Hospitalization of influenza-like illness patients recommended by general practitioners in France between 1997 and 2010.

Camille Pelat, Andrea Lasserre, Ana Xavier, Clément Turbelin, Thierry Blanchon, Thomas Hanslik

Hospitalization of influenza-like illness patients recommended by general practitioners in France between 1997 and 2010

Camille Pelat[1,2,3], Andrea Lasserre[1,2], Ana Xavier[1,2], Clément Turbelin[1,2], Thierry Blanchon[1,2], Thomas Hanslik[1,4,5].

1. UMR S 707, INSERM, F-75012, Paris, France

2. UPMC Univ Paris 6, F-75012, Paris, France

3. MRC Centre for Outbreak Analysis and Modelling, Department of Infectious Disease Epidemiology, Imperial College London, Faculty of Medicine, Norfolk Place, London W2 1PG, UK

4. Université Versailles Saint Quentin en Yvelines, Versailles, F-78000, France.

5. Assistance Publique Hôpitaux de Paris, service de Médecine Interne, Hôpital Ambroise Paré, Boulogne Billancourt, F-92100, France.

Running head: Hospitalization of ILI patients recommended by GPs

Keywords: case-hospitalization ratio; emerging pathogens; influenza pandemics; surveillance, severity.

Corresponding author (present address):

Dr. Camille Pelat

Department of Infectious Disease Epidemiology,

Imperial College,

St. Mary's Campus, Norfolk Place, Paddington

London. W2 1PG

UNITED KINGDOM

Tel: +44 (0) 20 7594 1379

Email: camille.pelat@gmail.com

ABSTRACT

BACKGROUND. The case-hospitalization ratio (CHR) is a key quantity for the management of emerging pathogens such as pandemic influenza. Yet, few running surveillance systems prospectively monitor the CHR during influenza epidemics. Here, we analyze the proportion of recommended hospitalizations (PRH) among influenza-like illness (ILI) patients attended in general practice in France and compare the PRH observed during the 2009-2010 A(H1N1) pandemic with the one of the twelve previous seasons.

METHODS. ILI cases were recorded by general practitioners (GPs) involved in surveillance, who indicated for each case whether they recommended hospitalization. We stratify the analysis by age, sex and viral subtype. We investigate the reasons why GPs recommended hospitalization and the presence of risk factors for pandemic A(H1N1) complications.

RESULTS. The average PRH over the seasons 1997-1998 to 2008-2009 was 3.4‰ (3−3.9). It was three times higher during the 2009-2010 pandemic than during seasonal influenza epidemics (OR=2.89, 95% CI: 2.28−3.64). The highest increase was among 20-39 year-old women: OR=11.8 (5.04−29.59). Overall, the principal reasons for recommending hospitalization were “respiratory problems” and “bad general condition”. However, during the pandemic, “age” (mainly associated with infants), “pregnancy” and “diagnostic” became more frequent than before ($p<0.001$). Finally, pregnancy was the reported risk factor for pandemic A(H1N1) complications that had the largest impact on hospitalization recommendation during the pandemic (OR=38.62, $p<0.001$).

CONCLUSION. Easily implemented in surveillance systems, this protocol has the potential to reveal changes in hospitalization recommendation by GPs. Moreover, if the right data are collected alongside, it could give timely insights into epidemic severity.

INTRODUCTION

Accurate and timely assessment of severity through measures such as the case-hospitalization ratio (CHR) is essential for the management of emerging pathogens, such as pandemic influenza [1]. The CHR was carefully analyzed to understand the severity of the 2009 A(H1N1) pandemic influenza and to measure its burden on the health care system [2, 3]. It was also a key quantity entering the calculation of the case-fatality ratio [4]. It has been discussed elsewhere how consistent monitoring of influenza CHRs over the long term can help characterize at-risk populations for different viral subtypes, measure the impact of prevention programs and inform future strategies [5, 6].

The estimation of the CHR usually relies on outbreak investigation studies of limited size, or on the ratio of hospitalized cases provided by one surveillance system over the number of influenza cases estimated by another one [4, 7, 8]. There are few surveillance systems specifically aimed at monitoring this quantity. Since 1997, the proportion of recommended hospitalizations (PRH) among patients attended for influenza-like illness (ILI) in general practice has been monitored in France by one "self-sufficient" surveillance system based on sentinel general practitioners (GPs): the *Sentinelles* network [9]. To achieve this goal, *Sentinelles* GPs have been recording those ILI cases for which they recommended hospitalization as part of their case reporting. The PRH is thus estimated as the proportion of recommended hospitalizations among *Sentinelles* GPs' ILI patients.

In the present study, we compare the PRH of the 2009-2010 A(H1N1) pandemic with the twelve preceding seasonal epidemics, stratifying by age, sex and viral subtype. We also investigate the reasons why GPs recommended hospitalization and the presence of risk factors for pandemic A(H1N1) complications. We finally evaluate the usefulness of this surveillance for public health information by monitoring the uncertainty of the PRH estimate throughout the pandemic.

METHODS

ILI surveillance by the Sentinelles network

The *Sentinelles* network is an epidemiological, real-time, electronic surveillance system based on voluntary sentinel general practitioners that has been monitoring the incidence of ILI in general practice since 1984 in France [10]. *Sentinelles* GPs are similar to other French GPs with regards to their regional distribution, the proportion of GPs in rural practice and the type of practice [11]. They use the following case definition for ILI: sudden onset of fever (39°C or above) with myalgia and respiratory signs [12]. Since January 1997, for each reported ILI case, *Sentinelles* GPs record if they recommended hospitalization for the patient.

We defined influenza epidemic periods using a periodic regression model fitted on historic non-epidemic data [13, 14]. This model provides an epidemic threshold that allows detection of an influenza epidemic. Each influenza season is further characterized by its dominant circulating viral subtype(s), thanks to virological surveillance data [15]: A(H1N1), A(H3N2), B or a combination. One subtype qualifies as dominant if it comprises more than 75% of the season's influenza isolates. Co-dominance of two subtypes could happen when neither of them accounted for more than 75% of a season's isolates.

Estimation of the PRH

We estimate the PRH among ILI cases attended in general practice in a given period *j* (PRH_j) as the proportion of reported ILI patients for whom *Sentinelles* GPs recommended hospitalization:

$$PRH_j = \frac{\text{Number of ILI cases for whom Sentinelles GPs recommended hospitalization in period j}}{\text{Total number of ILI cases reported by Sentinelles GPs in period j}}$$

PRHs were computed for each influenza epidemic from 1997-1998 to 2009-2010 by gender and for the following age groups: 0-19, 20-39, and ≥40 years-old. The GPs could indicate the

reason why they recommended hospitalization by selecting from the following list: "respiratory", "cardiac" and "other reason". They could also elaborate in writing any other reason(s). Since October 2009, the answer list was discarded: all answers had to be elaborated in writing. We compare the frequency of each reason between seasonal and pandemic influenza using Fisher's exact test.

Surveillance during 2009-2010 pandemic

Since October 2009, GPs were asked if their patients presented one or more risk factors for pandemic influenza complications, to be chosen from the following list: "pregnancy", "obesity", "chronic condition" and "other". Here, we evaluate with logistic regressions and Wald tests the impact of risk factors for complications on hospitalization odds during the pandemic.

