Impact factor 4.659

Eurosurveillance

Europe's journal on infectious disease epidemiology, prevention and control

Vol. 20 | Weekly issue 22 | 04 June 2015

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Influenza case definitions – optimising sensitivity and specificity

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Citation style for this article:
Penttinen P, Pebody R. Influenza case definitions – optimising sensitivity and specificity. Euro Surveill. 2015;20(22):pii=21148. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=21148

Article submitted on 03 June 2015 / published on 04 June 2015

Clinical case definitions used for surveillance struggle to satisfy two challenging and potentially conflicting needs – sensitivity and specificity. A more sensitive case definition is useful to estimate disease burden and identify outbreaks. It will identify a larger proportion of the true cases, but often at the cost of finding a large number of cases due to other causes. A more specific case definition, however, will provide a more accurate description of true cases. This is important to assess the evolution of the epidemiology and effect of measures such as vaccination, but often comes at the cost of missing true cases [1].

These needs are reflected in the World Health Organization (WHO) surveillance objectives for influenza surveillance [2].

Epidemiological surveillance of influenza relies on the one hand on a specific case definition of influenza-like-illness (ILI), because many influenza symptoms discriminate poorly from other respiratory or systemic illnesses, and on the other hand on a sensitive case definition, so that the start of the influenza season can be detected accurately and promptly. Experts performing influenza surveillance are engaged in a continuous debate of the appropriate composition of symptoms and signs to be used for ILI surveillance [3]. A non-specific clinical case definition could lead to false alerts for the start of the seasonal influenza epidemic, overestimate the burden of disease or the severity of an epidemic and underestimate the effectiveness of influenza vaccines. Likewise, a non-sensitive case definition could underestimate the severity of the epidemic and might fail to detect outbreaks or unusual epidemiological patterns.

Several influenza case definitions are applied internationally. The European Union (EU) case definition [4], used in the European surveillance of influenza differs from the current WHO [5] and the United States' Centers for Disease Control and Prevention (US CDC) [6] case definitions mainly in setting a specific temperature limit for fever (WHO: 38 °C; CDC 37.8 °C (100° F)). The EU case definition does not require fever or a measured temperature and allows for a larger variety of symptoms, therefore it will be more sensitive and less specific as compared with the WHO and CDC definitions. Due to this, for example, seasonal respiratory syncytial virus (RSV) epidemics are more likely to influence the EU influenza surveillance than the WHO and CDC surveillance.

In this issue of *Eurosurveillance* Jiang et al. [7] comprehensively assess the performance of surveillance case definitions for ILI recommended by WHO ('old' and 'new' definition), CDC and ECDC. Their exemplary study builds on previous assessments and also includes data on seroconversion of the infected portions of the cohort under study. The authors monitored symptoms and seroconversion in a cohort of 727 adult subjects in Singapore with up to three serum samples taken per subject before and during the 2009 influenza A(H1N1) pandemic. In total, 13.5% of the cohort seroconverted and 4.6% had presumptive influenza episodes. The authors show that the ECDC ILI case definition is more sensitive, but less specific than the ones recommended by WHO or CDC, mainly due to relying on self-reported history of fever rather than a measured temperature. The current, 'new', WHO case definition with fever defined as body temperature ≥ 38 °C plus cough, has the highest reported positive predictive value (PPV) of the four compared case definitions.

This study is limited in that it has been conducted during a pandemic which affected somewhat different age groups than seasonal influenza usually does. The studied cohort also did not include children, who are heavily affected by both seasonal and pandemic influenza. However, these limitations are unlikely to change the key conclusions suggested by the authors. It is also important to note that the integration of laboratory data based on respiratory sampling of cases can overcome some of the specificity issues and the use of statistical threshold methods, such as the Moving Epidemic Method [8], calculated using comparable, historical

surveillance data can further optimise the performance of national influenza surveillance systems to meet their objectives.

Nonetheless, the analysis of Jiang et al. provides appropriate additional evidence base to further evaluate the optimal use of current surveillance case definitions for ILI in Europe, the US and globally. National reference laboratories for influenza in the EU/European Economic Association (EEA) Member States are National Influenza Centres within the WHO Global Influenza Surveillance and Response System (GISRS), and are obliged to report influenza cases to both WHO and ECDC. Therefore, the two organisations are engaged in a process to gradually join the surveillance systems to the maximum extent possible. Currently all WHO European region countries report on a regular basis to the The European Surveillance System (TESSy – operated by ECDC) influenza cases from sentinel and other systems and as of the 2014–15 influenza season the European surveillance outcomes are reported by ECDC and WHO online on a joint web-based bulletin [9].

Changing case definitions for surveillance is in most cases a complex process at national and international levels, as they are normally agreed upon in a legislative process. Changing a case definition affects the comparability of data over time, which makes surveillance experts reluctant to change established definitions, unless there is an overriding public health need. The case definitions for ILI surveillance have been discussed extensively among the European experts over the past decade, leading to the adoption of the EU case definition as well as part of adopting the recent WHO case definition. The analysis by Jiang et al. will most likely generate a discussion on the need to review, once again, the case definitions currently in use in Europe at the upcoming annual meeting of the European Influenza Surveillance Network in June.

Conflict of interest

Both authors are involved in the coordination of the EU influenza surveillance.

Authors' contributions

PP and RP conceived and wrote this editorial with equal contributions.

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Performance of case definitions for influenza surveillance

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Citation style for this article:
Jiang L, Lee VJ, Lim WY, Chen MI, Chen Y, Tan L, Lin RT, Leo YS, Barr I, Cook AR. Performance of case definitions for influenza surveillance. Euro Surveill. 2015;20(22):pii=21145. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=21145

Article submitted on 27 May 2014 / published on 04 June 2015

Influenza-like illness (ILI) case definitions, such as those from the European Centre for Disease Control and Prevention, World Health Organization (WHO) and United States Centers for Disease Control and Prevention, are commonly used for influenza surveillance. We assessed how various case definitions performed during the initial wave of influenza A(H1N1) pdm09 infections in Singapore on a cohort of 727 patients with two to three blood samples and whose symptoms were reviewed fortnightly from June to October 2009. Using seroconversion (≥4-fold rise) to A/California/7/2009 (H1N1), we identified 36 presumptive influenza A(H1N1)pdm09 episodes and 664 episodes unrelated to influenza A(H1N1)pdm09. Cough, fever and headache occurred more commonly in presumptive influenza A(H1N1)pdm09. Although the sensitivity was low (36%), the recently revised WHO ILI case definition gave a higher positive predictive value (42%) and positive likelihood ratio (13.3) than the other case definitions. Results including only episodes with primary care consultations were similar. Individuals who worked or had episodes with fever, cough or sore throat were more likely to consult a physician, while episodes with Saturday onset were less likely, with some consultations skipped or postponed. Our analysis supports the use of the revised WHO ILI case definition, which includes only cough in the presence of fever defined as body temperature ≥38 °C for influenza surveillance.

Introduction

The emergence of influenza A(H1N1)pdm09 virus, a novel strain of influenza virus A(H1N1), in April 2009 and its subsequent rapid global spread have focused attention on influenza surveillance capabilities worldwide [1]. As one of the main components of influenza surveillance, surveillance for influenza-like illness (ILI) among outpatients or patients of emergency departments can provide early warning of increased influenza virus circulation and information on where influenza activity is occurring, track the course of influenza activity during the season, and serve as a source of samples for virus isolation [2]. It is hence important to have a reliable case definition for ILI. While the presence of fever and selected symptoms of acute respiratory tract infection are common features, case definitions used for ILI differ slightly from country to country and have also changed over time [3-8]. Notably, it remains unclear if any of these specific combinations of symptoms or temperature cut-off point is better than others for influenza surveillance.

There have been a number of studies evaluating the performance of ILI case definitions, but most of these studies were based on outpatients visiting EDs and general practices or hospitalised patients [7-12], which may be subject to biases arising from how different individuals and populations access medical care. Moreover, there have recently been initiatives to use self-reported symptoms based on telephone or Internet surveys for influenza surveillance [13], and it is unclear if ILI case definitions validated on cases seeking medical care are appropriate in such situations. Furthermore, the pattern of medical care consultations in influenza as well as non-influenza related acute illness episodes may also affect the performance of ILI case definitions for influenza surveillance. What is hence needed is a study that can capture data on symptoms in the community, verify which of these might be associated with influenza, and clarify how individual and episode level characteristics associated with medical care consultation might affect the quality of ILI surveillance data [2,14,15].

Singapore, a tropical south-east Asian city-state and global travel hub, detected its first imported case of

influenza A(H1N1)pdm09 in late May 2009. Sustained community transmission started in late June 2009, with epidemic activity peaking in early August and subsiding in September 2009 [16]. In this study, we exploited the combination of serological investigations and self-reported data on symptoms and medical consultations from a cohort established in the run-up to the pandemic to compare the ILI case definitions used by the European Centre for Disease Prevention and Control (as mandated by the European Union for communicable disease reporting, and henceforth abbreviated as EU-ECDC) [3,17], the United States Centers for Disease Control and Prevention (US-CDC) [6] and the World Health Organization (WHO) (previously used ('old') [4] and the January 2014 revised ('new') [5]) with regard to sensitivity, specificity, predictive value and likelihood ratio. We also illustrate the performance of various ILI-based approaches to estimating influenza incidence during the first wave of influenza A(H1N1) pdm09 in Singapore. Finally, we assessed factors associated with primary care consultation, to highlight how consultation patterns vary by population subgroups, disease, symptoms and timing, as these factors may additionally complicate the interpretation of ILI surveillance data.

Methods

Study design and recruitment

This prospective community cohort study was part of a larger study to determine serological conversion to influenza A(H1N1)pdm09 virus in different populations [18-20]. We recruited 838 community-dwelling adults aged 21–75 years and aimed to get three blood samples from each participant. Banked samples were used for the baseline sample (sample 1); these were obtained during 29 June 2005 to 27 June 2009, before widespread community transmission of influenza A(H1N1) pdm09 virus in Singapore. Two additional blood samples were obtained: an intra-epidemic sample (sample 2) collected about four weeks after the peak of the epidemic (20–29 August 2009) and a post-epidemic sample (sample 3) collected about four weeks after the epidemic had subsided (6–11 October 2009). Only individuals who contributed at least two blood samples were included in this analysis.

