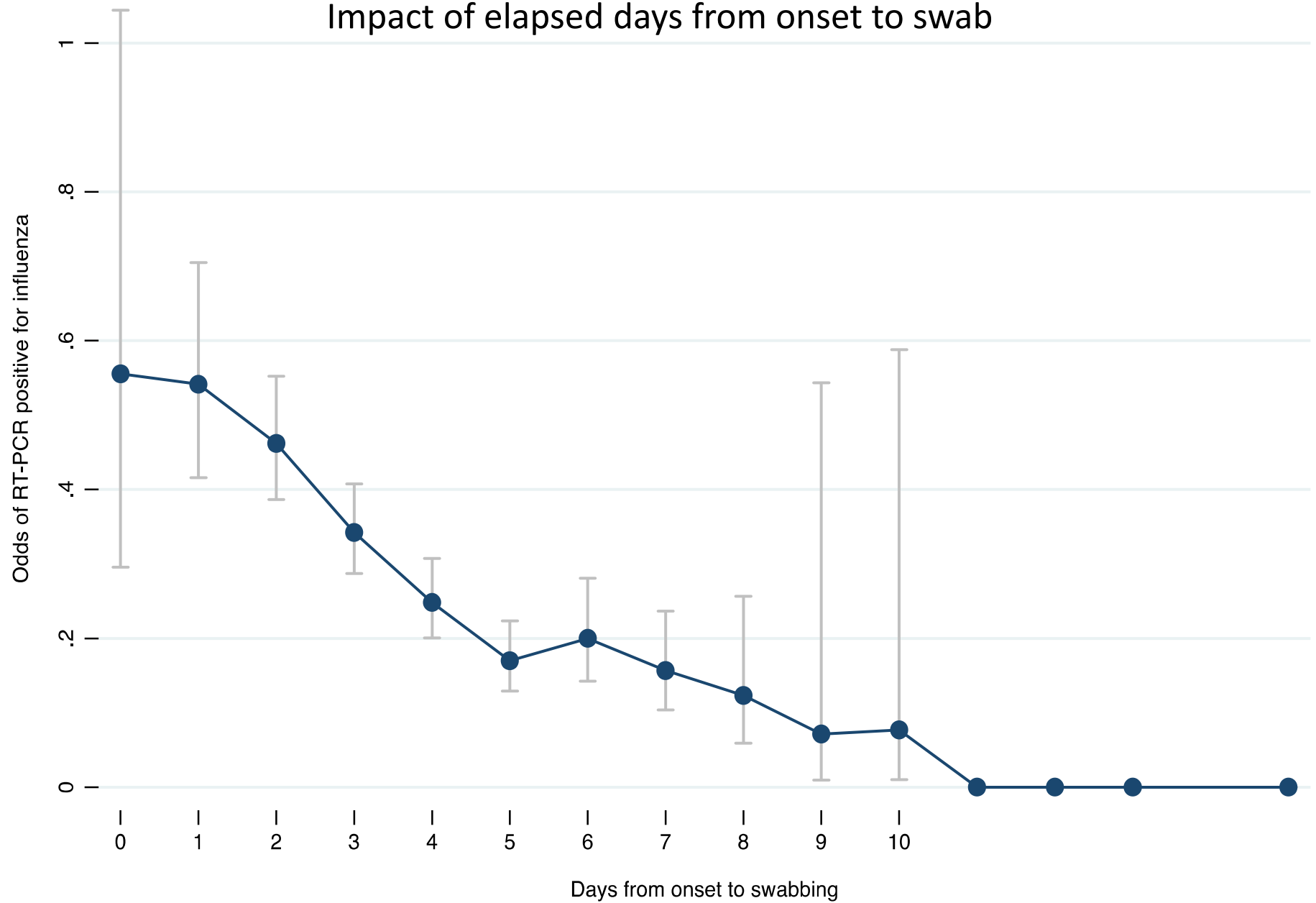
GIHSN 2012-2013 and 2013-2014 study



## Clinical signs and symptoms among admissions according to RT-PCR result ( $\geq 18$ )

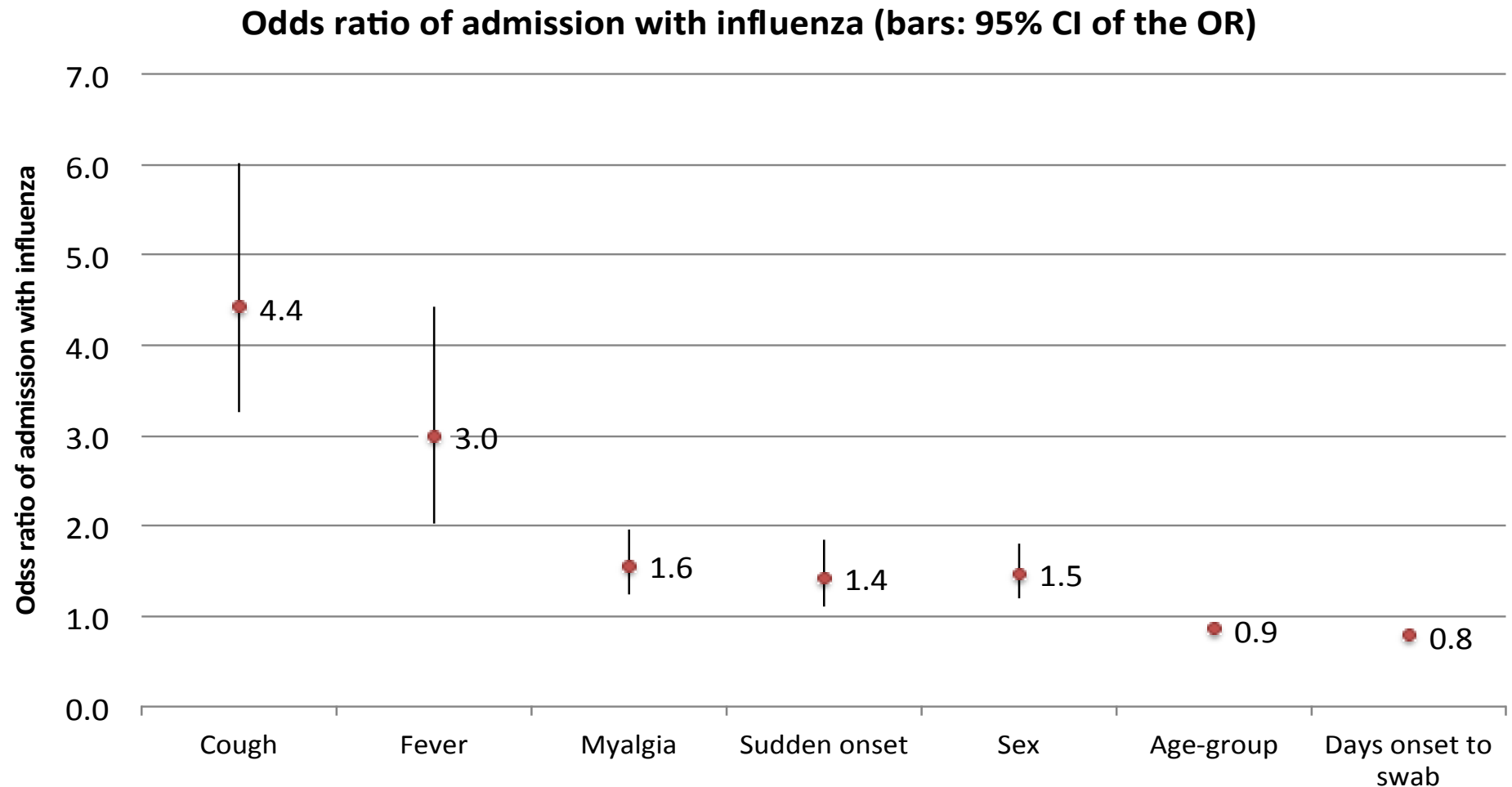
	RT-PCR positive for Influenza				
	No		Yes		P-value
	n	%	n	%	
Cough	3551	75.47	1506	87.35	<0.0001
Fever	3795	80.73	1607	93.21	<0.0001
Sore throat	2021	43	759	44.1	0.4300
Shortness of breath	2736	58.15	671	38.92	<0.0001
Malaise	3535	75.2	1232	71.54	0.0030
Headache	1667	35.47	719	41.78	0.0010
Myalgia	1312	27.91	518	30.15	0.079
Sudden onset	1918	77.56	632	84.83	<0.0001
Fever plus cough	2821	60.03	1408	81.67	<0.0001
Fever, cough and sudden onset	948	29.81	446	52.1	<0.0001