We assess if the pandemic context made patients consult more by asking, since October 2009, the following question to *Sentinelles* ILI patients: "*Would you consult your GP for the same symptoms if there was not the current pandemic context?*". To assess potential changes in the way GPs attended ILI cases, a telephonic survey was conducted by a medical resident on 41 GPs, with the following question: *"Would you recommend hospitalization for this patient, for the same symptoms, if there was not the current pandemic context?"*. On this occasion, GPs were also asked about the future of the patients for whom they recommended hospitalization.

Finally, we use the pandemic to exemplify the real-time estimation of the PRH by the *Sentinelles* surveillance system. In 2009 in France, the first signal of unusual ILI activity was detected in week 28 (July) [16], and the epidemic officially began in week 37 (September). However, pandemic A(H1N1) is believed to have spread in France since week 19 (May) [17]. To assess how the CHR estimate evolved from May to December, successive weekly estimations were undertaken. For each week from 2009/19 to 52, estimations relied on the

cumulative ILI cases reported by then from week 19. We define relative uncertainty (in %) as half the confidence interval divided by the estimate and multiplied by 100. The analysis was carried out with the R software package version 2.13.0. Confidence intervals for means, proportions and odds-ratio were obtained with the profile likelihood method [18]. A Bayesian adjustment was made when the number of hospitalizations was zero to move the log-likelihood function away from infinity [19].

We finish the analysis by studying two potential factors in the PRH variability: the composition of the *Sentinelles* GPs and the the intensity of influenza seasons, as measured by the cumulative consultation rate for ILI in general practice over each epidemic.

Composition of the Sentinelles network across the study period

We analyze the number, age, sex ratio and turnover of the GPs that have been reporting to the *Sentinelles* system between 1997 and 2010. A GP is reporting in a given year *Y* when he/she reports at least once to the system during year *Y*. The turnover in year *Y* is measured as the proportion of reporting GPs that joined the *Sentinelles* network in year *Y* among all *Sentinelles* GPs that have been reporting in year *Y*. We monitor for each year the number of GPs present from the start of the study period (i.e. who joined in 1997 or earlier) as a measure of "stability" of the network.

We also assess the number of consultations and visits per year per reporting GP, and the age distribution of patients, thanks to a subset of GPs who provided their activity report form (RIAP). RIAPs are given to GPs by the French national health insurance, usually annually or quarterly, and are based on reimbursement records. In this forms, the number of consultations and visits is given for the following age groups: 0-15 year-old, 16-59 year-old, 60-69 year-old

and 70 year-old and over. As we did not have a RIAP per year per reporting GP, the closest in time to each study year (within a limit of three years) was chosen.

Relationship between the PRH and ILI consultation rates

We assess the relationship between the PRH and the cumulative rate of ILI consultations by season per 100,000 inhabitants using Pearson's linear correlation coefficient (ρ) and linear regression models. We repeat this analysis for each age group. To obtain ILI consultation rates overall and by age group, the weekly number of consultations reported by *Sentinelles* GPs is extrapolated to all French GPs and standardized on the current French population using a procedure in use since 1984 [10]. It ensures that estimated incidences are independent of the number of reporting GPs. The 2009-2010 season is excluded from the analysis, as it is an outlier both by its magnitude and by its PRH.

RESULTS

Over the thirteen epidemics analyzed herein, GPs reported 76,059 ILI cases, and recommended hospitalization for 326 of them. Detailed numbers by season, age group and gender are provided in Table 1. The largest PRH among ILI patients occurred during the 2009-2010 pandemic period (Figure 1). It was then equal to 9.7‰ (95% confidence interval: 8−11.7), when the average PRH over the seasons 1997-1998 to 2008-2009, was 3.4‰ (3−3.9). This increase was statistically significant, with an odds-ratio (OR) equal to 2.89 (95% CI: 2.28−3.64, Chi-square test for equal distributions: $p<0.001$).

PRH by viral subtype

The PRH varied substantially according to the dominant circulating influenza subtype(s) (logistic regression likelihood-ratio (LR) test: $p<0.001$, for detailed PRH by subtype see Table 2). Compared to the only seasonal A(H1N1) epidemic (2000-2001), the odds of hospitalization were significantly higher when A(H3N2) circulated: OR=3.44 (1.31−13.92, Wald z-statistic p=0.034). Co-circulation of A(H1N1) and B or dominance of B viruses did not significantly increase the odds of hospitalization: respectively OR=1.06 (0.34−4.65, p=0.929) and 2.46 (0.68−11.43, p=0.192). The 2009 A(H1N1) pandemic was associated with hospitalization odds increased by 8.52 fold compared to seasonal A(H1N1) (3.21−34.65, $p<0.001$).

PRH by age group

The PRH was the highest among patients above 40 years-old for every viral dominant subtype(s), yet to different extents (Table 2). During the A(H3N2) epidemics, the hospitalization odds of ≥40 year-old patients were 4.44 fold (3.13−6.45) those of 0-19 year-old patients (Wald z-statistic $p<0.001$), and 6.96 fold (4.39−11.77) those of 20-39 year-old patients ($p<0.001$). During the B and B-A(H1N1) epidemics, the difference between age groups was not statistically significant (respective LR test: p=0.12 and p=0.38). During the only seasonal A(H1N1) epidemic, few ILI cases were reported, and GPs recommended hospitalization only for 40 year-old or older patients, with a PRH of 5.7‰ (1.4−14.8). During the 2009-2010 pandemic, the differences in PRH between age groups flattened: the hospitalization odds of the ≥40 years-old were 1.15 fold the ones of 0-19 years-old (0.69−1.86, p=0.58) and 1.47 fold the ones of the 20-39 years-old (0.80−2.73, p=0.21). The PRH of ILI patients over 40 years-old was not statistically higher during the 2009-2010 pandemic than in seasonal epidemics: OR=1.5 (0.92−2.32), p=0.081. Two A(H3N2) epidemics, 2006-2007 and 1997-1998, presented higher PRHs for this age group than the

pandemic (Table 1). On the contrary, the PRHs of 0-19 and 20-39 year-old patients were higher during the pandemic than in any previous season, with OR=6.10 (4.16−9.02, p<0.001) for the 0-19 years-old and OR=6.94 (3.77−12.79, p<0.001) for the 20-39 years-old.

Furthermore, the relative ILI attack rate of the 0-19 year-olds was more important during the pandemic: 58% of reported ILI cases belonged to this age group versus 40% during seasonal epidemics, whereas the contrary was observed among ≥40 year-old: 17% versus 31%. The relative attack rate in intermediate ages remained stable 25% versus 29%. The hypothesis of equal age distributions in the two periods was significantly rejected (Chi-square test p<0.001). Therefore, this unusually high relative attack rate in the 0-19 year-old combined with the unusually high PRHs in the younger age groups resulted in a significantly lowered mean age of ILI patients requiring hospitalization during the 2009-2010 A(H1N1) pandemic: 20.5 years (15.1−26.0, median 11 years), when it was 55.6 years (51.9−59.4, median 67.5 years) for seasonal epidemics. This difference was statistically significant (Student's T test for equal means: p<0.001).

PRH by sex

The PRHs of men and women were not statistically different during seasonal influenza epidemics: OR=0.95 (0.73−1.24, p=0.713), see values in Table 2. The odds of hospitalization increased by 3.57 fold in women during the pandemic (2.60−4.86, p<0.001), and by 2.21 fold for men (1.52−3.15, p<0.001). At this time, the PRH of women was significantly above that of men: OR=1.53 (1.04−2.30, p=0.035). The relative ILI attack rate for each gender did not change during the pandemic: women represented 51% of all ILI cases during the pandemic, as much as in seasonal epidemics (Pearson's Chi-squared test p=0.66).

