Author’s response to reviews

Title: Assessment of two complementary influenza surveillance systems: Sentinel primary care Influenza-like Illness versus severe hospitalized laboratory-confirmed influenza using the moving epidemic method

Authors:

Nuria Torner (nuria.torner@gencat.cat)
Luca Basile (chags@gencat.cat)
Ana Martinez (a.martinez@gencat.cat)
Cristina Rius (crius@aspb.cat)
Pere Godoy (pere.godoy@gencat.cat)
Mireia Jane (mireia.jane@gencat.cat)
Angela Dominguez (angela.dominguez@ub.edu)

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Author’s response to reviews:

Assessment of two complementary influenza surveillance systems: Sentinel primary care Influenza-like Illness versus severe hospitalized laboratory-confirmed influenza using the moving epidemic method

First of all the authors would like to thank the reviewers for their extensive contribution to the improvement of this work. We have thoroughly taken into account all suggestions and introduced them to the content as far as possible according to available data in order to improve quality.

Reply to reviewers comments:

Reviewer 1:

This study is based on surveillance data of ILI incidence rates from primary care sentinel surveillance, virology results from sampling by sentinel primary care physicians and severe laboratory-confirmed influenza (SHLCI) that required hospital admission during seven influenza epidemic seasons, from 2010 to 2017, in Catalonia. The authors assess the parallelism of community primary care activity and severe hospitalisations related to influenza during seven influenza seasons using the Moving Epidemic Method (MEM). MEM has been recently (2011-2013) endorsed by ECDC and WHO Europe and is actually in the focus of the public health
community [1-5]. The integration of ILI/ARI data with virological information should improve and validate MEM usefulness and has been covered recently and is an actual ongoing field of study [2,4,6,7].

The manuscript should, therefore, be of interest to BMC Public Health audience, but, in its current format, it needs a major revision before being accepted for publication.

English use, wording (Mobile is to be named Moving), underpinning conceptual framework presentation, a more concise and ordered discussion and recent MEM references should be included and discussed.

Paper goal

The authors compare two surveillance systems in their capacity to describe epidemic intensity levels.

1. Sentinel primary care Physicians / (ILI) and ILI with laboratory-confirmed influenza
2. Reporting hospitals: / (SHLCI) severe hospitalised with laboratory-confirmed influenza cases.

And conclude that:

1. Influenza sentinel surveillance system combining primary care and hospital data provides a timely and accurate syndromic and virological assessment of influenza epidemic intensity.
2. The implementation of a third hospital warning system based on data from emergency department records for laboratory-confirmed influenza would be desirable.

1. Wording Mobile has been changed throughout and replaces by Moving

Title

Actual:

"Assessment of two complementary influenza surveillance systems: Sentinel primary care Influenza-like Infection versus severe hospitalised laboratory-confirmed influenza."

Is Sentinel primary care a proxy for Primary care Sentinel Surveillance System?
Its Sentinel primary care "Influenza-like Infection"? Or "Influenza-like illness"? Please clarify both.

The sentence "using the moving epidemic method" should be added at the end of the title. All this would convey a more explicit message to readers.

Sentinel primary care is a proxy for Primary care Sentinel Surveillance System

Yes, just not to make the title so long and

Infection has been changed to illness

The title has been changed to: Assessment of two complementary influenza surveillance systems: Sentinel primary care Influenza-like Infection versus severe hospitalised laboratory-confirmed influenza using the moving epidemic method

Abstract

Page 2

Line 13: Suggest: "...epidemiological study carried out during seven influenza seasons (2010-2017) in Catalonia, with data from…"

Line 13, where it says: "data from influenza sentinel surveillance of primary care physicians."

What is reported by primary care physicians? If it is ILI

Suggest: data from sentinel surveillance of primary care physicians reporting influenza-like illness (ILI)

Sentences have been changed as suggested

Line 15, can be misread, do hospitals provide data on outpatients?

Suggest:

and 12 hospitals that provided data on severe hospitalised cases with laboratory-confirmed influenza (SHLCI).
Line 18 and 19, it says:
"Epidemic thresholds for incidence rates were assessed by the Mobile Epidemics Method."