## Impact of elapsed days from onset to swab



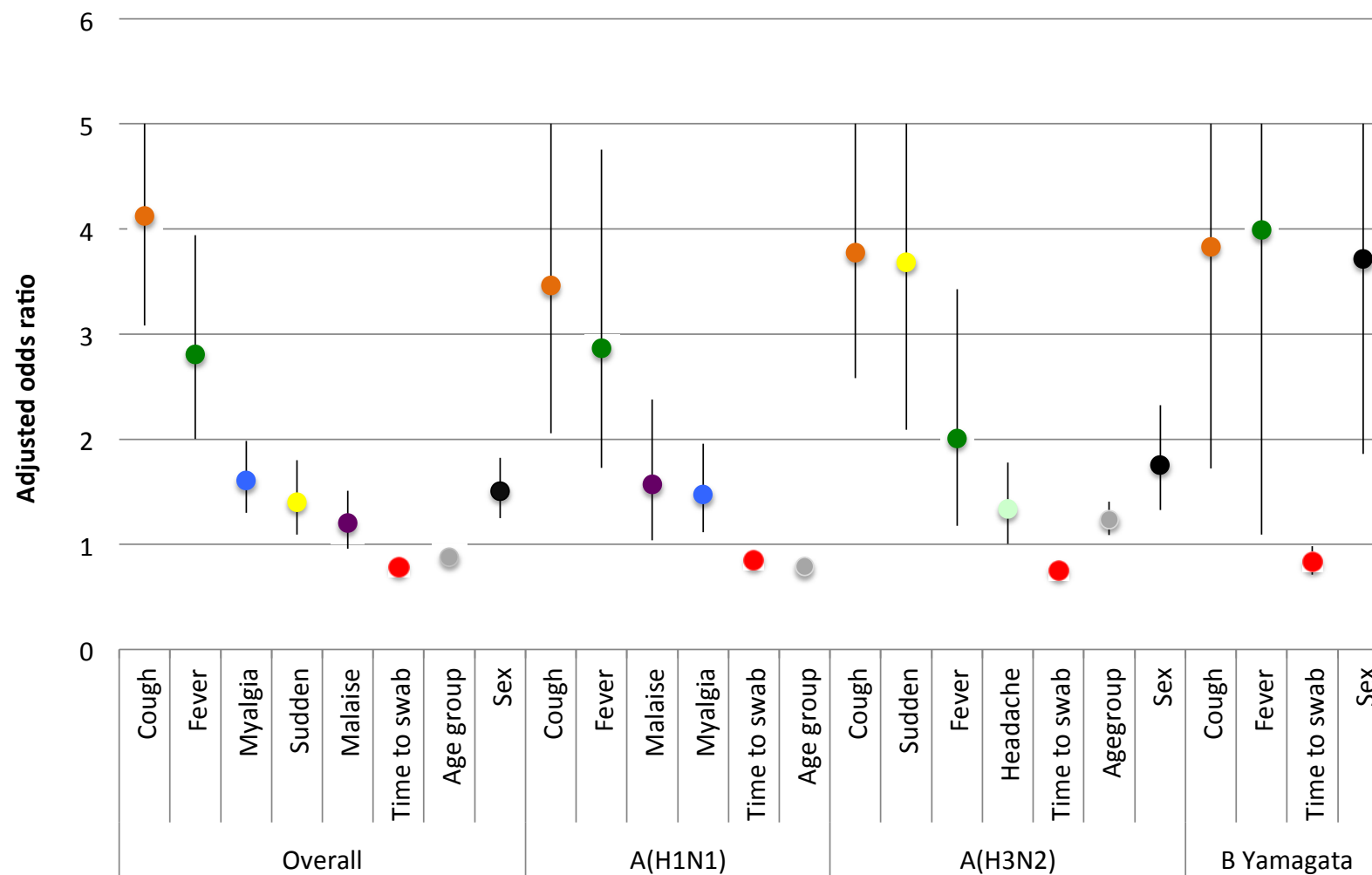


# Clinical signs and symptoms predictors of admission with influenza infection in GHSN patients 18 and over\*



\*stepwise, pr(.15) pe(.1) lockterm1: logistic flu age group sex place sampling time fever malaise headache myalgia cough sore-throat dyspnea sudden-onset

# Clinical signs and symptoms predictors of admission with influenza by type and subtype in patients 18 and over GIHSN 2012-2014



# Isolated clinical signs and symptoms predicting admission with influenza infection.

GIHSN patients (18 and over).