We further assessed the age × gender categories in which patients' hospitalization odds increased the most during the pandemic. Women aged 20-39 years-old had hospitalization odds increased by 11.8 fold during the pandemic (5.04−29.59, p<0.001). It can be noted that

this first category is composed of women of childbearing age. They were followed by 0-19 year-old girls (OR=8.65, 4.90−15.88, p<0.001), 0-19 year-old boys (OR=4.58, 2.68−7.86, p<0.001) and 20-39 year-old men (OR=3.92, 1.47−9.58, p=0.004). While hospitalization odds of the oldest women increased slightly during the pandemic (OR=1.89, 1.04−3.18, p=0.025), no change affected the oldest men (OR=0.86, 0.30−1.94, p=0.75).

Reasons for hospitalization

There were 278 patients for whom the reason for requiring hospitalization was stated: 174 in seasonal epidemics and 104 during the pandemic (Table 3). The distribution of reasons significantly differed between the two periods (Two sided Fisher's exact test: p<0.001). For seasonal epidemics, most patients (64%) were sent to hospital for respiratory reasons, followed by cardiac reasons (13.2%) and bad general condition (11.5%). During the 2009-2010 pandemic, although the main reasons remained respiratory problems (44.2%) and bad general condition (17.3%), "pregnancy", "diagnostic" and "age" became more frequent. The latter concerned seven infants less than one year old, two children aged 1 and 11 years-old, and an adult of 96 years. One of the two patients sent to hospital for an age reason during seasonal epidemics was under 1 year-old, and the age of the other one was unknown.

Surveillance during 2009-2010 pandemic

The presence/absence of risk factors for pandemic influenza complications was described for 8,878 ILI patients during the 2009-2010 season. The PRH was 5.2‰ (3.7−6.9) in the 8,152 patients without risk factors, and 56.5‰ (41.2−74.8) in the 725 ones presenting at least one risk factor (OR=11.56, 7.45−17.92, p<0.001). Specifically, pregnancy multiplied the odds of hospitalization by 38.62 (15.05−87.26, p<0.001), coexistence of chronic condition and obesity by 20.69 (4.82−61.37, p<0.001), chronic condition alone by 7.12 (3.79−12.65, p<0.001) and obesity alone by 5.22 (0.29−25.00, p=0.107) (Table 4).

When asked by their GPs, 6,383 out of 7,758 patients (82%) thought that they would have consulted for the same symptoms in a regular seasonal epidemic. This fraction was significantly larger in the subgroup of patients requiring hospitalization: 70 out of 72 patients, i.e. 97%, (OR=7.44, 2.34−45.33, p=0.005). The 41 GPs interviewed over the phone accounted for 60 out of the 105 recommended hospitalizations during the pandemic. When asked their personal views, they thought that they would have recommended hospitalization for only 32 of the 60 patients (53%) during a regular epidemic. When asked about the future of these 60 patients, they answered that 27 (45%) were admitted to hospital, 20 (33.33%) only had a consultation there and were rapidly discharged, two did not go to the hospital (3.33%), and one did not go and died at home (1.67%). What happened of the remaining 10 patients was unknown (16.67%).The weekly prospective monitoring of the PRH during the 2009-2010 season is shown in Figure 2. Real-time weekly estimation of the proportion of ILI patients for whom GPs recommended hospitalizations (plain line) and its 95% confidence interval (dotted lines), for each week between week 2009/19 and 2009/52, based on cumulative cases from week 2009/19.. Estimations culminated at 25.6‰ (10.3−51.2) in week 29, then decreased to reach 11.3‰ (8−15.3) in week 44 (last week of October), and remained quite stable until week 52 (10.2‰, 8.5−12.2). Note that this final estimate differs slightly from the one in Table 1, which is based only on data reported from week 37 to 52. The relative uncertainty of the PRH estimate was above 300% in week 19. It steeply decreased to reach 32% in week 44, i.e. two weeks before the epidemic peak, which occurred in week 46, and 18% in week 52.

Influence of the Sentinelles network's composition and of epidemic intensity

After decreasing from 339 in 1997 to 220 in 2002, the number of GPs reporting to the *Sentinelles* network augmented to reach 372 in 2010 (Table 5 and Figure 3). The mean

turnover (the proportion of new reporting GPs) was 23% per year (range: 8%-36%). The proportion of GPs present from the start of the study period (1997) decreased from 100% in 1997 to 23% in 2009, and increased to 25.5% in 2010 as the total number of *Sentinelles* GPs decreased. The proportion of women fluctuated between 11% in 1999 and 18% in 2001, 2008, 2009 and 2010, with an overall upward trend. The median age also augmented from 45 year-old in 1997 to 53.5 year-old in 2010. Across the study period, the median number of consultations and visits per reporting GP per year was quite stable (from 4690 in 1997 to 4665 in 2010) (Figure 3). The median proportion of patients also remained roughly stable for all age groups, with a slight decrease (from 24% to 22%) in the 0-15 year-old and a slight increase (from 54% to 55%) for the 16-59 year-old.

Finally, no significant correlation was found between the PRH and the cumulative seasonal consultation rate for ILI in general practice: $\rho=0.32$ (p-value: $p=0.30$). Furthermore, this relationship did not have the same direction in all age groups and, for each of them, fell far from statistical significance (see Figure 4).

DISCUSSION

Interpretation of the results

Sentinelles GPs recommended hospitalization of ILI patients three times more frequently during the 2009-2010 A(H1N1) pandemic than during seasonal influenza epidemics (OR=2.89, 95% CI: 2.28−3.64). The highest increase was among 20 to 39 year-old women: OR=11.8 (5.04−29.59). Alone, this indicator does not allow understanding what magnitude of increase was due to severity and what was precautionary, but this increase is consistent both with 2009 A(H1N1) presenting more severely in young adults, especially if pregnant, as was

reported early in the course of the pandemic [20, 21] and with the pandemic guidelines recommending hospital-based diagnosis for pregnant ILI patients [22].

Some pitfalls arise in the interpretation of the PRH presented in this work. First, the positive predictive value of the *Sentinelles* definition of ILI was reported around 40% for seasonal influenza, implying that the PRH based on these clinical data could be an underestimation of the true influenza PRH [12]. Second, this ILI definition has a limited sensitivity as it misses the asymptomatic cases and the symptomatic cases that do not feel bad enough to consult a GP. This leads to overestimating the influenza PRH by biasing the case ascertainment to the most severe ones. Third, it might be worthy to note once again that, herein, we monitor the proportion of *recommended* hospitalizations. Some of the patients might not go to the hospital, and some might only have a consultation there. In that respect, the present measure overestimates the true CHR. On the other hand, some patients for whom GPs did not recommend hospitalization could have been hospitalized afterwards, for example if their condition persisted or got worse after their consultation with the GP, making the present measurement an underestimation of the CHR.

Finally, the specific hospitalization criteria set up for pandemic A(H1N1) patients may have encouraged French GPs to send ILI patients to hospital [23], biasing our numerator, while the heavy media coverage and fear of the pandemic might have boosted the public concern and health-seeking behaviours, biasing our denominator. In particular, guidelines incited French GPs to send pregnant ILI patients to hospital consultations dedicated to viral identification of pandemic A(H1N1) [22]. It is thus possible that some *Sentinelles* GPs reported ambiguously directing a patient to hospital for consultation or hospitalization. The fact that GPs thought that they would have required hospitalization during a regular epidemic for only 53% of the patients seen during the pandemic is in accordance with this hypothesis (even if the magnitude of this bias doesn't explain the tripling of the PRH observed during the pandemic).