A baseline telephone interview with a standardised questionnaire was conducted at recruitment, followed by fortnightly interviews throughout the epidemic period for new onset of the following symptoms, with dates of onset for each of the individual symptoms collected:

- respiratory symptoms – cough, sore throat, runny or blocked nose and breathlessness;
- constitutional symptoms – fever, myalgia and headache;
- gastrointestinal symptoms – abdominal pain, nausea, vomiting and diarrhoea.

All participants provided written consent, and the study was approved by the Institutional Review Board of the National University of Singapore.

Laboratory methods and definition of seroconversion

Haemagglutination-inhibition assay was performed according to standard protocols of the WHO Collaborating Centre for Reference and Research on Influenza in Melbourne, Australia, as previously described [18]. We defined seroconversion as a fourfold or greater increase in antibody titres to influenza A/California/7/2009 (H1N1) pandemic virus between any successive pairs of blood samples. For each subject, we assigned a 'seroconversion date', against which the timing of various illness episodes was assessed. This would be the date of collection of sample 2 if seroconversion had occurred by then, regardless of additional changes in titre in sample 3. We also recorded the date of sample 3 collection if seroconversion was detected then but not in sample 2.

Illness episodes and case definitions

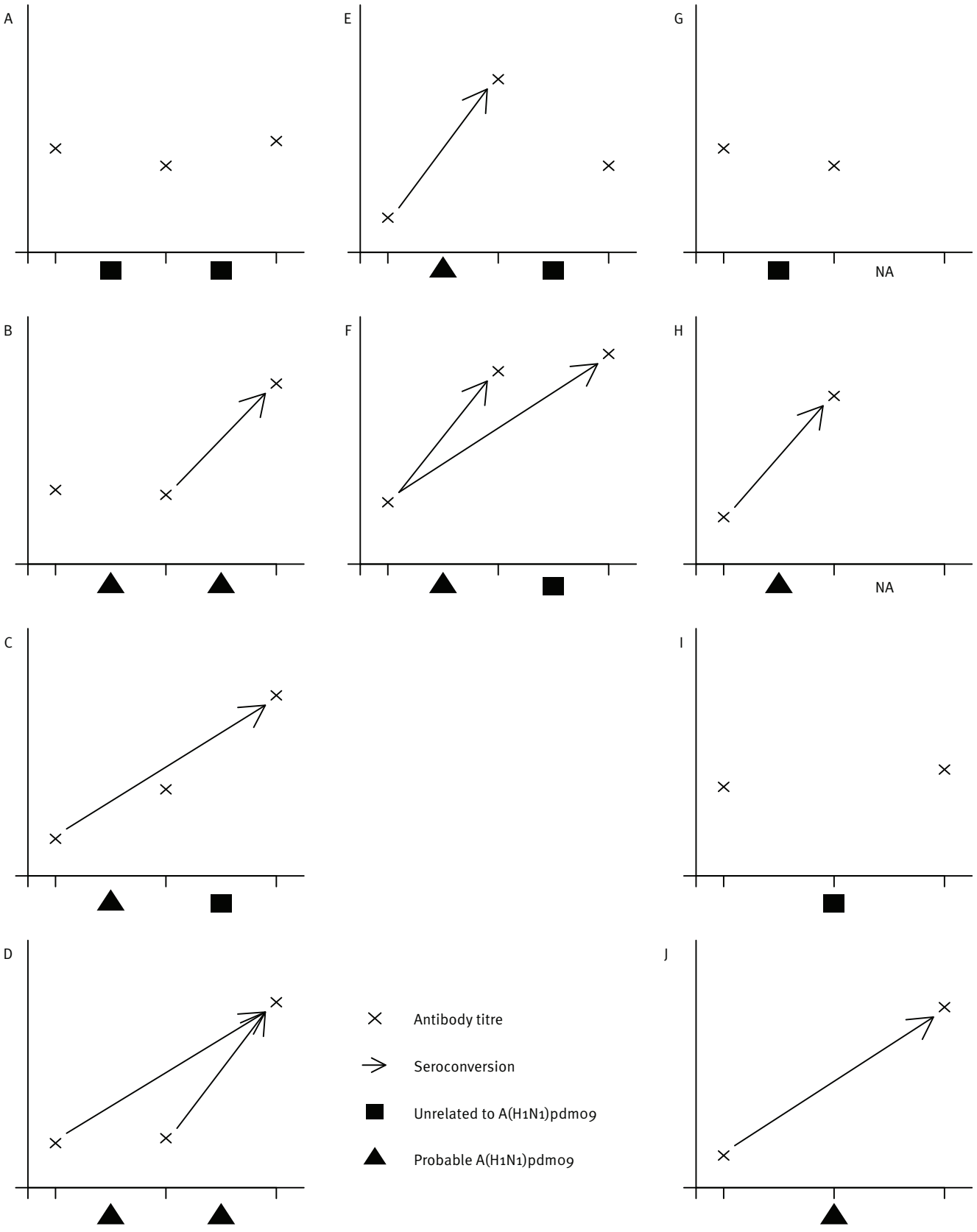
We defined an illness episode as acute onset of at least one of the symptoms listed in the earlier section on study design and recruitment. As symptoms due to an infection could start on different days, we defined onset of an illness episode as a cluster of symptoms starting within seven days of each other, and defined the onset date of that illness episode based on the earliest symptom in the cluster. Any symptoms starting after these seven days were then considered as part of a new illness episode. Since infection with influenza A(H1N1)pdm09 and the resultant illness episode had to have an onset date consistent with the seroconversion date, we therefore defined a probable influenza A(H1N1)pdm09-related episode as an episode in which the earliest symptom occurred at least one day before the seroconversion date. Illness episodes occurring on or after the day when seroconversion was detected, or in individuals who did not seroconvert, could then be classified with some certainty as being unrelated to influenza A(H1N1)pdm09. All combinations of episode occurrences relative to seroconversion, and how these are classified, are given in Figure 1. In some seroconverting individuals, there was more than one probable influenza A(H1N1)pdm09-related episode, based on the timing of symptoms. Since we cannot definitively identify which of these episodes was caused by influenza A(H1N1)pdm09, we opted to exclude such observations, and thus defined a presumptive influenza A(H1N1)pdm09 episode as those episodes that occurred in individuals who had only a single probable influenza A(H1N1)pdm09-related episode.

Several specific case definitions commonly used for influenza surveillance were analysed:

- acute respiratory illness (ARI) – we defined an ARI episode as acute onset of any of the following respiratory symptoms: cough, shortness of breath,

Figure 1

Permutations of illness episode occurrence relative to seroconversion and classification of illness episode



NA: not applicable.

Algorithm for classifying illness episodes as probable influenza A(H1N1)pdm09-related (triangles) and unrelated to influenza A(H1N1)pdm09 (boxes), based on when seroconversion (arrows, which denote a fourfold or greater increase in antibody titre) occurred. We defined a probable influenza A(H1N1)pdm09-related episode as an episode in which the earliest symptom occurred at least one day before the seroconversion date.

The vertical axis and horizontal axis denote antibody titre and time respectively using an arbitrary scale. The right-hand part of the horizontal axis is not applicable if only the first two blood samples are collected.

Episodes that occur in the corresponding time intervals with different permutations for seroconversion are classified as shown in panels A to J.

sore throat or nasal congestion (runny nose or blocked nose);

- febrile respiratory illness (FRI) – ARI with self-reported fever, regardless of body temperature measurement;
- modified EU-ECDC ILI – sudden onset of symptoms with one or more respiratory symptoms (cough, sore throat and/or shortness of breath) plus one or more systemic symptoms (self-reported fever, headache and/or myalgia); this is an approximation of the EU-ECDC ILI case definition [3,17] (which additionally has malaise as one of the systemic symptoms);
- US-CDC ILI – fever defined as body temperature ≥ 37.8 °C plus cough and/or sore throat in the absence of a known cause other than influenza [6];
- WHO old ILI – sudden onset of fever defined as body temperature › 38 °C plus either cough or sore throat [4];
- WHO new ILI – fever defined as body temperature ≥ 38 °C plus cough and with onset within the last 10 days [5].

Statistical analysis

To assess the performance of different case definitions, we compared how well different symptoms, as well as commonly used case definitions, could distinguish presumptive influenza A(H1N1)pdm09 episodes from those classified as unrelated to influenza A(H1N1) pdm09. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), odds ratio (OR), positive likelihood ratio (LR+), negative likelihood ratio (LR–) and 95% confidence intervals (CIs) for OR, LR+ and LR– were calculated.