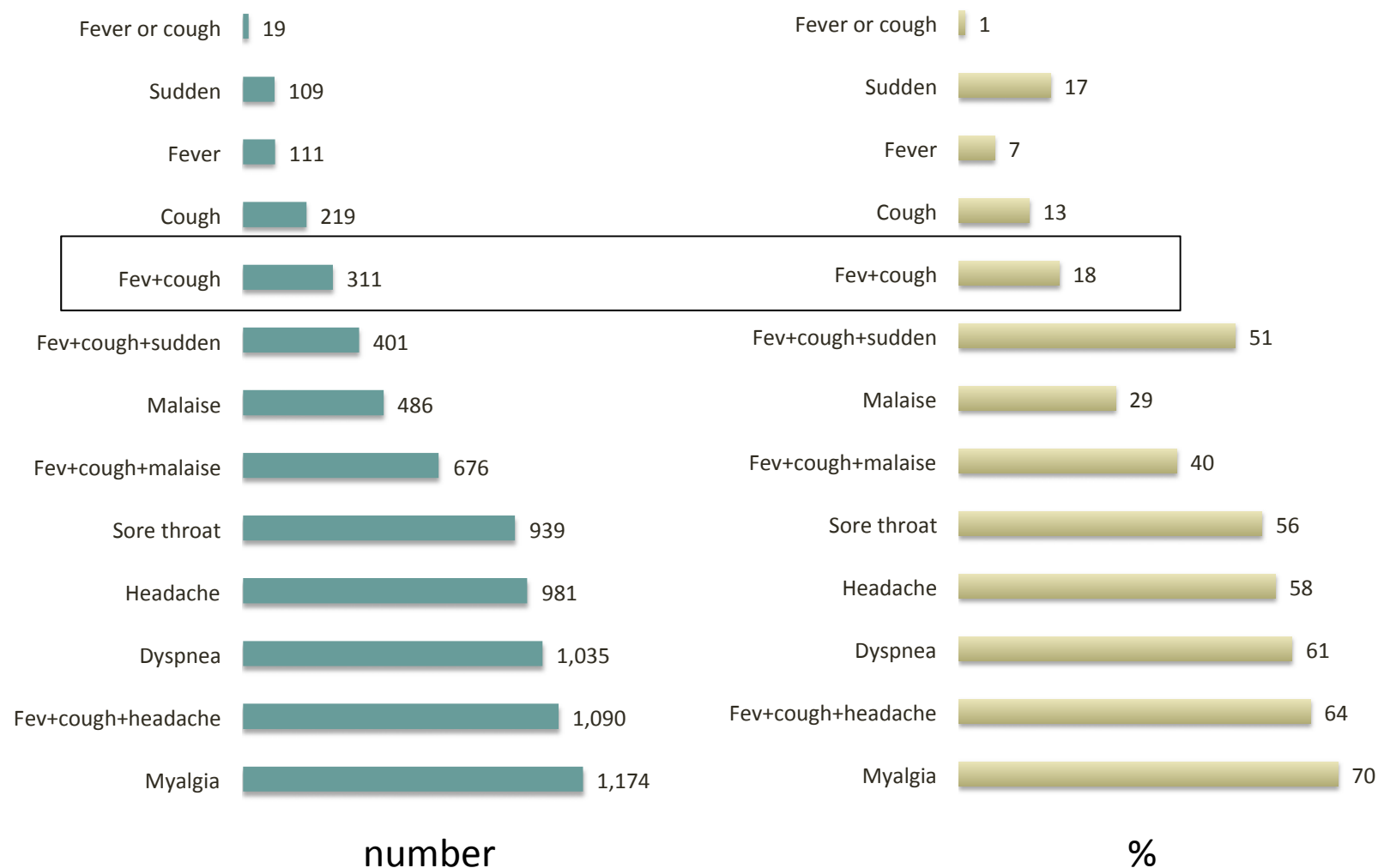
Symptoms	Sensitivity	Specificity	ROC	LR+	LR-	PPV	NPV
	%	%	%			%	%
Fever	94	20	57	1.2	0.3	30	89
Cough	87	23	55	1.1	0.6	30	83
Sudden onset	83	27	55	1.2	0.6	26	66
Malaise	71	24	51	0.9	1.2	26	70
Myalgia	30	72	51	1.1	1.0	27	75
Sore Throat	45	59	52	1.1	1	28	74
Headache	42	65	53	1.2	0.9	31	75
Dyspnea	39	40	40	0.7	1.5	10	64

# Combinations of clinical signs and symptoms predicting admission with influenza infection.

GIHSN patients (18 and over)

Symptoms	Sensitivity	Specificity	ROC	LR+	LR-	PPV	NPV
	%	%	%			%	%
Fever & cough	82	40	61	1.4	0.5	33	86
Fever & cough & sudden onset	52	70	61	1.8	0.7	32	85
Fever & cough & malaise	60	56	58	1.4	0.7	33	79
Fever & cough & headache	36	78	57	1.6	0.8	37	78
Fever & cough & sore throat	32	78	55	1.5	0.9	35	76
<b>Fever OR cough</b>	<b>99</b>	<b>4</b>	<b>51</b>	<b>1</b>	<b>0.3</b>	<b>27</b>	<b>91</b>

## What is lost out of 1769 admissions\* with influenza if the presence of clinical signs and symptoms were required



\*Both, 2012-2013 and 2013-2014 preliminary data (18 and over) with the exception of sudden onset, then 745 influenza cases in 3432 subjects 18 and over (2013-2014 season) considered

# SARI vs. GIHSN (eligibility + ILI (no sudden))

## 2013-2014 season

### (18 years of age and over)

#### **SARI case definition**

An acute respiratory infection with:

- history of fever or measured fever of  $\geq 38\text{ C}^\circ$ ;
- and cough;
- with onset within the last seven days;
- and requires hospitalization.