Thus, the PRH observed during the 2009-2010 pandemic does not readily reflects severity but, instead, the increased burden on the health-care system.

Enhancing surveillance for a better interpretation of the PRH

To disentangle severity from patients' behaviour and GP's practice inside the PRH and allow comparison between seasons, it is necessary to collect data both on the GP's tendency to recommend hospitalization (numerator) and on the patients' tendency to seek heath care (denominator). Questions in that respect could be asked to GPs and to their patients in each electronic case report. During the pandemic, we used a telephonic survey to assess the former and included the latter in the online questionnaire. The formulation and the suggested answer list should be allowed to change dynamically with the context (seasonal or pandemic in particular) while ensuring that the right data for inter-annual comparability are collected.

To infer from the PRH the *true hospitalization* ratio of ILI patients seen by general practitioners, and thus the true burden of the disease on hospitals, it would be also necessary to know 1) how many patients for whom hospitalization was recommended went to hospital and how many of them were admitted, and 2) how many ILI patients were hospitalized without GP recommendation. For question (1), it could be thought of GPs logging back into the system to complete a previous report. However, because reported cases are currently anonym in the system, this would imply rethinking the collection design. An annual cross-sectional survey among GPs' ILI patients could instead be contemplated to collect information on both points (1) and (2). To this respect, a pilot survey was launched during the 2009 pandemic to shed light on the future of 60 patients for whom GPs recommended hospitalization. GPs were contacted by phone in the days following their declaration. They knew whether or not their patients went to the hospital for 50 patients (83.33%). Among those, 27 were admitted, 20 had a consultation, and only three did not go to the hospital. This

pilot protocol has an encouraging response rate and should be considered for yearly implementation.

Finally, to assess the case-hospitalization ratio of *confirmed influenza* patients seen by general practitioners, both the PRH and the necessary side data described above should be collected on virologically confirmed patients. The *Sentinelles* network only implements virological surveillance in Corsica on a small number of patients, so currently these developments are not contemplated.

Influence of the Sentinelles network's composition and of epidemic intensity

We assessed if the composition of the *Sentinelles* network changed over the whole study period. We found that the average age of reporting GPs slightly increased and smoothly over the whole study period. The proportion of women also slightly increased, although with more fluctuations. Both increases are also observed in the French medical population as a whole [24, 25]. No noticeable trend or seasonal fluctuations in the number of consultations and visits or in the age distribution of patients was evidenced. Thus, it seems unlikely to us that the composition of the *Sentinelles* GPs explains the observed variations in the PRH, in particular the 2009-2010 increase. We also found no significant linear correlation between the PRH and the cumulative consultation rate for ILI in general practice, for all age groups and overall. Hence, the intensity of influenza seasons does not seem to influence the probability that GPs recommend hospitalization for ILI patients.

Conclusion

To sum up, the surveillance protocol presented herein do not provide immediately interpretable CHRs unlike ad-hoc surveys based on virologically or serologically confirmed

cases. Nevertheless, with the right data collected alongside to help with interpretation and assess inter-annual comparability, this system can help measuring the severity of epidemics on a scale defined by the GPs' concern about their patients' health. Furthermore, nested in a routine surveillance system, this protocol allows the continuous collection of baseline data on influenza-like illness severity. Besides, by linking hospitalizations to ILI cases at the individual level, the data presented here allows direct estimation of the probability of hospitalization among cases, and there is no delay between GPs' and hospitals notifications to be corrected for. Finally, the *Sentinelles* network was able to provide a PRH estimate with a relative uncertainty of ±32% two weeks before the peak of the 2009-2010 pandemic, and with a relative uncertainty of ±18% at the end of the pandemic. In conclusion, if data collection can be enhanced to help disentangling severity from behaviors and practices, this protocol is a promising tool for generating timely insights into the severity of influenza epidemics and their burden on the health care system.

ACKNOWLEDGEMENTS

We would like to thank all the general practitioners of the *Sentinelles* network who participated in the surveillance. This work was supported by the French medical research institute (Institut National de la Santé et de la Recherche Médicale) and by the University Pierre et Marie Curie – Paris 6. We also thank Cécile Souty for her analyses of the *Sentinelles* network composition.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

1. Van Kerkhove MD, Asikainen T, Becker NG, et al. Studies needed to address public health challenges of the 2009 H1N1 influenza pandemic: insights from modeling. PLoS Med. 2010 Jun;7(6):e1000275.

2. Lipsitch M, Riley S, Cauchemez S, Ghani AC, Ferguson NM. Managing and reducing uncertainty in an emerging influenza pandemic. N Engl J Med. 2009 Jul 9;361(2):112-5.

3. Presanis AM, De Angelis D, Hagy A, et al. The severity of pandemic H1N1 influenza in the United States, from April to July 2009: a Bayesian analysis. PLoS Med. 2009 Dec;6(12):e1000207.

4. Garske T, Legrand J, Donnelly CA, et al. Assessing the severity of the novel influenza A/H1N1 pandemic. BMJ. 2009;339:b2840.

5. Simonsen L, Fukuda K, Schonberger LB, Cox NJ. The impact of influenza epidemics on hospitalizations. J Infect Dis. 2000 Mar;181(3):831-7.

6. Monto AS. Epidemiology of influenza. Vaccine. 2008 Sep 12;26 Suppl 4:D45-8.

7. Donaldson LJ, Rutter PD, Ellis BM, et al. Mortality from pandemic A/H1N1 2009 influenza in England: public health surveillance study. BMJ. 2009;339:b5213.

8. Wilson N, Baker MG. The emerging influenza pandemic: estimating the case fatality ratio. Euro Surveill. 2009 Jul 2;14(26).

9. Flahault A, Blanchon T, Dorleans Y, Toubiana L, Vibert JF, Valleron AJ. Virtual surveillance of communicable diseases: a 20-year experience in France. Stat Methods Med Res. 2006 Oct;15(5):413-21.

10. Valleron AJ, Bouvet E, Garnerin P, et al. A computer network for the surveillance of communicable diseases: the French experiment. Am J Public Health. 1986 Nov;76(11):1289-92.

11. Chauvin P, Valleron AJ. Attitude of French general practitioners to the public health surveillance of communicable diseases. Int J Epidemiol. 1995 Apr;24(2):435-40.

12. 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 Feb;28(2):283-90.

13. Costagliola D, Flahault A, Galinec D, Garnerin P, Menares J, Valleron AJ. A routine tool for detection and assessment of epidemics of influenza-like syndromes in France. Am J Public Health. 1991 Jan;81(1):97-9.

14. Pelat C, Boelle PY, Cowling BJ, et al. Online detection and quantification of epidemics. BMC Med Inform Decis Mak. 2007;7:29.

15. Cohen JM, Mosnier A, Grog I. [Influenza surveillance in France]. Med Sci (Paris). 2003 Feb;19(2):239-42.

16. Turbelin C, Pelat C, Boelle PY, et al. Early estimates of 2009 pandemic influenza A(H1N1) virus activity in general practice in France: incidence of influenza-like illness and age distribution of reported cases. Euro Surveill. 2009;14(39).

17. Vaux S, Brouard C, Fuhrman C, et al. [Dynamic and impact of the A(H1N1)2009 epidemic in mainland France, 2009-2010]. Bulletin épidémiologique hebdomadaire. 2010;24-25-26:259-64.

18. Venzon DJ, Moolgavkar SH. A Method for Computing Profile-Likelihood-Based Confidence-Intervals. Appl Stat-J Roy St C. 1988;37(1):87-94.