All the literature refers to the "Moving Epidemic Method" (see [1-5,8]). This is a significant drawback. If the term Mobile is used, it will prevent retrieval as this is not the widely accepted (ECDC, Who Europe, see references) of how the method should be named.

Were it says:
"Epidemic thresholds for incidence rates were assessed by the Mobile Epidemics Method "

It should say

"Epidemic thresholds for ILI incidence rates and (which SHLCI metric was used, % Of positives by week? Admissions with Influenza lab confirmed population rates?) were assessed by the Moving Epidemic Method (MEM)"

Swap "Mobile" by "Moving" all over the text.

SHLCI metric used are the number of hospital admitted severe influenza confirmed cases.

All changes have been done.

Line 25 and Line 31 PIDIRAC. FLU, ILI, FLUA and FLUB are unexplained acronyms. There is extreme use of non-standard abbreviations.

Considering influenza A and influenza B, plus influenza overall adds a layer of complexity that is not adequately covered in the Abstract background or Methods. Moreover, subtype analysis would be the proper approach given the differences between A(H3N2) and A(H1N1)pdm09, even between B/Yamagata and B/Victoria lineages, and it should be discussed if this is robust approach given the small number of training seasons to implement MEM.

Was, therefore, a study goal to further differentiate by influenza virus type? If this were the case, this should be included in the Abstract Background or Methods, in the appropriate same manuscript sections.

Abreviations and subtype analysis have been added to the methods section. Strain differentiation as not been taken into account because it is out of the range of this paper. The aim of this work is
in regard to how both systems behave in the forecasting of epidemic activity onset and severity allowing for healthcare preparedness.

Lines: 38 to 40 This conclusion cannot be implied from the data presented and would be more adequately argued in the Discussion's last paragraph. I do not see, however, that the results presented and what is already published support adding this new layer on top of reported admissions with severe hospitalised laboratory-confirmed influenza cases (SHLCI). So the authors should offer reasoning or fact supported evidence to justify that statement.

The phrase has been moved to Discussion’s lasta paragraph . And a new conclusion sentence has been added in the abstract.

Background

Page 3


Reference has been replaced

Line 58, "Random" or "systematic sampling"? A sampling method can be either systematic or random, but not both. Review that also in Methods.

Random has been deleted or replaces by systematic

Page 4

Line 7. Is this the case in Catalonia or are it and overall characteristic in those systems?, please, provide evidence (i.e. Reference(s))

This affirmation is in reference to the European guidelines that were set forth after Influenza A pandemic in 2009 which were adopted also by the Spanish Influenza surveillance System to which Catalonia reports. Other references as to European and other countries has been stated here also.

Line 18, the first appearance of an acronym in the text should be preceded by its explanation, please, include it here.

On line 8 PIDIRAC acronym has been written out

Lines 29-37

How do severe cases reach the hospital and are admitted? This paragraph is a bit confusing, are not the majority of severe cases admitted to the hospital after discharge to admission from the Emergency Department? Please make this clear.

Cases may reach the hospital through emergency room after discharge, but some do not. We register those cases sentinel physician or epidemiologist in charge of the SHLCI surveillance in that particular facility notified because of ICU or ward admission, regardless of whether they have been admitted after discharge from ER or not.

Sentence has been clarified in the text to point out this fact.

Moreover, Reference 6, is the Catalan health care system similar to Australia's… are included hospital third level care hospitals?

Which rates (parameters) are considered when including SLCIH? Population rates by n/time? Percentage of positives by week? Explain.
The Australian System considers any Influenza confirmed hospital admission and therefore rates severity taking into account total influenza admissions, the Catalan System did not have this data available, thus the incidence rate of severe influenza is calculated taking as denominator the population assigned to each hospital facility. That is why the reference was stated in this sentence.

Hospital facility admitted to the SHLCI System is required to be able to confirm type of influenza virus. Unless this is so, it cannot be included in the surveillance network.

Line 38, When was the Primary Care Sentinel Surveillance System was implemented? Please, explain.

Reference to the PIDIRAC primary care guidelines has been included and year of implementation of the System as well.

Methods,

Data sources

Page 4,

line 59

Omit the bullet points, and introduce your "Data sources" subsection in the Methods section as such, in a single heading.

Subheadings for the Primary Care based ILI Surveillance System and Severe Admissions with lab-confirmed influenza can be included if needed. But, a describing paragraph for each one should suffice.