(WHO) WHO. WHO interim global epidemiological surveillance standards for influenza. 2012. Available:

<http://www.who.int/influenza/resources/documents/INFSURVMANUAL.pdf>.

Accessed: 18 September 2013

# SARI performance when applied to GIHSN included patients

2013-2014 season (18 years of age and over)

Parameter	Estimate	95% Confidence interval	
Prevalence	22%	21%	24%
Sensitivity	83%	80%	86%
Specificity	42%	40%	44%
ROC area	0.62	0.61	0.64
Likelihood ratio (+)	1.43	1.36	1.50
Likelihood ratio (-)	0.40	0.34	0.48
Diagnostic odds ratio	3.55	2.83	4.43
Positive predictive value	29%	27%	31%
Negative predictive value	90%	88%	91%

# SARI vs. GIHSN (eligibility + ILI (no sudden))

2013-2014 season  
(18 years of age and over)

	SARI					
	No		Yes		Total	
	(1,028)		(1,827)		(2,855)	
Influenza	N	%	N	%	N	%
No	921	89.59	1,294	70.83	2,215	77.58
<b>Yes</b>	<b>107</b>	<b>10.41</b>	<b>533</b>	<b>29.17</b>	<b>640</b>	<b>22.42</b>

\* 107 (17%) of 640 GIHSN ascertained influenza cases missed



# SARI vs. GIHSN (eligibility + ILI (no sudden))

2013-2014 season  
(18 years of age and over)

	SARI					
	No (1,028)		Yes (1,827)		Total (2,855)	
	N	%	N	%	N	%
Influenza						
No	921	89.59	1,294	70.83	2,215	77.58
Yes	<b>107</b>	<b>10.41</b>	<b>533</b>	<b>29.17</b>	<b>640</b>	<b>22.42</b>

\* 107 (17%) of 640 GIHSN ascertained influenza cases missed

Reported results are consistent with previous published evidence on the performance of clinical signs and symptoms, and their combinations <sup>(1-5)</sup>

1. Carrat F, Tachet A, Rouzioux C, Housset B, Valleron AJ. Evaluation of clinical case definitions of influenza: detailed investigation of patients during the 1995-1996 epidemic in France. Clin Infect Dis **1999**;28:283-90 Boivin G, Hardy I, Tellier G, Maziade J. Predicting influenza infections during epidemics with use of a clinical case definition. Clin Infect Dis **2000**;31:1166-9
2. Monto AS, Gravenstein S, Elliott M, Colopy M, Schweinle J. Clinical signs and symptoms predicting influenza infection. Arch Intern Med **2000**;160:3243-7
3. Call SA, Vollenweider MA, Hornung CA, Simel DL, McKinney WP. Does this patient have influenza? JAMA **2005**;293:987-97
4. Michiels B, Thomas I, Van Royen P, Coenen S. Clinical prediction rules combining signs, symptoms and epidemiological context to distinguish influenza from influenza-like illnesses in primary care: a cross sectional study. BMC Fam Pract **2011**;12:4
5. Hirve S, Chadha M, Lele P, Lafond KE, Deoshatwar A, Sambhudas S, et al. Performance of case definitions used for influenza surveillance among hospitalized patients in a rural area of India. Bull World Health Organ **2012**;90:804-12

# GIHSN approach

## Strengths

- Consecutive sampling and sensitivity: minimize selection bias
- Specificity: minimize classification bias

## Challenges

- Efficiency:
  - Trade-offs between cost per ascertained case and information lost even if this loss does not introduce a bias.
- Feasibility

# Conclusions

- Overall cough and fever are consistently associated with influenza A and B Yamagata lineage
- Clinical signs and symptoms are of little use for clinical purposes (far from optimal LR+ and LR- values) to rule-in influenza.
- Absence of fever or cough is strongly predictive of no influenza (useful to “rule-out”)

GIHSN uses a flexible ("OR" + "AND" and "reported" vs. "measured") approach to sieve through ***broadly defined eligible consecutive admissions***, previous to swab and RT-PCR, that is well suited to its aims