19. Dorai-Raj S. Binomial Confidence Intervals For Several Parameterizations. 2009 [cited 2011 19 Sept]; Available from: http://cran.r-project.org/web/packages/binom/binom.pdf.

20. Centers for Disease Control Prevention. Hospitalized patients with novel influenza A (H1N1) virus infection - California, April-May, 2009. MMWR Morb Mortal Wkly Rep. 2009 May 22;58(19):536-41.

21. Centers for Disease Control Prevention. Novel influenza A (H1N1) virus infections in three pregnant women - United States, April-May 2009. MMWR Morb Mortal Wkly Rep. 2009 May 15;58(18):497-500.

22. French ministry for Health. [Handling and treatment of influenza A/H1N1 in pregnant women: recommendations as of Decembre 8, 2009]. 2009 [cited 2011 05 Sept]; Available from: http://www.sante.gouv.fr/IMG/pdf/Fiche_memo-femme_enceinte.pdf.

23. French committee of fight against influenza. [Hospitalization criteria of A(H1N1)v patients in pandemic situation (August 6, 2009)]. [cited 2011 05 Sept]; Available from: http://www.pds78.org/Pdf/Recos%20hospitalisation%20grippe.pdf.

24. Attal-Toubert K, Vanderschelden M. La démographie médicale à l'horizon 2030 : de nouvelles projections nationales et régionales détaillées. French Ministry of Health, DRESS. Dossiers solidarité et santé n°12. 2009.

25. Niel X. La démographie médicale à l'horizon 2020 : une réactualisation des projections à partir de 2002. French Ministry of Health, DRESS. Etudes et Résultats n°161. 2002.

TABLES

Table 1. Case-hospitalization ratio (‰) with 95% confidence limits, calculated as the ratio of recommended hospitalizations among ILI patients reported by *Sentinelles* GPs, for all influenza seasons from 1997-1998 to 2009-2010.

		Case-hospitalization ratio (‰) [95% confidence interval], # recommended hospitalizations (# ILI patients)					
			By age group (years)*			By gender*	
Season	**Subtype**	**Overall**	**0-19**	**20-39**	**≥40**	**Male**	**Female**
1997-1998	A(H3N2)	5.3 [3.8–7.3] 36 (6738)	2 [0.7–4.3] 5 (2508)	1.1 [0.2–3.3] 2 (1853)	12.2 [8.3–17.2] 29 (2377)	5.2 [3.1–8.1] 17 (3261)	5.5 [3.4–8.3] 19 (3477)
1998-1999	A(H3N2)	3.5 [2.3–5.1] 25 (7136)	2.2 [0.8–4.6] 5 (2314)	1.9 [0.6–4.4] 4 (2111)	5.9 [3.5–9.3] 16 (2711)	3.8 [2.1–6.2] 13 (3457)	3.3 [1.7–5.5] 12 (3679)
1999-2000	A(H3N2)	5.3 [3.7–7.2] 35 (6635)	1.2 [0.2–3.7] 2 (1677)	1.5 [0.4–3.9] 3 (2006)	10.2 [7–14.2] 30 (2947)	4.8 [2.8–7.5] 16 (3345)	5.8 [3.6–8.8] 19 (3290)
2000-2001	A(H1N1)	1.2 [0.3–3] 3 (2605)	0 [0–2.5] 0 (1354)	0 [0–4.6] 0 (725)	5.7 [1.4–14.8] 3 (525)	0.8 [0.1–3.3] 1 (1317)	1.6 [0.3–4.8] 2 (1288)
2001-2002	A(H3N2)	3.7 [2.1–6] 14 (3769)	2 [0.5–5.2] 3 (1489)	0.9 [0.1–3.9] 1 (1130)	8 [3.8–14.3] 9 (1132)	3.3 [1.3–6.6] 6 (1835)	4.1 [1.9–7.7] 8 (1934)
2002-2003	B	2.8 [1.2–5.5] 7 (2473)	1.5 [0.3–4.6] 2 (1332)	1.7 [0.2–7.2] 1 (606)	7.6 [2.4–17.6] 4 (525)	2.3 [0.6–6.1] 3 (1278)	3.4 [1.1–7.9] 4 (1173)
2003-2004	A(H3N2)	3.6 [2.3–5.3] 22 (6130)	2.8 [1.3–5] 9 (3219)	1.2 [0.2–3.7] 2 (1648)	8.8 [4.6–15.1] 11 (1247)	3.9 [2.1–6.5] 12 (3071)	3.3 [1.7–5.8] 10 (3004)
2004-2005	A(H3N2)	3.2 [2–4.8] 21 (6578)	0.8 [0.1–2.6] 2 (2396)	0 [0–1.8] 0 (1878)	8.3 [5.1–12.6] 19 (2293)	4 [2.2–6.6] 13 (3262)	2.2 [0.9–4.2] 7 (3253)
2005-2006	A(H1N1) & B	1.5 [0.6–3.1] 6 (3886)	1.3 [0.3–3.3] 3 (2326)	2.3 [0.4–7.1] 2 (867)	1.5 [0.1–6.4] 1 (686)	2.1 [0.6–4.8] 4 (1942)	1 [0.2–3.2] 2 (1911)
2006-2007	A(H3N2)	6.6 [4.6–9.1] 33 (4979)	4.7 [2.4–8.3] 10 (2122)	2.1 [0.5–5.4] 3 (1446)	14.4 [9–21.6] 20 (1388)	6.7 [3.9–10.5] 16 (2390)	6.8 [4–10.5] 17 (2510)
2007-2008	A(H1N1) & B	1 [0.4–2] 6 (5951)	0.8 [0.1–2.5] 2 (2434)	0 [0–1.9] 0 (1798)	2.4 [0.7–5.5] 4 (1690)	1 [0.3–2.7] 3 (2902)	1 [0.3–2.6] 3 (2980)
2008-2009	A(H3N2)	1.5 [0.9–2.6] 13 (8388)	0.3 [0–1.3] 1 (3338)	1.2 [0.3–3.2] 3 (2453)	3.5 [1.7–6.2] 9 (2597)	1.7 [0.8–3.4] 7 (4001)	1.2 [0.4–2.5] 5 (4282)
2009-2010	A(H1N1)	9.7 [8–11.7] 105 (10791)	10 [7.8–12.7] 63 (6279)	7.8 [4.9–11.6] 21 (2685)	11.5 [7.3–17.2] 21 (1820)	7.6 [5.5–10.2] 40 (5241)	11.7 [9–14.8] 63 (5402)

* Some patients' age and/or sex might be unknown.

Table 2. Case-hospitalization ratio among ILI patients reported by *Sentinelles* GPs during influenza seasons 1997-1998 to 2009-2010, aggregated by dominant circulating viral subtype(s).