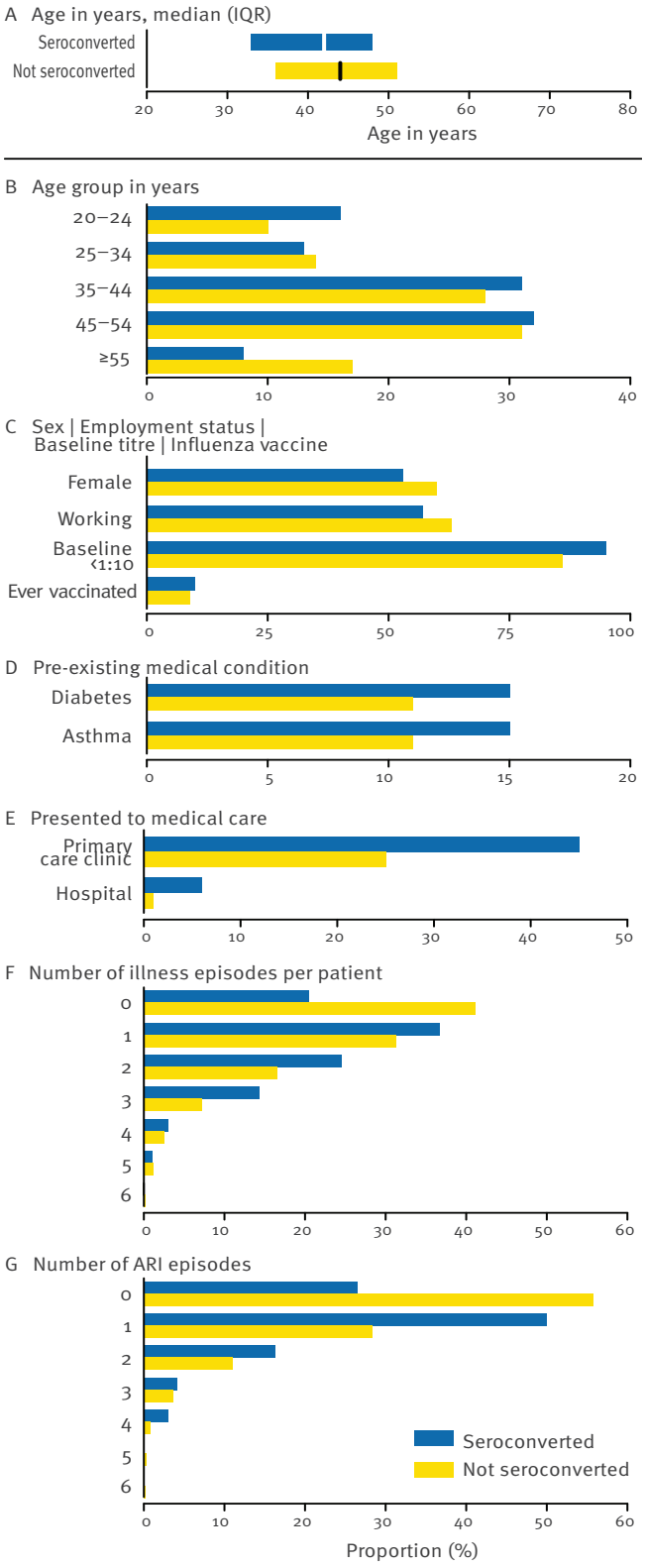
For each case definition, we also used the total number of episodes per 100 individuals, the number of episodes involving primary care consultation per 100 individuals, and the proportion of individuals who ever had such an episode, to illustrate how these measures might perform in monitoring the progress of an epidemic compared with virological surveillance of ILI based on positive samples from sentinel general practices submitting respiratory samples to the National Public Health Laboratory. We also compared the respective estimates of influenza attack rates with serological data.

Finally, we investigated if demographics, timing of episode onset by day of the week and nature of symptoms affected presentation to primary care, with the outcome of interest being whether that illness episode was associated with a primary care consultation within seven days after onset.

Because each individual could have had more than one illness episode during the whole study period, a multilevel model was used in all logistic regression analyses to control for the effects of multiple episodes in the same individual. All statistical analysis was done with

Figure 2

Characteristics of participants, by seroconversion status, included in study of case definition performance for influenza surveillance, Singapore, June–October 2009 (n = 727)



ARI: acute respiratory illness; IQR: interquartile range.

A. Median age in years (central line), interquartile range. Proportion (%) of individuals by (B) age group; (C) sex, employment status, baseline haemagglutination-inhibition assay titre < 1:10 and ever had previous influenza vaccination; (D) pre-existing medical conditions; (E) presented to medical care; (F) number of illness episodes per patient; and (G) number of ARI episodes. Blue and yellow bars represent those who seroconverted and those who did not seroconvert respectively.

Table 1

Comparison of symptoms between presumptive and episodes unrelated to influenza A(H1N1)pdm09, Singapore, June–October 2009 (n = 700)

Episodes	Symptoms	Number of cases by serological classification		Sensitivity %	Specificity %	PPV %	NPV %	Crude OR (95% CI)	Adjusted OR (95% CI)
		A(H1N1) pdm09[a]	Unrelated[b]						
All reported episodes	Respiratory								
	Cough	30	248	83	63	11	99	8.4 (3.4–20.5)	8.8 (3.5–21.9)
	Shortness of breath	3	19	8	97	14	95	3.1 (0.9–11.0)	1.2 (0.2–7.4)
	Sore throat	13	139	36	79	9	96	2.1 (1.1–4.3)	0.9 (0.4–2.1)
	Nasal congestion	16	226	44	66	7	96	1.6 (0.8–3.1)	1.0 (0.5–2.2)
	Constitutional								
	Fever (self-reported)[c]	18	92	50	86	16	97	6.2 (3.1–12.5)	4.3 (1.8–10.2)
	Myalgia	8	85	22	87	9	95	2.0 (0.9–4.4)	1.2 (0.5–3.1)
	Headache	13	141	36	79	8	96	2.1 (1.0–4.3)	3.1 (1.3–7.8)
	Gastrointestinal								
	Abdominal pain	0	33	0	95	0	95	NC	NC
	Nausea and/or vomiting	2	45	6	93	4	95	0.8 (0.2–3.5)	1.0 (0.1–7.3)
	Diarrhoea	3	90	8	86	3	95	0.6 (0.2–1.9)	0.9 (0.2–3.7)
Episodes with primary care consultation	Respiratory								
	Cough	16	100	89	50	14	98	8.1 (1.8–35.8)	17.2 (3.8–87.9)
	Shortness of breath	2	7	11	97	22	92	3.5 (0.7–18.1)	2.0 (0.1–49.0)
	Sore throat	11	63	61	69	15	95	3.4 (1.3–9.4)	2.4 (0.7–8.2)
	Nasal congestion	11	81	61	60	12	94	2.3 (0.9–6.3)	1.03 (0.3–3.7)
	Constitutional								
	Fever (self-reported)[c]	11	57	61	72	16	95	4.0 (1.5–10.7)	3.9 (1.1–13.6)
	Myalgia	4	32	22	84	11	92	1.5 (0.5–4.9)	0.3 (0.1–1.3)
	Headache	10	39	56	81	20	95	5.2 (1.9–14.0)	21.2 (5.2–86.4)
	Gastrointestinal								
	Abdominal pain	0	11	0	95	0	91	NC	NC
	Nausea and/or vomiting	0	20	0	90	0	91	NC	NC
	Diarrhoea	0	24	0	88	0	91	NC	NC

CI: confidence interval; NC: not calculable and omitted in logistic regression analyses; NPV: negative predictive value; OR: odds ratio; PPV: positive predictive value.

[a] Number of presumptive influenza A(H1N1)pdm09 episodes where n = 36 for all episodes, and n = 18 for episodes with primary care consultation.

[b] Number of episodes unrelated to influenza A(H1N1)pdm09 where n = 664 for all episodes, and n = 201 for episodes with primary care consultation.

[c] Self-reported feeling of having a fever.

Stata 11.0 and R version 3.0.0; p values reported are two-tailed, with a significance level of 0.05.

Results

Our analysis included 727 individuals who provided two or more blood samples (Figure 2), of whom 98 (13.5%) seroconverted. Those who seroconverted were significantly younger (42.4 vs 44.3 years, p = 0.027), more likely to have baseline haemagglutination-inhibition assay titres < 1:10 (94.9% (95% CI: 88.6–97.8) vs 85.5% (95% CI: 82.6–88.1), p = 0.011) and more likely to report illness episodes (79.6% (95% CI: 70.3–87.1) vs 58.8% (95% CI: 54.9–62.7), p < 0.001) and ARI (73.5% (5% CI: 63.6–81.9) vs 44.2% (95% CI: 40.3–48.2), p < 0.001). About a quarter (n = 159, 25.3% (95% CI: 21.9–28.9)) of non-seroconverting individuals had a primary care consultation compared with almost half (n = 44, 44.9% (95% CI: 34.8–55.3), p < 0.001) of those who seroconverted; the difference was even more marked for visits to hospital (1% (95% CI: 0.4–2.1) vs 6% (95% CI: 2.3–12.9) respectively, p = 0.002). However, even in those who seroconverted, the majority (n = 44, 95.7% (95% CI: 85.2–99.5)) of consultations were at primary care, and of the six individuals who sought care at a hospital, only two did not also first have a primary care consultation.

Table 2

Performance of case definitions in distinguishing presumptive influenza A(H1N1)pdm09 from unrelated illness episodes, Singapore, June–October 2009 (n = 700)

Episodes	Case definition[a]	Number of cases by serological classification		Sensitivity %	Specificity %	PPV %	NPV %	LR+ (95% CI)	LR– (95% CI)
		A(H1N1) pdm09[b]	Unrelated[c]						
All reported episodes	ARI	33	432	92	35	7	99	1.4 (1.3–1.6)	0.2 (0.1–0.7)
	FRI	18	66	50	90	21	97	5.0 (3.4–7.5)	0.6 (0.4–0.8)
	Modified EU-ECDC ILI	22	99	61	85	18	95	4.1 (3.0–5.6)	0.5 (0.3–0.7)
	US-CDC ILI	14	31	39	95	31	97	8.3 (4.9–14.2)	0.6 (0.5–0.8)
	WHO old ILI	13	20	36	97	39	97	12.0 (6.5–22.1)	0.7 (0.5–0.8)
	WHO new ILI	13	18	36	97	42	97	13.3 (7.1–25.0)	0.7 (0.5–0.8)
Episodes with primary care consultation	ARI	17	147	94	27	10	98	1.3 (1.1–1.5)	0.2 (0.0–1.4)
	FRI	11	41	61	80	21	96	3.0 (1.9–4.7)	0.5 (0.3–0.9)
	Modified EU-ECDC ILI	14	54	78	73	21	97	2.9 (2.1–4.1)	0.3 (0.1–0.7)
	US-CDC ILI	9	19	50	91	32	95	5.3 (2.8–9.9)	0.6 (0.4–0.9)
	WHO old ILI	8	13	44	94	38	95	6.9 (3.3–14.4)	0.6 (0.4–0.9)
	WHO new ILI	8	11	44	95	42	95	8.1 (3.8–17.6)	0.6 (0.4–0.9)

ARI: acute respiratory illness; CI: confidence interval; ECDC: European Centre for Disease Prevention and Control; EU: European Union; FRI: febrile respiratory illness; ILI: influenza-like illness; LR+: positive likelihood ratio; LR–: negative likelihood ratio; NPV: negative predictive value; PPV: positive predictive value; US-CDC: United States Centers for Disease Control and Prevention; WHO: World Health Organization.