Changes have been made accordingly

Page 5,

Line 4, omit "random", "systematic sampling of the first 2 patients"… is perfectly adequate

Random has been omitted
Lines 10 and 11, other respiratory viruses are not of interest here, but how the samples are treated is of relevance. RT-PCR? Subtyping? Reporting consistency (timeliness)? When dealing with hospital cases, we are told that positives were subtyped. If primary care lab-confirmed influenza (LCI) cases were or not subtyped. Is this primary care information included in Figure 1?

Information as to laboratory processing of samples has been added, along with a reference to extended methodology. Yes, this information is included in Figure 1.

As sampling was performed in the first two cases each week, could you explain which rates and how they were estimated for primary LCI influenza cases (PIDIRAC-FLUA and FLUB)? Please, add in the discussion how it could impact the comparison with the thresholds obtained from hospital LCI cases.

The PIDIRAC ILI rates are calculated according to weekly population under surveillance by the System. That is the population assigned to each sentinel physician of the network that is reporting.

Line 20. Clarify the meaning of incidence rates here, (denominator, per 100,000 inhabitants? per week?) that will facilitate the interpretation of the information reported thereon.

The PIDIRAC ILI rates are calculated according to weekly population under surveillance by the System. That is the population assigned to each sentinel physician of the network that is reporting.

Some information as to calculation of incidence rates has been included to clarify.

Line 29, "Mobile" -> "Moving" "Epidemics" -> "Epidemic"

Lines 29 to 36 should move to the Statistical analysis section, preceding Page 6, line 24.

See also my comment below for Table 1.

Page 6.

Line 9 and 13 both mention rates. Before in the text, we have been told that no population denominators were available and that (because) some (all?) hospitals were reference hospitals (level of care?) Please clarify, which rates do you refer to in lines 9 and 13?

Rates have been clarified before in the methods section.
Do not duplicate rates description for SLCIH.

Duplication has been deleted.

Line 11, in MEM thresholds, are estimated to predict the beginning of the epidemic season and to describe levels of intensity. I would counsel to omit the word activity in the text. It is used with different meanings in different parts of the manuscript, and that use as a proxy of different situations is in detriment of exposition clarity.

Activity has been either deleted or changed to other expressions such as circulation or intensity for clarification.

Line 13 to 19, should under the Statistical analysis section, following the paragraph (lines 23-29, page 5) that should open the Statistical analysis Methods subsection.

Statistical analysis

Line 22

MEM is part of the Statistical analysis and should be referred here as the first paragraph of Statistical analysis subsection in methods, explaining here that it was used to estimate statistics (enumerate and describe) for both Primary Care and Hospital derived data, as requested above.

Paragraph has been changed to this position under the Statistical analysis subheading.

Overall, the paragraph in lines

Line 31, "activity" -> intensity, the activity is here redundant, delete, or say intensity levels.

Done.

Lines 38 to 45, review those two incomplete "sentences or depended on clauses" as one presents the problem and the second tells how it will be solved, but instead of being connected as a logical flow, they are separated by a period and presented as two different things. I suggest the authors transform both into a single sentence, with a problem and its solution.
Change has been done

Line 40, "activity"-> epidemic

Line 42. "Level" -> "estimated epidemic threshold".

All in all, the sentences contained in lines 30 to 45 are critical to understanding how the authors will compare the different systems. The analysis is, however, presented first by comparing intensity levels and their thresholds estimated for the surveillance systems considered followed by the ability to predict the epidemic onset. Notice that this is not a logical order, as first, we expect an epidemic to begin to know afterwards about its intensity. This contrarian presentation of issues does not help reading and understanding. Please, consider.

Could you add the predicted epidemic onset in the figures?

Sentences contained in lines 30 to 45 have been clarified for better understanding and order has been changed accordingly.

Could you add the predicted epidemic onset in the figures?

There is no predicted epidemic onset as such, what we compare is how the different indicator pairs behave with respect to each other. So it what forecasts each season is the baseline epidemic threshold that is different for each pair of set indicators.

What is used as forecasting is the epidemic threshold level that is already in the figures.

Results

Page 6,

Line 53.