	Case-hospitalization ratio (‰) and 95% confidence interval					
		By age group (years)*			By gender*	
Dominant subtype(s)	**Overall**	**0-19**	**20-39**	**≥40**	**Male**	**Female**
A(H1N1)	1.2 [0.3−3]	0 [0−2.5]	0 [0−4.6]	5.7 [1.4−14.8]	0.8 [0.1−3.3]	1.6 [0.3−4.8]
A(H1N1) & B	1.2 [0.7−2]	1.1 [0.4−2.3]	0.8 [0.1−2.3]	2.1 [0.8−4.5]	1.4 [0.6−2.8]	1 [0.4−2.2]
A(H1N1) 2009	9.7 [8−11.7]	10 [7.8−12.7]	7.8 [4.9−11.6]	11.5 [7.3−17.2]	7.6 [5.5−10.2]	11.7 [9−14.8]
A(H3N2)	4 [3.4−4.5]	1.9 [1.4−2.6]	1.2 [0.8−1.9]	8.6 [7.2−10]	4.1 [3.3−4.9]	3.8 [3.1−4.6]
B	2.8 [1.2−5.5]	1.5 [0.3−4.6]	1.7 [0.1−7.2]	7.6 [2.4−17.6]	2.3 [0.6−6.1]	3.4 [1.1−7.9]
All subtypes except A(H1N1) 2009	3.4 [3−3.9]	1.7 [1.2−2.2]	1.1 [0.7−1.7]	7.7 [6.6−9]	3.5 [2.9−4.1]	3.3 [2.7−4]

* Some patients' age and/or sex might be unknown

Table 3. Number of recommended hospitalizations for ILI patients, by category of reason, and percentage over the columns.

	Seasonal epidemics 1997-1998 to 2008-2009	2009-2010 A(H1N1) pandemic	Overall
Age	2 (1.1%)	10 (9.6%)	12 (4.3%)
Bad general condition	20 (11.5%)	18 (17.3%)	38 (13.7%)
Cardiac	23 (13.2%)	5 (4.8%)	28 (10.1%)
Confusion	6 (3.4%)	1 (1.0%)	7 (2.5%)
Dehydration	2 (1.1%)	2 (1.9%)	4 (1.4%)
Diagnostic	0 (0.0%)	9 (8.7%)	9 (3.2%)
Meningitis	5 (2.9%)	3 (2.9%)	8 (2.9%)
Pregnancy	1 (0.6%)	6 (5.8%)	7 (2.5%)
Respiratory	111 (64.0%)	46 (44.2%)	157 (56.6%)
Risk Factor	2 (1.1%)	2 (1.9%)	4 (1.4%)
Social	2 (1.1%)	2 (1.9%)	4 (1.4%)
Total	174	104	278

Table 4. Case hospitalization ratio of ILI patients by risk factor, as reported by the general practitioners from the *Sentinelles* network.

Risk factor	Case-hospitalization ratio (‰) and 95% confidence interval	Recommended hospitalizations (total ILI patients)
None	5.2 [3.7−6.9]	42 (8152)
Pregnancy	166.7 [75.3−297.5]	7 (42)
Chronic condition & obesity	96.8 [25.2−232.1]	3 (31)
Chronic condition	35.5 [20.6−56.1]	15 (422)
Obesity	26.3 [3.3−110.8]	1 (38)
Other	77.7 [45.5−121.1]	15 (193)
At least one risk factor	56.5 [41.2−74.8]	41 (726)
Overall	9.3 [7.5−11.5]	83 (8878)

Table 5. Characteristics of the GPs reporting to the *Sentinelles* network surveillance system from 1997 to 2010.

		Age (in years)							Sex				Year joined the *Sentinelles* network		
Year	Number of GPs	Min	1st quartile	Median	Mean	3rd quartile	Max	Unknown	Women	Men	Unknown	% of women	1997 or earlier	Current year	After 1997 and before current year
1997	339	31	40	45	45.32	50	68	2	40	299	0	12	339	-	-
1998	275	32	42	46	46.23	50	69	2	34	240	1	12	252	23	-
1999	252	32	43	47	47.42	51	70	4	28	223	1	11	221	24	7
2000	236	31	43	48	47.98	52	69	3	32	203	1	14	183	35	18
2001	268	30	42	47	47.17	52	69	1	48	219	1	18	158	80	30
2002	220	31	43	48	47.61	53	76	2	32	187	1	15	109	60	51
2003	237	29	44	49	48.49	53	77	6	34	202	1	14	104	83	50
2004	228	30	45	50	49	54	78	6	35	193	0	15	96	54	78
2005	242	31	46	51	50.08	55	79	17	31	211	0	13	90	75	77
2006	255	30	46	52	50.74	56	80	16	36	219	0	14	88	54	113
2007	283	28	47	52.5	51.36	57	81	15	36	247	0	13	92	68	123
2008	379	29	46	53	51.39	58	82	18	68	311	0	18	106	138	135
2009	452	29	46.25	53	51.77	58	83	18	81	371	0	18	104	136	212
2010	372	30	47	53.5	52.3	59	84	14	67	305	0	18	95	36	241