[a] ARI: we defined an ARI episode as acute onset of any of the following respiratory symptoms: cough, shortness of breath, sore throat or nasal congestion (runny nose or blocked nose). FRI: ARI with self-reported fever, regardless of body temperature measurement. Modified EU-ECDC ILI: one or more respiratory symptoms (cough, sore throat and/or shortness of breath) plus one or more systemic symptoms (self-reported fever, headache and/or myalgia); this is an approximation of the EU-ECDC ILI case definition [3,17] (which additionally has malaise as one of the systemic symptoms). US-CDC ILI: fever defined as body temperature ≥ 37.8 °C together plus cough and/or sore throat in the absence of a known cause other than influenza [6]. WHO old ILI: fever defined as body temperature > 38 °C plus either cough or sore throat [4]. WHO new ILI: fever defined as body temperature ≥ 38 °C plus cough [5].

[b] Number of presumptive influenza A(H1N1)pdm09 episodes where n = 36 for all episodes, and n = 18 for episodes with primary care consultation.

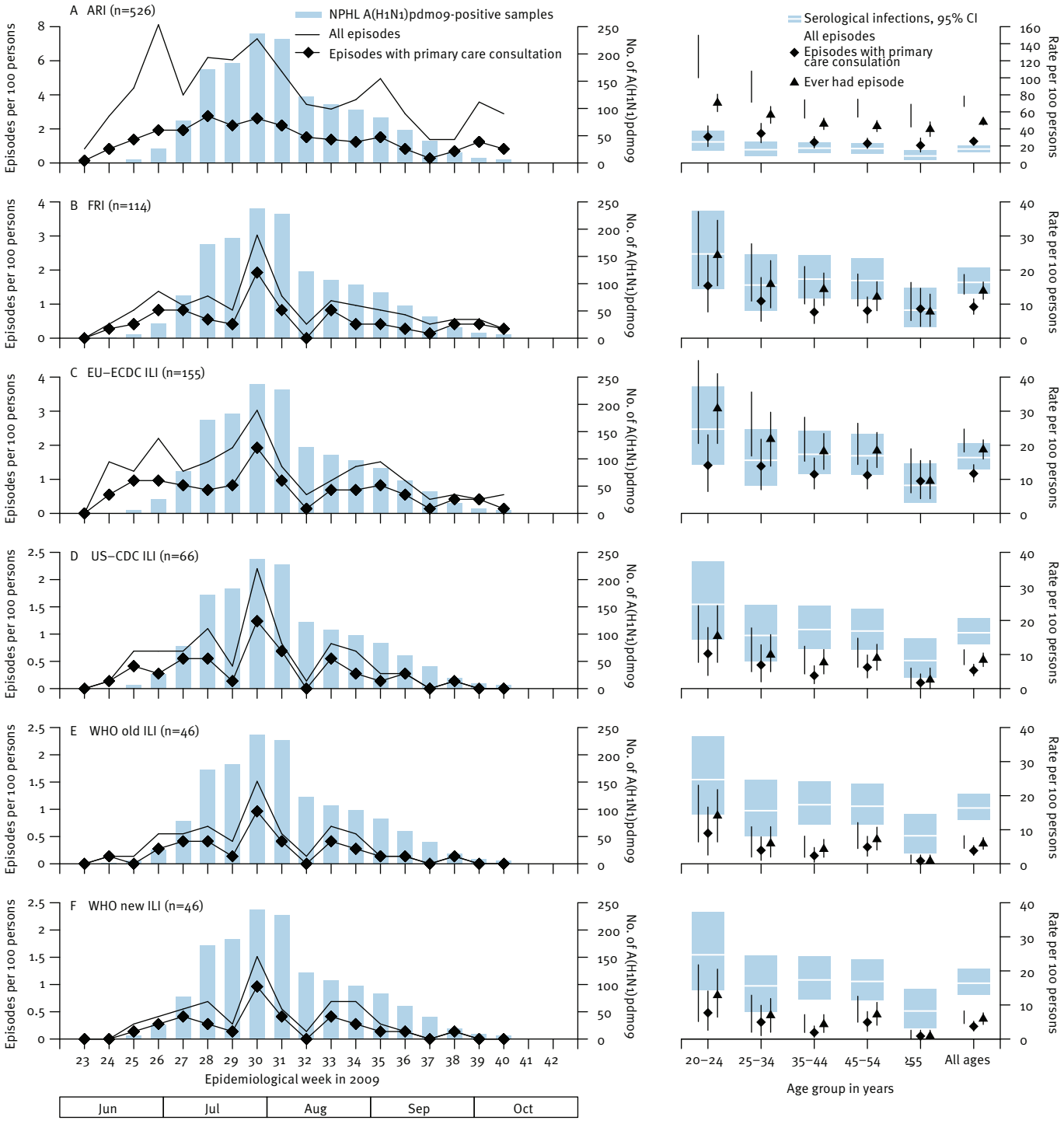
[c] Number of episodes unrelated to influenza A(H1N1)pdm09 where n = 664 for all episodes, and n = 201 for episodes with primary care consultation.

Of 788 reported illness episodes, there were 36 (4.6%) presumptive influenza A(H1N1)pdm09 episodes and 664 (84.3%) episodes unrelated to influenza A(H1N1) pdm09; the corresponding numbers were 18 (7.2%) and 201 (80.7%) if restricting to those episodes with primary care consultation (n = 249). Reported symptoms for presumptive influenza A(H1N1)pdm09 episodes and episodes unrelated to influenza A(H1N1) pdm09 are shown in Table 1. Among the 36 presumptive influenza A(H1N1)pdm09 episodes, cough (n = 30) and fever (n = 18) were the most common respiratory and constitutional symptoms respectively, while gastrointestinal symptoms were rare. Cough, sore throat, fever and headache were significantly more common among presumptive influenza A(H1N1)pdm09 episodes in the univariate analysis; with the exception of sore throat, these were also significant in the multivariate analysis. The ORs for cough, fever and headache in the multivariate model were 8.8, 4.3 and 3.1 respectively. Results for the small number of presumptive influenza A(H1N1)pdm09 episodes for which there had been primary care consultation were similar.

The performance of different case definitions in distinguishing presumptive influenza A(H1N1)pdm09 from unrelated illness episodes is shown in Table 2. Of the 36 presumptive influenza A(H1N1) pdm09 episodes identified, only three did not fulfil any of the case definitions we assessed (one episode where only headache was reported, and two episodes which both had nausea and vomiting only). Among all the case definitions we looked at, ARI gave the highest sensitivity (92%) but the lowest specificity (35%). Using FRI improved the specificity to 90% but reduced the sensitivity to 50%. Among the four ILI case definitions, the modified EU-ECDC ILI case definition was more sensitive (61%) than for FRI but less specific (85%). The other three ILI case definitions had similar sensitivity (36–39%) and specificity (95–97%). On comparing predictive values and likelihood ratios, all four case definitions gave similar NPVs (95–97%), but the WHO new ILI case definition had the highest PPV (42%), followed by the WHO old ILI case definition (39%), the US-CDC ILI case definition (31%) and the modified EU-ECDC ILI case definition (18%). Similarly, while all case definitions gave similar LR–, the WHO new ILI case definition had the highest LR+ (13.32), followed by the WHO old ILI case definition (11.99), US-CDC ILI case definition (8.33) and the modified EU-ECDC case definition (4.10). The performance of the four ILI case definitions relative to

Figure 3

Illness episode rates using different case definitions for all episodes and episodes involving primary care consultation compared with laboratory surveillance and serological attack rates, Singapore, June–October 2009



ARI: acute respiratory illness; CI: confidence interval; ECDC: European Centre for Disease Prevention and Control; EU: European Union; FRI: febrile respiratory illness; ILI: influenza-like illness; NPHL: National Public Health Laboratory; US-CDC: United States Centers for Disease Control and Prevention; WHO: World Health Organization.

Left-hand graphs: number of episodes per 100 persons obtained from the case definition (lines) and number of influenza A(H1N1)pdm09 samples obtained from sentinel general practices (bars), by epidemiological week of the episode onset date, from week 23 (7 June 2009 to 13 June 2009) to week 40 (4 October 2009 to 10 October 2009). Right-hand graphs: rates per 100 persons from serological infections (midline with bars giving 95% CIs) and estimated rates from the case definitions (lines). Panels A to F are for ARI, FRI, EU-ECDC ILI, US-CDC ILI, WHO old ILI, and WHO new ILI case definitions.

ARI: we defined an ARI episode as acute onset of any of the following respiratory symptoms: cough, shortness of breath, sore throat or nasal congestion (runny nose or blocked nose). FRI: ARI with self-reported fever, regardless of body temperature measurement. Modified EU-ECDC ILI: one or more respiratory symptoms (cough, sore throat and/or shortness of breath) plus one or more systemic symptoms (self-reported fever, headache and/or myalgia); this is an approximation of the EU-ECDC ILI case definition [3,17] (which additionally has malaise as one of the systemic symptoms). US-CDC ILI: fever defined as body temperature ≥ 37.8 °C together plus cough and/or sore throat in the absence of a known cause other than influenza [6]. WHO old ILI: fever defined as body temperature > 38 °C plus either cough or sore throat [4]. WHO new ILI: fever defined as body temperature ≥ 38 °C plus cough [5].