The first sentence refers to Table 1, note that in the submission Table1 is positioned after Table 2. Please, order the tables consecutively, first 1, then 2.
In the text, we are told that epidemic levels are presented there, but the title in Table 1 refers to "threshold levels."

Change has been made in the text

In fact, the table reports (?) "threshold levels" such as epidemic and intensity, but not activity threshold levels, according to the results usually obtained (and named) when applying the MEM approach.

Caption include intensity to replace activity

Accordingly, I suggest:

a. I would recommend that this is made clear beforehand in the text by the authors, describing in Methods, Statistical Analysis, MEM, the definition and meaning of threshold level(s), epidemic and intensity levels. I would suggest that this is also made clear in the text and that the Table caption and column headings are both consistent with the main text and table contents.

Caption include intensity to replace activity

b. The table caption should be following the text and explicitly mention that what is presented in the Table is the threshold value for epidemic onset and for intensity levels.

c. The first column heading. This column will show Data Sources. Not rates for the surveillance systems described.

d. Second column title should be Epidemic threshold, notice that baseline and threshold levels are not the same estimate (see Vega et al., 2013).

Data sources

Baseline Epidemic Threshold

(x 100,000 h x week) Low Intensity Threshold

(x 100,000 h x week) Medium Intensity Threshold

(x 100,000 h x week) High Intensity Threshold
(x 100,000 h x week)

e. Rest of column heading are thresholds for intensity (activity) levels: low, medium, high. Please make this clear with an umbrella heading with levels as subheadings.
f. Footnote, specify rates of what/per how many/time.

Page 7,

Line 38, severity or intensity?

Line 55-56, epidemic activity weeks, which is the difference between "epidemic weeks"? The word "activity" is redundant, see my comment above.

Has ben changed accordingly

Table 2 does not report rates whatsoever, why duplicate the footnotes in Table 1 in which rates are actually reported.

Footnote has been corrected accordingly

Discussion

Page 8.

First paragraph, lines 11 to 35 is out of place, it probably would fit in the Introduction, where the definition of the context and background of the main manuscript theme is being explained.

This paragraph, however, does not fit the manuscript content as the logical conclusion of the ideas exposed would be that an annual influenza vaccine effectiveness monitoring system is needed. The goal of the manuscript goes about predicting the beginning of the influenza season and levels of intensity and peaks by two different reporting systems, primary care ILI and hospital virological data and additionally primary care and hospital virological information.

Paragraph has been moved to the introduction section
The next page paragraph, lines 38 to 51, is definitely a first paragraph for the Discussion of results and methods.

This paragraph is now at the beginning of the Discussion section

Line 49 What do you mean here by "activity", season onset? Peak? Intensity?

Activity has been replaced by onset for a better comprehension

I would suggest a carriage return in line 51, to make a clear distinction between what has been observed versus the proper discussion of what is the interpretation of the observed results and its limitations. "Case definition…" should be the beginning of a new paragraph.

Done

Lines 55 to 60. While interference among respiratory viruses has been previously described, regarding the surveillance of influenza epidemics the interference or variability of MEM sensitivity and specificity due to the circulation of other viruses has been observed in ARI based surveillance systems. Can the authors discuss this?

Some extension on this issue has been added along with reference (Green et al. Harmonizing influenza primary-care surveillance in the United Kingdom: piloting two methods to assess the timing and intensity of the seasonal epidemic across several general practice-based surveillance schemes. Epid Infect. 2015 ;143(1) 1-12

Page 9,

Lines 9 to 20, could the authors review and compare their arguments here with Murray et al. findings in the UK (Murray JLK, Marques DFP, Cameron RL, et al. Moving epidemic method (MEM) applied to virology data as a novel real time tool to predict peak in seasonal influenza

We have introduced some similarity in the limitations to our study as well as future Research according to our observations amnd those of Murray et al.

Line 22. The authors introduce the "strengths and limitations" discussion, but this section does not follow a step by step reasoning thread.

Limitations have been stated as such and in orderly manner

Lines 27 and 29.

MEM is intended to trigger harm reduction activities due to its sensitivity and specificity in predicting season onset and peak. In addition of intensity, accordingly "intensity and severity" are outplaced, as is the preeminent influenza epidemic in itself, independently of intensity and severity, that will trigger those measures justified by an over the baseline circulation of influenza, for instance, the crossing of the therapeutic threshold for the use of antivirals, public communication, resources allocation… non-pharmacological measures and so on. Please, review that phrase.