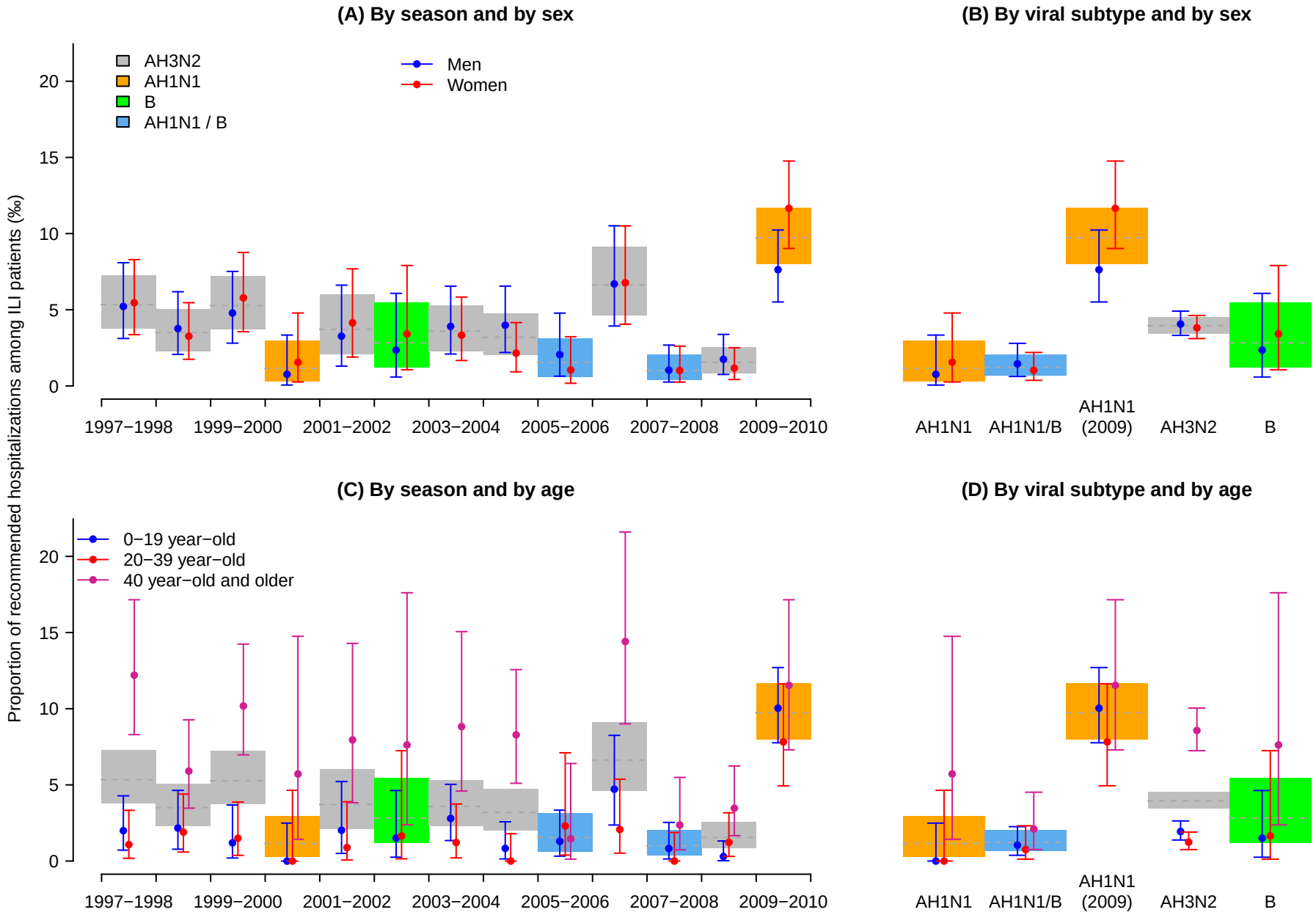
FIGURE LEGENDS

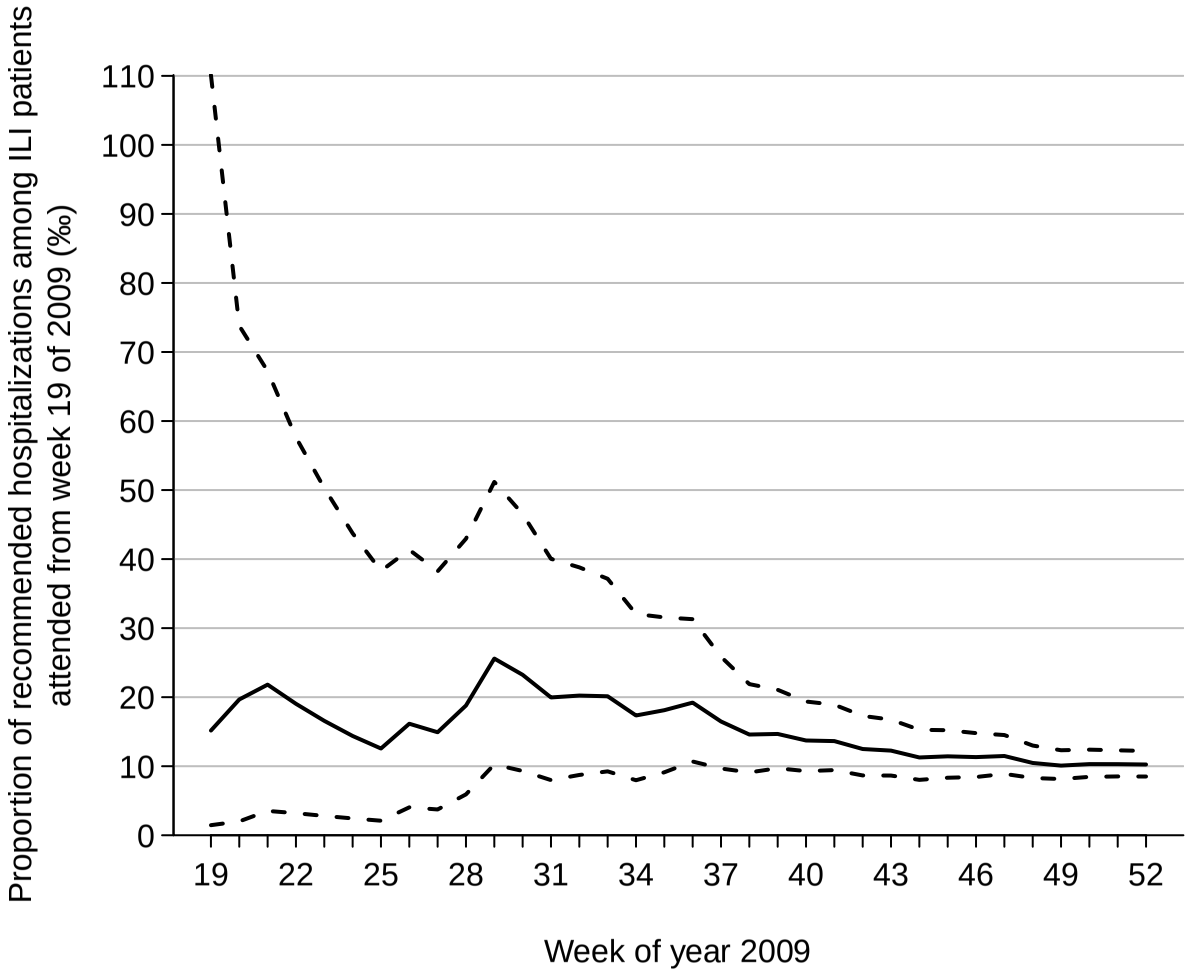
Figure 1. Proportion of recommended hospitalizations among ILI patients (‰) by season (panels A and B) or by subtype (panels C and D), distinguishing by sex and age group.

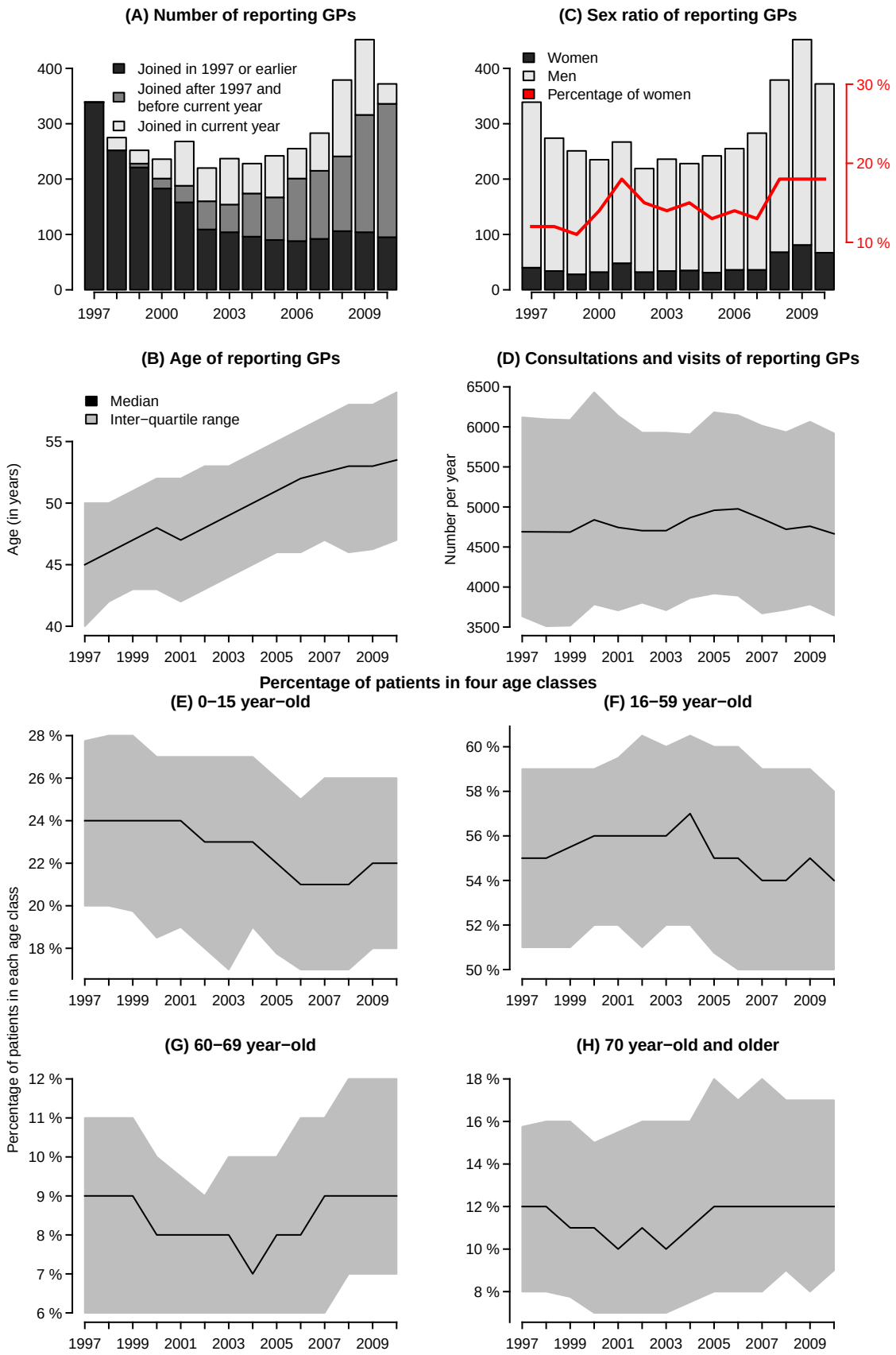
Figure 2. Real-time weekly estimation of the proportion of ILI patients for whom GPs recommended hospitalizations (plain line) and its 95% confidence interval (dotted lines), for each week between week 2009/19 and 2009/52, based on cumulative cases from week 2009/19. Highlighted in red is the proportion of recommended hospitalization in week 44 (11.3‰).