Table 3

Participant and illness episode-level characteristics associated with seeking primary care, Singapore, June–October 2009 (n = 700 episodes)

Characteristics	Number of episodes	Number (%) with primary care consultation	Crude OR (95% CI)	Adjusted OR (95% CI)
Age group in years				
20–24	101	22 (22)	1.0 (–)	1.0 (–)
25–34	119	45 (38)	2.2 (1.1–4.2)	2.2 (1.0–4.6)
35–44	190	64 (34)	1.8 (1.0–3.3)	1.9 (1.0–3.5)
45–54	200	61 (31)	1.6 (0.9–2.8)	1.8 (0.9–3.6)
≥ 55	90	27 (30)	1.5 (0.8–3.0)	2.1 (0.9–4.7)
Sex				
Male	281	98 (35)	1.0 (–)	1.0 (–)
Female	419	121 (29)	0.8 (0.5–1.1)	1.1 (0.7–1.7)
Employment outside home				
No	252	49 (19)	1.0 (–)	1.0 (–)
Yes	448	170 (38)	2.5 (1.7–3.7)	2.5 (1.6–3.9)
Episode onset during school-term break[a]				
No	550	183 (33)	1.0 (–)	1.0 (–)
Yes	150	36 (24)	0.6 (0.4–0.9)	1.1 (0.7–1.9)
Day-of-the-week and holidays for episode onset				
Monday to Friday	518	171 (33)	1.0 (–)	1.0 (–)
Saturday	102	21 (21)	0.5 (0.3–0.9)	0.5 (0.3–0.8)
Sunday or holiday	80	27 (34)	1.0 (0.6–1.7)	1.0 (0.6–1.7)
Epidemic phase in 2009				
7 Jun to 8 Jul	215	49 (23)	1.0 (–)	1.0 (–)
9 Jul to 29 Jul	152	53 (35)	1.8 (1.1–2.9)	1.9 (1.1–3.4)
30 Jul to 28 Aug	149	62 (42)	2.4 (1.5–3.8)	1.5 (1.3–4.6)
29 Aug to 8 Oct	184	55 (30)	1.4 (0.9–2.3)	1.6 (1.0–2.8)
Baseline HAI titre				
< 1:10	612	191 (31)	1.0 (–)	1.0 (–)
≥ 1:10	88	28 (32)	1.0 (0.6–1.8)	1.5 (0.9–2.8)
Ever had previous influenza vaccination				
No	614	195 (32)	1.0 (–)	1.0 (–)
Yes	86	24 (28)	0.8 (0.5–1.4)	0.7 (0.4–1.3)
Pre-existing medical conditions[b]				
Diabetes	70	24 (34)	1.2 (0.7–2.0)	1.3 (0.7–2.4)
Asthma	95	31 (33)	1.1 (0.6–1.8)	1.3 (0.8–2.2)
Serological classification				
Unrelated to influenza[c]	664	201 (30)	1.0 (–)	1.0 (–)
Presumptive influenza[d]	36	18 (50)	2.3 (1.2–4.6)	1.1 (0.5–2.4)
Symptoms[b]				
Cough	278	116 (42)	2.2 (1.6–3.1)	1.8 (1.2–2.7)
Shortness of breath	22	9 (41)	1.5 (0.7–3.7)	1.1 (0.3–4.2)
Sore throat	152	74 (49)	2.6 (1.8–3.9)	1.9 (1.2–3.0)
Nasal congestion	240	92 (38)	1.6 (1.1–2.2)	1.5 (0.9–2.2)
Fever (self-reported)[e]	110	68 (62)	4.7 (3.1–7.2)	3.5 (2.1–5.7)
Myalgia	93	36 (39)	1.5 (0.9–2.3)	1.1 (0.6–2.0)
Headache	154	49 (32)	1.0 (0.7–1.5)	1.3 (0.8–2.1)
Abdominal pain	33	11 (33)	1.1 (0.5–2.3)	1.5 (0.6–4.1)
Nausea and/or vomiting	247	20 (8)	1.7 (0.9–3.1)	2.3 (1.2–4.5)
Diarrhoea	93	24 (26)	0.7 (0.4–1.2)	1.0 (0.5–1.8)

HAI: haemagglutination-inhibition assay; OR: odds ratio.

[a] School term breaks as designated by the Ministry of Education, Singapore, for primary and secondary schools in Singapore, specifically from 30 May 2009 to 28 June 2009 and from 5 September 2009 to 13 September 2009.

[b] Reference category is individuals without that condition or symptom.

[c] Episodes unrelated to influenza A(H1N1)pdm09.

[d] Presumptive influenza A(H1N1)pdm09 episodes.

[e] Self-reported feeling of having a fever.

each other was unchanged when repeating the analysis using episodes in which the individuals had presented to primary care, but the sensitivities were slightly higher while the specificities and LR+s, PPVs and LR+s were lower.

We further explored how the respective case definitions would have performed in capturing influenza A(H1N1)pdm09 episodes in our cohort. Since only a minority of ARI was influenza A(H1N1)pdm09, ARI performed poorly in monitoring epidemic progression (Figure 3, panel A), where we were unable to discern a clear epidemic pattern as compared with the pattern in influenza A(H1N1)pdm09-positive samples from sentinel general practices. There were, however, no substantive differences in the epidemic curves when using the other five case definitions (Figures 3, panels B to F). For attack rates, we present estimates derived from all self-reported episodes, ever having had an episode, and episodes having a consultation at a general practice; these would reflect what might be obtained through repeated Internet or telephone surveys, retrospective surveys after the epidemic for ever having had an episode, and surveillance based on primary care episodes respectively. Estimates using all self-reported ARI episodes and having ever had an ARI episode gave much higher rates than serological attack rates, although overall general practice clinic consultation rates were (perhaps coincidentally) similar. The estimates numerically closest to serological attack rates for all episodes and ever having an episode were those for FRI; estimates from the modified EU-ECDC ILI were slightly higher, while those from the US-CDC ILI, WHO old ILI, and WHO new ILI were substantially lower.

The influence of participant characteristics and the type and timing of symptoms on determining presentation to primary care is shown Table 3. Having self-reported fever, cough or sore throat was associated with an increase in likelihood to seek primary care both in univariate and multivariate analysis. On the other hand, episodes that were presumptive influenza A(H1N1) pdm09, while significantly associated with seeking primary care in univariate analysis, were not more likely to result in primary care consultation after adjusting for the type of symptoms experienced. For participant characteristics, in the multivariate analysis, those aged 25–34 years and those employed in work outside the home were significantly more likely to seek care. The timing of episodes also affected the probability of seeking care: individuals with episodes in which onset was on a Saturday were significantly less likely to seek care. Individuals with episodes occurring from 9 July to 28 August were also marginally more likely to seek care.

When considering all illness episodes for which primary care was sought, consultations occurred more frequently on Mondays and less frequently on Saturdays and Sundays as compared with other days of the week (Figure 4). Illness episodes with onset on weekdays (Figure 4, panels B to F) were most likely to consult on the day of onset and the day after (Figures 4, panels B to E), while those with onset on weekends would often delay consultation until Monday (Figure 4, panels G and H); this consultation pattern was consistent regardless of the case definition used (data not shown).

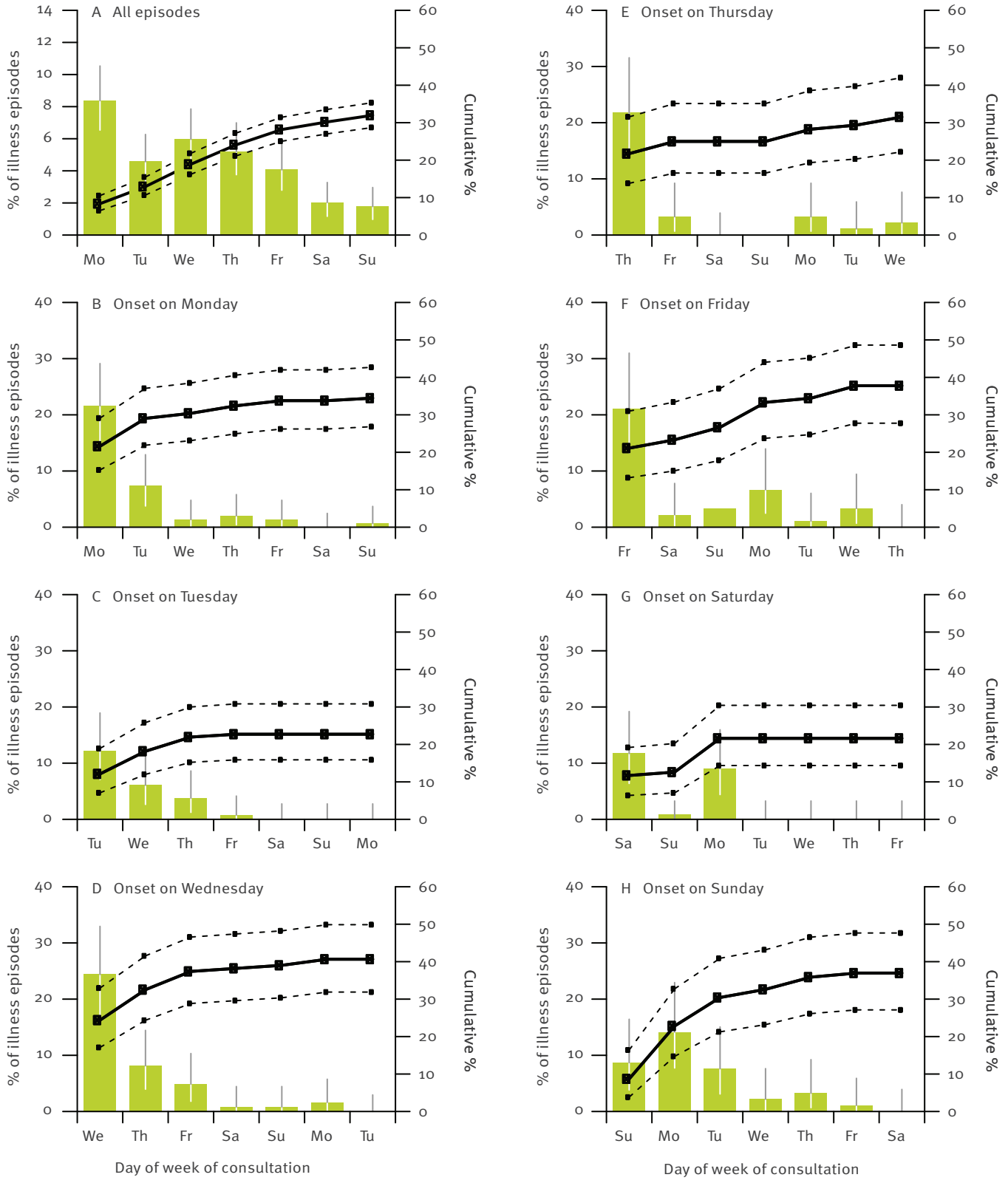
Discussion

Cough, sore throat and fever are commonly included in ILI case definitions [4,6,8]. In our study, cough, sore throat and fever were significantly more common among presumptive influenza A(H1N1)pdm09 episodes in univariate analysis, although sore throat was not in the multivariate model. This is because most influenza episodes with sore throat would also have a cough [21]; in our data, more than 90% of presumptive influenza A(H1N1)pdm09 episodes with sore throat also reported having a cough. Headache is another symptom that physicians associate with influenza [22], and headache was significantly more common among presumptive influenza A(H1N1)pdm09 episodes in both univariate and multivariate analysis in our study. A similar study among schoolchildren in Taiwan also indicated that headache had a significant association with influenza infection [23], although this was not found to be the case in several other studies [7,9,11].

Previous work assessing the appropriateness of influenza case definitions have focused only on patients who seek care for respiratory symptoms or those presenting with a fever [8,10,11], whereas our study captures all events with serological evidence of influenza A(H1N1)pdm09 virus infection. Our results show that the modified EU-ECDC ILI performed rather differently from the other three ILI case definitions, with a much higher sensitivity and a relatively lower specificity, mainly because the EU-ECDC ILI case definition does not require a measured fever, in contrast to the other case definitions (body temperature in US-CDC ILI: ≥ 37.8 °C, WHO old ILI: › 38 °C, WHO new ILI: ≥ 38 °C). One of the objectives of influenza surveillance is to signal the start of an influenza season or influenza epidemic, and an ILI case definition with higher sensitivity integrated with laboratory surveillance can be better at detecting the start of sustained community circulation of influenza, although it may also be more resource intensive in terms of requirements for laboratory testing [4]. The sensitivities and specificities of the other three ILI case definitions were very similar, but the PPVs and LR+s were different, with the US-CDC ILI having the lowest and the WHO new ILI having the highest PPV and LR+. In the analysis using all reported episodes as well as episodes with primary care consultation, the LR+ calculated for the WHO new ILI case definition was higher (13.32 and 8.12 respectively) and provides support for the simplification of removing sore throat as a component of the case definition. Interestingly, although the number of presumptive influenza A(H1N1)pdm09 episodes with primary care consultation was small, the LR+ of 5.29 for the US-CDC ILI and 6.87 for the WHO old ILI case definition was fairly similar to the previous LR+ estimates reported by the studies of Govaert et al.

Figure 4

Distribution of illness episodes for which care was sought by day of week of onset and consultation, and cumulative proportion of individuals who sought care, by day of week of consultation, Singapore, June–October 2009 (n = 788 episodes)



CI: confidence interval.

For all episodes (A), and for episodes with onset from Monday to Sunday (B to H respectively). Bars and horizontal axes denote day of week of consultation; columns and left-hand vertical axes are the proportion of primary care consultations on that day for that panel, while solid lines and right-hand vertical axes are the cumulative proportion of all ARI episodes that included primary care consultations. Error bars and dashed lines give the corresponding 95% CIs. Since we included only consultations occurring within seven days of symptom onset, and horizontal axes are ordered to start on the day of onset in panels B to H, these panels also illustrate the corresponding delay from episode onset to consultation.

[24] and Stein et al. [25] in individuals who sought care for symptoms suggestive of influenza.

When comparing the accuracy of estimates obtained from the various case definitions against serological attack rates, the use of ARI is clearly inadequate due to the substantial noise from episodes unrelated to influenza A(H1N1)pdm09. While the FRI estimates for all episodes and ever having an episode are numerically closest to serological attack rates, we suspect this is an artefact due to causes of FRI unrelated to influenza A(H1N1)pdm09 compensating for the imperfect sensitivity of the case definition, an effect that cannot be expected to be consistent in future epidemics or across regions. The US-CDC ILI, WHO old ILI, and WHO new ILI definitions all underestimate infection rates, as not all cases present with the requisite symptoms, and therefore data on the proportion of infections not meeting these case definitions would be needed as a multiplier to estimate overall attack rates [15]. Feasibly, this proportion could be obtained from serological studies performed with similar influenza strains elsewhere, and may not need to be repeated in different locations and time points, though it may be preferable to use external data only provisionally and later validate estimates with serological data from the same setting and outbreak.

Our previous data also illustrate, however, that how individuals seek care is an important determinant of the performance characteristics of surveillance data collected from primary care doctors [15]. When exploring how various factors influenced consultations, presumptive influenza A(H1N1)pdm09 was not independently associated with seeking care after adjusting for the type of symptoms experienced (specifically, fever, cough and sore throat) and as such the clinical presentation of the particular strain of influenza virus would affect the performance of ILI surveillance based on primary care consultations. Not surprisingly, those employed in work outside the home were significantly more likely to seek care, probably due to the need for time off work, which in Singapore usually requires a physician's certificate. An Israeli study also found that obtaining a sick-leave note was the main reason to seek medical care for patients aged 30–65 years with influenza-like symptoms [26]. It is also noteworthy that consultations more frequently occurred on Mondays and much less frequently on Saturdays and Sundays, and individuals with episodes with onset on Saturday were significantly less likely to seek care, which is possibly related to the need for certifying absenteeism from work, although it could also reflect heterogeneities in the infection risk across the week, as has been found for dengue [27]. Estimates of infection rates derived from primary care consultations are therefore most stable if performed on a weekly basis to smooth out these fluctuations, or if daily fluctuations are explicitly accounted for in the analysis [28]. In addition, the slightly increased probability of consultation during some weeks of the pandemic (in particular the period 9 July to 29 July (Table 3)), also shows the importance of early and repeated surveys during the course of an epidemic as failure to account for changes in health-seeking behaviour may lead to misleading estimates.

This study has several limitations that should be addressed in future work. Attack rates and clinical presentations of influenza virus infection often vary by age [29,30]. The adult-only cohort (21–75 years) may not be representative of all age groups, and we only identified 36 presumptive influenza A(H1N1)pdm09 episodes with which to assess various case definitions. Moreover, differences in clinical symptoms between influenza virus subtypes [31,32] mean that the case definition may have to be adjusted depending on the circulating strain. Other limitations include the possibility of non-seroconversion upon infection [33], which may lead to systematic errors in the estimates. Recall bias, in spite of the short interval between surveys, may be present, and we did not consider the timing of symptoms relative to presentation (e.g. sore throat may precede cough). Knowing about the study objectives or that there was a pandemic may also have led participants to seek healthcare more, or over-report certain symptoms. Finally, multiple general practice consultations were not considered as it was not possible to ascertain if individuals fulfilled the case definitions across all consultations.

In conclusion, we evaluated the performance of the modified EU-ECDC ILI, US-CDC ILI, WHO old ILI and WHO new ILI case definitions in detecting illness episodes due to influenza A(H1N1)pdm09. The recently revised WHO ILI case definition was found to be an improvement over the others, with a higher PPV and LR+. Regardless of the performance of the different case definitions, health-seeking behaviour was strongly associated with several factors independent of the symptoms and disease under consideration, and population- and episode-level characteristics, such as the proportion who work and day-of-week effects respectively, would need to be accounted for when interpreting surveillance data based on ILI case definitions.

Acknowledgments

This project was funded by the grant PPG10-09 from the National Medical Research Council of Singapore. M.I.C., Y.C. and A.R.C. are supported by the Centre for Infectious Disease Epidemiology and Research at the Saw Swee Hock School of Public Health, National University of Singapore and National University Health System. The WHO Collaborating Centre for Reference and Research on Influenza, Melbourne, is supported by the Australian Government Department of Health and Ageing.

Conflict of interest

V. J. L. has received unrelated research grants from GlaxoSmithKline.

Authors' contributions

Mark I. Chen designed the study and directed its implementation. Mark I. Chen, Wei-Yen Lim, Yee Sin Leo and Linda Tan W.L. supervised the field work. Ian Barr and Raymond T. P. Lin designed and supervised laboratory analyses of the samples collected. Mark I. Chen, Lili Jiang, Vernon J. Lee and Alex R. Cook came up with the study hypothesis and devised the plan for data analysis. Mark I. Chen, Lili Jiang, Yirong Chen and Alex R. Cook conducted the data analysis and interpreted the results. Mark I. Chen, Lili Jiang and Vernon J. Lee helped draft the manuscript. Mark I. Chen, Lili Jiang, Vernon J. Lee and Alex R. Cook conducted critical revision of the manuscript.

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Hepatitis C virus infection among pregnant women in Slovenia: study on 31,849 samples obtained in four screening rounds during 1999, 2003, 2009 and 2013

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Citation style for this article:
Kopilović B, Poljak M, Seme K, Klavs I. Hepatitis C virus infection among pregnant women in Slovenia: study on 31,849 samples obtained in four screening rounds during 1999, 2003, 2009 and 2013. Euro Surveill. 2015;20(22):pii=21144. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=21144

Article submitted on 01 October 2014 / published on 04 June 2015

The majority of people infected with hepatitis C virus (HCV) are unaware of their infection. Assessment of the prevalence of HCV infection in the general population and in key populations at increased risk is needed for evidence-based testing policies. Our objectives were to estimate the prevalence of antibodies to HCV (anti-HCV), the prevalence of HCV viraemia (HCV RNA), and to describe HCV genotype distribution among pregnant women in Slovenia. Unlinked anonymous testing was performed on residual sera obtained from 31,849 pregnant women for routine syphilis screening during 1999, 2003, 2009, and 2013. Anti-HCV reactive specimens were tested for HCV RNA and HCV genotypes were determined. Annual prevalence of anti-HCV ranged between 0.09% (95% confidence interval (CI): 0.03–0.18) in 2009 and 0.21% (95% CI: 0.12–0.34) in 2003 and HCV RNA positivity between 0.06% (95% CI: 0.02–0.14) in 2009 and 0.14% (95% CI: 0.07–0.25) in 2003. We observed no statistically significant differences in anti-HCV or HCV RNA prevalence between age groups (<20, 20–29 and ≥30 years) in any year and no trend in time. Of 29 HCV active infections, 19 were with genotype 1 and 10 with genotype 3. HCV infection among pregnant women was rare suggesting a low burden in the Slovenian general population. Antenatal screening for HCV in Slovenia could not be recommended.