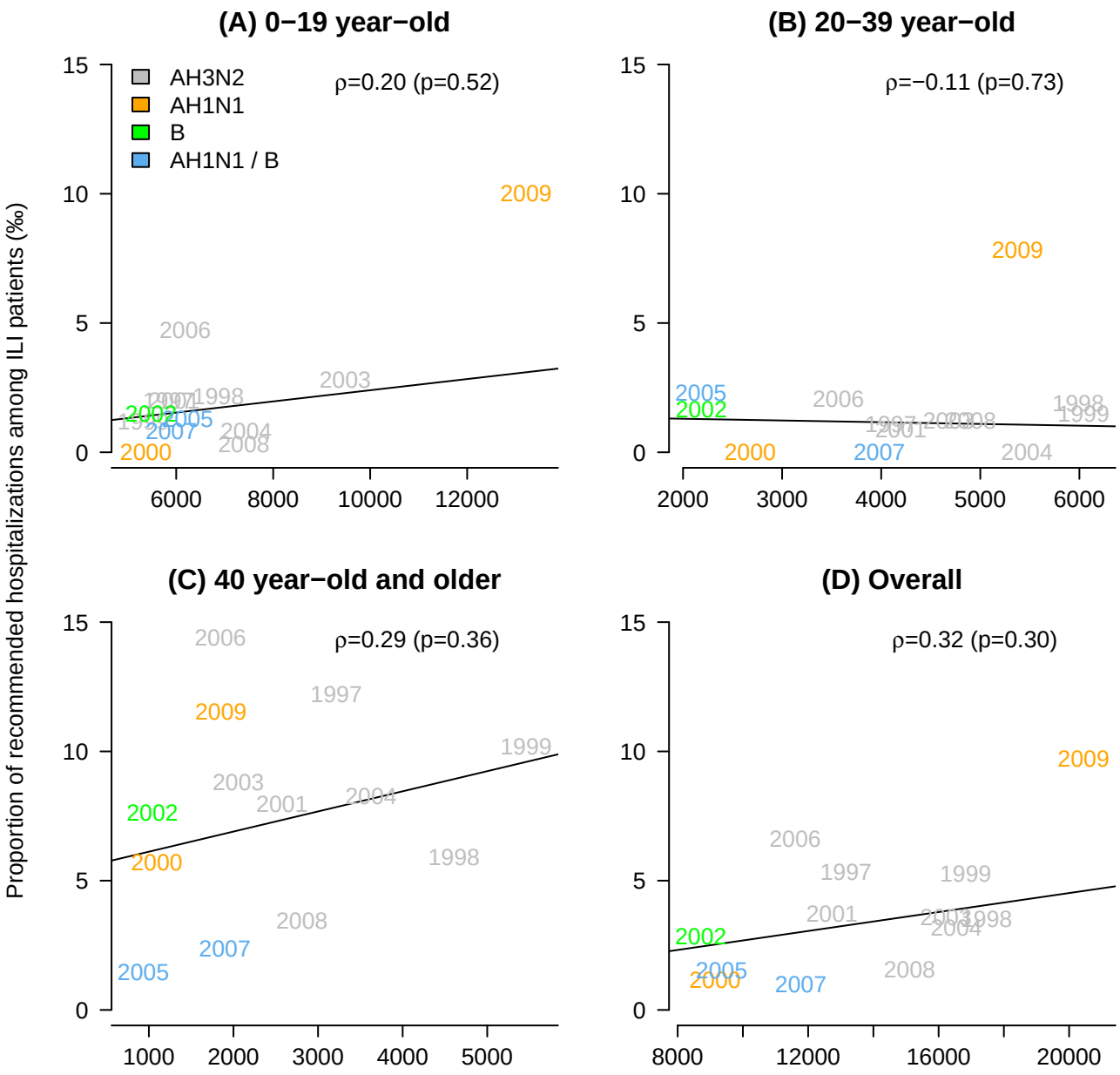
Figure 3. Characteristics of the GPs reporting to the *Sentinelles* network surveillance system from 1997 to 2010 (A: number and turnover, B: sex, C: age, D: activity). E-H: age distribution of *Sentinelles* GPs' patients in four age groups. Panel D to H are based on a subset of GPs that provided an activity report form within three years of each study year.

Figure 4. Proportion of ILI patients for whom *Sentinelles* GP recommended hospitalization versus the cumulative rate of ILI consultations by influenza season: (A) among the 0 to 19 year-old, (B) the 20 to 39 year-old, (C) the 40 and more year-old, (D) overall.


(A) By season and by sex
(B) By viral subtype and by sex
(C) By season and by age
(D) By viral subtype and by age
Proportion of recommended hospitalizations among ILI patients (‰)
AH3N2
AH1N1
B
AH1N1 / B
Men
Women
0−19 year−old
20−39 year−old
40 year−old and older
0
5
10
15
20
1997−1998
1999−2000
2001−2002
2003−2004
2005−2006
2007−2008
2009−2010
AH1N1
AH1N1/B
AH1N1 (2009)
AH3N2
B


Proportion of recommended hospitalizations among ILI patients attended from week 19 of 2009 (‰)
110
100
90
80
70
60
50
40
30
20
10
0
19
22
25
28
31
34
37
40
43
46
49
52
Week of year 2009


(A) Number of reporting GPs
Joined in 1997 or earlier
Joined after 1997 and before current year
Joined in current year
(C) Sex ratio of reporting GPs
Women
Men
Percentage of women
30 %
20 %
10 %
(B) Age of reporting GPs
Median
Inter−quartile range
Age (in years)
(D) Consultations and visits of reporting GPs
Number per year
Percentage of patients in four age classes
(E) 0−15 year−old
(F) 16−59 year−old
Percentage of patients in each age class
(G) 60−69 year−old
(H) 70 year−old and older


(A) 0−19 year−old
(B) 20−39 year−old
(C) 40 year−old and older
(D) Overall
AH3N2
AH1N1
B
AH1N1 / B
ρ=0.20 (p=0.52)
ρ=−0.11 (p=0.73)
ρ=0.29 (p=0.36)
ρ=0.32 (p=0.30)
Proportion of recommended hospitalizations among ILI patients (‰)
Cumulative ILI consultation rate per 100,000 inhabitants over each season, by age group