Introduction

Hepatitis C virus (HCV) is among the most common blood-borne viruses [1]. In ca 75% to 85% of cases of infection, HCV persists as a chronic infection and one third of chronically infected individuals is predicted to develop liver cirrhosis or hepatocellular carcinoma [2]. Although treatment success has substantially improved in recent years [3,4], most infected people are unaware of their infection and/or do not have access to treatment [5]. According to estimates published in 2013, by 2005, more than 185 million people around the world were infected with HCV, of whom 350,000 die annually [1]. The prevalence of antibodies to HCV (anti-HCV) in central Europe was estimated to be 2.4% (>2.9 million people infected), in eastern Europe 2.9% (>6.2 million people infected) and in western Europe 2.4% (>10 million people infected) [1]. Compared with other geographical areas in the world these figures indicate a moderate prevalence (1.5%–3.5%) [1]. A recent review of available data from Europe indicated a wide variation in HCV infection prevalence between countries, ranging from 0.1% to 6.0% [6]. The lowest HCV prevalence (≤0.5%) estimates were from Scandinavian countries and the Netherlands, and the highest (≥5%) from Romania [7-10].

As HCV shows great diversity in prevalence in different parts of the world, the 2010 World Health Assembly resolution urged Member States to generate reliable information as a foundation for building prevention and control measures that match the local epidemiological profile and health system capacities [11]. In 1998, the United States (US) Centers for Disease Control and Prevention had already recommended routine HCV testing for several population groups at increased risk for HCV, based on HCV risk factors ascertainment, but not for pregnant women and the general population [12]. In 2012, once per lifetime HCV testing for adults born between 1945 and 1965 without prior ascertainment of HCV risk factors was added as a recommendation since the prevalence of anti-HCV among the US population born during these years was estimated to be 3.25% (95% confidence interval (CI): 2.80–3.76) and persons born during these years accounted for approximately three quarters of all chronic HCV infections among adults [13].

In 2014, the World Health Organisation (WHO) recommended to offer anti-HCV testing to individuals who are part of a population with high HCV prevalence or who have a history of HCV risk exposure or behaviour, and suggested that nucleic acid testing for the detection of

Figure

Sentinel sites involved in collection of residual sera specimens from pregnant women that were used to test for antibodies to hepatitis C virus[a], Slovenia, 1999–2013 (n=7)

General hospital Maribor
Institute of Blood Transfusion of the Republic of Slovenia, Ljubljana
Institute of Public Health Celje
Institute of Public Health Koper
Institute of Public Health Kranj
Institute of Public Health Maribor
Institute of Public Health Nova Gorica
Institute of Public Health Novo mesto

The site in Maribor comprised two participating laboratories. All other sites included one respective laboratory.

[a] Sera used in this study to test for antibodies to hepatitis C virus had been originally collected for syphilis screening and subsequently systematically sampled for unlinked anonymous human immunodeficiency virus prevalence monitoring for surveillance purposes.

HCV RNA be used following a positive HCV serological test to establish the diagnosis of chronic HCV infection as part of the assessment for starting treatment [14]. WHO identified the following populations at increased risk for HCV: persons who inject drugs, recipients of infected blood products or invasive procedures in healthcare facilities with inadequate infection control practices, children born to mothers infected with HCV, people with sexual partners who are HCV-infected, persons with human immunodeficiency virus (HIV) infection, in particular men who have sex with men, people who have used intranasal drugs, and people who have had tattoos or piercings. National testing policies based on the best assessment of the prevalence of HCV infection in the general population and in key populations at increased risk are needed for evidence-based HCV control policy [14].

Due to under-ascertainment and under-reporting, Slovenian HCV surveillance data, which are based on mandatory reporting of new hepatitis C diagnoses, do not provide a full picture of the epidemiology of HCV infection [15]. In Slovenia, we have some anti-HCV prevalence estimates for groups at higher risk (haemodialysis patients, people who inject drugs, HIV infected individuals) and data about the distribution of HCV genotypes among patients with HCV infection [16-20]. During the period from 2009 to 2013, the prevalence of anti-HCV among confidentially tested people who inject drugs entering or re-entering treatment within the network of Centres for the Prevention and Treatment of Illicit Drug Addiction ranged from the lowest 21.5% in 2010 to the highest 31.3% in 2013. These values were relatively low in comparison to a number of other countries in Europe where the prevalence among people who injected drugs during the period from 2011 to 2012 varied from 19% to 84%, with seven of the 11 countries with national data reporting a prevalence exceeding 50% (Austria, Cyprus, Greece, Latvia, Norway, Portugal, Turkey) [21]. We also have data about anti-HCV prevalence among blood donors for the period from 2001 to 2010 with an average of 0.0067% anti-HCV positive donations [22]. By 2013, we had neither reliable data about past and/or active HCV infection prevalence among pregnant women and in the general population nor about possible trends over time.

To complement available information on the prevalence of HCV infection in different population groups in Slovenia, our objectives were to estimate the prevalence of anti-HCV, the prevalence of HCV viraemia (HCV RNA), and to describe HCV genotype and subtype distribution among pregnant women in Slovenia for years 1999, 2003, 2009, and 2013. In addition, we wanted to explore whether there were any differences in anti-HCV and HCV RNA prevalence between different age groups of pregnant women in any of these years and possible changes in anti-HCV and HCV RNA prevalence through time.

Methods

Samples

In Slovenia, syphilis screening for pregnant women is universal. For this study, 31,849 sera stored at the National Institute of Public Health that were obtained from pregnant women for syphilis screening purposes and were systematically sampled for unlinked anonymous testing for HIV surveillance purposes during 1999, 2003, 2009, and 2013 were included. The sampling strategy for unlinked anonymous testing of pregnant women for HIV surveillance purposes was described previously [23,24]. Briefly, residual sera from specimens obtained from pregnant women for syphilis screening were continuously and consecutively sampled in eight participating laboratories. The eight laboratories were located at seven different sites across Slovenia, whereby one site comprised two laboratories (Figure). The second inclusion of specimens obtained from the same women during the same calendar year was prevented by keeping a separate list of identifying information on women whose sera had already been included into the sample during a particular year, which was checked before storing any new specimen. All specimens were labelled only with the information about the laboratory where samples were collected, sampling period (calendar year), and age group of the pregnant woman (<20, 20–24, 25–29, and ≥30 years) from whom the serum specimen had been obtained

for syphilis screening. They were frozen and stored at -20 °C until testing [23].

Laboratory testing strategy

All 31,849 specimens were initially tested for the presence of anti-HCV in pools of 12 specimens by using Ortho HCV Version 3.0 ELISA Test system. Individual specimens from screen reactive pools were retested with the same test. To identify pregnant women with active hepatitis C infection all screen repeatedly anti-HCV reactive specimens were further tested for the presence of HCV RNA by reverse transcriptase polymerase chain reaction (RT-PCR)-based COBAS Amplicor HCV 2.0 (Roche Molecular Systems, Branchburg, NJ, US) test. Anti-HCV screen positive pregnant women with measurable HCV RNA were considered as actively infected with hepatitis C. Anti-HCV screen positive pregnant women without measurable HCV RNA were further tested with Hepatitis C Virus Encoded Antigen CHIRON RIBA HCV 3.0 Strip Immunoblot Assay (Chiron Corporation, Emeryville, US) to distinguish pregnant women with false positive anti-HCV screen test (negative with Immunoblot Assay) from those who spontaneously cleared hepatitis C in the past (positive with Immunoblot Assay). In all HCV RNA positive specimens, HCV genotype was determined with InnoLiPa HCV 2.0 test (Innogenetics, Zwijndrecht, Belgium).

Analyses

Statistical analyses were performed using STATA package version 10.0 (Stata Statistical Software: release 10.0 College Station. TX: Stata Corporation). We estimated the overall and annual prevalence of anti-HCV and HCV RNA together with 95% CIs, overall and according to age groups of pregnant women. Chi-squared test was used to assess the differences between the prevalence of anti-HCV and HCV RNA in pregnant women of different ages for respective calendar years and for the differences between different calendar years.

Ethical consent

Ethical consent to unlinked anonymous testing of pregnant women screened for syphilis for HIV surveillance purposes (consent number 54/09/00) and ethical consent for HCV unlinked anonymous testing of specimens collected in 1999, 2003, 2009, and 2013 (consent number 86/04/13) were obtained from the Medical Ethics Committee at the Ministry of Health in Slovenia.

Results

Among a total of 31,849 sera specimens tested, 41 were anti-HCV positive, corresponding to the pooled prevalence estimate of anti-HCV of 0.13% (95% CI: 0.09–0.17). The 41 positive samples originated from all seven sentinel sites. Among 41 sera specimens positive for anti-HCV, 29 were positive for HCV RNA, corresponding to the pooled prevalence estimate of HCV RNA of 0.09% (95% CI: 0.06–0.13).

Annual prevalence estimates for anti-HCV ranged between 0.09% (95% CI: 0.03–0.18) in 2009 and 0.21% (95% CI: 0.12–0.34) in 2003 and for HCV RNA positivity between 0.06% (95% CI: 0.02–0.14) in 2009 and 0.14% (95% CI: 0.07–0.25) in 2003 (Table). We observed no statistically significant differences in anti-HCV or HCV RNA prevalence between age groups (<20, 20–29 and ≥30 years) in any calendar year and no trend in time.

Among a total of 29 pregnant women positive for HCV RNA, 19 were infected with genotype 1 (12 with subtype 1b, 3 with subtype 1a, while in 4 cases subtype could not be determined) and 10 with genotype 3 (all subtype 3a). Infection with HCV genotypes 2, 4, 5 or 6 was not detected.

Discussion

The prevalence of antibodies to HCV and HCV viraemia among pregnant women in Slovenia was relatively low and we have not identified any changes during this 15 years period.

In comparison to available data from other European countries, our estimates of prevalence of anti-HCV among pregnant women were more similar to published prevalence estimates among pregnant women in some western European countries (in the United Kingdom (UK): 0.2%, April 1997–June 1998; in Amsterdam, the Netherlands: 0.3%, 2003). Our estimates were however lower than in some southern European countries (in northern Greece: 1.9%, March 1996–February 1997; in Bergamo, Italy: 2.4%, January 1995–December 1998) and eastern European countries (in Moldova: 2.3%, 1994) [25-29]. We should be cautious in comparing our results with the published results of similar studies, as different approaches were used for laboratory testing and for sampling/enrolling pregnant women into the studies (for example invitation to be voluntarily and confidentially tested accompanied with HCV related counselling in contrast to our unlinked anonymous testing of sera specimens obtained from a sera bank, which had been initially collected for syphilis screening purposes).

Relatively low estimated anti-HCV and HCV RNA prevalence among pregnant women in Slovenia in comparison to many other European countries may correspond to relatively low prevalence of anti-HCV among confidentially tested people who inject drugs [21]. Although some researchers have reported that anti-HCV prevalence among pregnant women increases with age, we did not found a statistically significant association between age group and prevalence in our study [25,30].

Only genotypes 1 and 3 were identified in our study which is consistent with the results of another Slovenian study in which chronic hepatitis C patients were enrolled and 93.8% of patients had genotypes 1 and 3 [20]. The fact that we did not find any patients with genotypes 4, 5 and 6, could be partly explained by the observation that the introduction of genotype 4,

Table

Annual prevalence of antibodies to hepatitis C virus (HCV) and HCV viraemia among pregnant women, overall and by age group, 1999, 2003, 2009, and 2013, Slovenia (n=31,849)

Age group in years	Year											
	1999			2003			2009			2013		
	Anti-HCV % (95% CI)	HCV RNA % (95% CI)	N	Anti-HCV % (95% CI)	HCV RNA % (95% CI)	N	Anti-HCV % (95% CI)	HCV RNA % (95% CI)	N	Anti-HCV % (95% CI)	HCV RNA % (95% CI)	N
<20	0.27 (0.01–1.51)	0.27 (0.01–1.51)	367	0.00 (0.00–1.41)[a]	0.00 (0.00–1.41)[a]	259	0.00 (0.00–2.72)[a]	0.00 (0.00–2.71)[a]	134	0.00 (0.00–2.16)[a]	0.00 (0.00–2.16)[a]	169
20–29	0.11 (0.04–0.25)	0.09 (0.02–0.22)	4,573	0.27 (0.14–0.47)	0.16 (0.06–0.32)	4,475	0.07 (0.01–0.21)	0.07 (0.01–0.21)	4,185	0.11 (0.03–0.25)	0.09 (0.02–0.22)	4,645
≥30	0.10 (0.01–0.36)	0.05 (0.00–0.28)	1,990	0.12 (0.02–0.34)	0.12 (0.02–0.34)	2,547	0.11 (0.03–0.27)	0.05 (0.01–0.19)	3,745	0.13 (0.05–0.27)	0.08 (0.02–0.22)	4,760
Total	0.12 (0.05–0.23)	0.09 (0.03–0.19)	6,930	0.21 (0.12–0.34)	0.14 (0.07–0.25)	7,281	0.09 (0.03–0.18)	0.06 (0.02–0.14)	8,064	0.11 (0.06–0.21)	0.08 (0.04–0.16)	9,574

Anti-HCV: antibodies to HCV; N: number of sera collected from pregnant women for syphilis serology screening subjected to unlinked anonymous testing for anti-HCV or HCV RNA; CI: confidence interval.

[a] One-sided, 97.5% confidence interval.

5 and 6 in European countries has been related mostly to immigration from Africa and in Slovenia immigration from Africa has been relatively low [20].

Since the available estimates of HCV infection among pregnant women in Europe are generally relatively low, only two countries (Norway and Spain) introduced antenatal screening programs for hepatitis C [31], while for example, in the UK, routine antenatal screening for hepatitis C virus infection was decided against [25].

Our approach to obtain estimates of anti-HCV and HCV RNA prevalence by unlinked anonymous testing of rather large convenience samples of stored residual sera specimens obtained from pregnant women for syphilis screening in four calendar years spanning the period from 1999 to 2013, has proven to be logistically feasible. The strengths of such unlinked anonymous monitoring are minimised participation bias, non-invasive specimen collection and a very cost-efficient approach to collecting substantial number of specimens in laboratories. By repeating cross-sectional studies using the same methodology over time, we can monitor possible trends. As syphilis screening in Slovenia is universal and the numbers of residual sera tested corresponded to substantial proportions of pregnancies in respective calendar years (equivalent to 38% to 46% of deliveries), we believe that our prevalence estimates reflect quite accurately the true HCV prevalence among Slovenian pregnant women in those years. Pregnant women cannot be assumed to be representative of the general population. However, we believe that the estimated level of HCV infection prevalence among pregnant women may fairly well reflect the level of HCV infection prevalence in the Slovenian general population of reproductive ages, as suggested by others [32]. Other countries with constrained resources may consider using similar, logistically relatively simple and rather cost-effective, approaches to obtain better population HCV prevalence data.

Our study had several limitations. We tested residual sera specimens from convenience and not probability samples of pregnant women in Slovenia during the respective years. We did not have information on additional risk behaviour for pregnant women (for example, information on possible history of sharing injecting equipment) and women whose sera specimens had not been included into our samples may have been at a different risk for HCV infection. Finally, we may have slightly underestimated the prevalence of HCV RNA, as only screen repeatedly anti-HCV reactive specimens were tested for the presence of HCV RNA and not all 31,849 sera specimens. However, we believe that because of very low anti-HCV prevalence and consequent extremely low probability for a specimen to be collected before seroconversion (recently infected person who is still anti-HCV negative while already HCV RNA positive), little, if any, loss of sensitivity for ascertainment of HCV RNA positivity would result from our testing algorithm. Thus we assumed that the estimation of HCV viraemia prevalence by our laboratory testing algorithm fairly well reflected the true prevalence of HCV viraemia.

To conclude, our data represent the first reliable estimates of the relatively low burden of hepatitis C among pregnant women in Slovenia and suggest a relatively low burden of hepatitis C in the Slovenian general population. This suggests that the anti-HCV prevalence estimate for central Europe (2.4%) published in 2013 [1] may have been an overestimation and should be revised according to new information available. But it should be noted, that considerable heterogeneity in the HCV infection prevalence may exists among different countries of central Europe. Based on our results, opportunistic screening for HCV should not be recommended for pregnant women or the general population in Slovenia, however, voluntary HCV testing should be offered when there is a history of risk exposure or behaviour or a medical condition suggestive of HCV

infection. Opportunistic screening for HCV should only be targeted to groups at increased risk, such as people who inject drugs, persons with HIV infection, in particular men who have sex with men, and other groups at increased risk for HCV as defined by the WHO [14].

Acknowledgments

We thank the personnel from the syphilis serology laboratories in the following healthcare institutions: General Hospital Maribor, Institute of Blood Transfusion of the Republic of Slovenia, Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Institute of Public Health Celje, Institute of Public Health Koper, Institute of Public Health Kranj, Institute of Public Health Maribor, Institute of Public Health Nova Gorica, Institute of Public Health Novo mesto. We also thank Ms. Zdenka Kastelic for her dedicated support in coordination of the national unlinked anonymous HIV prevalence monitoring surveillance system and Robi Krošelj for his excellent support in laboratory testing.

Conflict of interest

None declared.

Authors' contributions

BK contributed to the design of the study, analysed the data and drafted the manuscript. MP contributed to the design of the study, supervised the testing and commented on the final version of the manuscript. KS contributed to the supervision of testing and commented on the final version of the manuscript. IK designed the study, supervised analyses and contributed to drafting the manuscript. All authors participated in interpretation of the results and approved the final version of a manuscript.

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ECDC publishes new interactive online tool: West Nile fever maps for 2015

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Citation style for this article:
Eurosurveillance editorial team. ECDC publishes new interactive online tool: West Nile fever maps for 2015 . Euro Surveill. 2015;20(22):pii=21147. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=21147

Article published on 04 June 2015

On 5 June, the European Centre for Disease Prevention and Control (ECDC) will start publishing maps in anticipation of the 2015 West Nile fever transmission season. The West Nile fever maps data [1] will be displayed through an interactive web-based tool, based on the Surveillance Atlas of Infectious Diseases [2].

Weekly maps and tables of reported autochthonous human cases in Europe and the Mediterranean basin, will be presented through an interconnected webpage, updated every Friday. The updates are based on information obtained from the countries' health authorities and refer to human autochthonous cases of West Nile fever only. Users will be able to see the location of an area and its epidemiological situation at a glance. A table on the number of cases according to countries and areas will further add to the user friendliness of the tool.

The objective of the West Nile maps project is to inform the competent authorities responsible for blood safety, of areas with ongoing transmission of West Nile virus to humans, in order to support the implementation of European Union (EU) blood safety legislation [3]. According to the legislation, efforts should be made to defer all blood donations from areas with ongoing transmission of West Nile virus WNV to humans to prevent its onward spread. An important consequence of the deferral of blood donations from areas with West Nile fever is the impact on the blood supply for those areas.

To date, no West Nile fever cases have been reported in the EU or neighbouring countries in 2015.

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