The phrase has been reviewed and corrected

Line 40 to line 3 on page 10. The authors introduce here a discussion on intensity and severity appreciation that is not related to the proper strengths and limitations of this particular study.

They then discuss alternative surveillance systems, some of them no longer active (Google flu trends, for instance), all in all, this alternative source description is misplaced here.

Google flu trends is still available, although it is not easily available as before, actually we include this data for the modelling of influenza forecast mapping during the epidemic season

Paragraph has been rephrased as a possible solution to the limitation stated

Lines 53-54, please, provide evidence (reference reporting empirical observation) supporting the assertion that "Case definitions with a lower relative specificity for influenza, such as ILI can decrease the specificity of the model to detect an influenza season."

Reference has been provided ([ Green Epid & Infect 2015]

Page 10.

Lines 4 to 13 to

Can the author consider moving this whole paragraph and the discussion on alternative surveillance systems that begins in line 58 of page 9, at the end of the discussion of the limitations, just before conclusions, that is to line 46 in age 10.

Done

References


Reviewer 2 (Reviewer 2): PEER REVIEWER ASSESSMENTS:

OBJECTIVE - Full research articles: is there a clear objective that addresses a testable research question(s) (brief or other article types: is there a clear objective)?

No - there are minor issues

DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?

No - there are minor issues

EXECUTION - Are the experiments and analyses performed with technical rigor to allow confidence in the results?

Yes - experiments and analyses were performed appropriately

STATISTICS - Is the use of statistics in the manuscript appropriate?

Not sure - I am not able to assess the statistics in this study

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?

Yes - the author's interpretation is reasonable

OVERALL MANUSCRIPT POTENTIAL - Is the current version of this work technically sound? If not, can revisions be made to make the work technically sound?
Probably - with minor revisions

PEER REVIEWER COMMENTS:

GENERAL COMMENTS: This manuscript aimed at comparing two existing surveillance systems for ILI and Influenza-associated hospitalized-patient. Although methodology could be revised for a better understanding, the overall objective of this manuscript is reached. Authors demonstrated that these two systems are complementary and useful to monitor influenza activity. Use of the MEM methods seems adequate at least in Spain to estimate threshold for the two systems. Nevertheless, I have some concerns that should be addressed by authors.

REQUESTED REVISIONS:

Page 5, Line 4: I'm confused. If it is the first 2 ILI patients, we can't really say "random swab"? Please correct your sentence.

Sentence has been corrected to systematic swab sampling (nasal or nasopharyngeal)

Page 5-6: Can authors explain better the SHLCI system. If hospital only report lab-confirmed flu cases, do they also report syndromic case (eq. SARI)? It is indeed difficult to estimate the rate of FLU among total hospitalization or at least among patient with SARI. It is really confusing the use of SHLCI based on laboratory-confirmed influenza and the SHLCI case definition. What are "clinical features compatible with influenza"?

The System is based only of Severe laboratory confirmed influenza cases that meet the ECDC definition.

Clinical features compatible with influenza have been added according to the UE definition of ILI


I somehow understand the idea, but the text really needs some rewording for reader to understand. I supposed that the entry point for patient is the equivalent of ILI case definition then with at least one severity criteria (pneumonia, ARDS, etc…), and if they are tested positive for Flu then they are considered as SHLCI?

Yes

I have some concern regarding parameter used to calculate threshold. Indeed, authors consider just the number of cases (either for ILI, Flu A positive, etc..) and not the proportion of ILI among total visit and rate of Flu positive among specimen tested. Using weekly counts of ILI or Flu
cases means that the system relies on sites/clinician that must consistently notify cases. It is maybe the case in Catalonia, but authors should mention discuss that aspect (in particular, specificity and sensitivity).

This aspect concerns as to the sentinel System’s nature in itself, it is explained in the reference available online if there is a need for more detailed explanation.

In any case the sentinel System provides for the historical data to apply to the MEM System and estimate the thresholds. Rates are considered throughout the calculations.

I don't think that authors should mention the term prediction. Indeed, I think that using MEM is appropriate to establish threshold not really to predict. To me, parameters/indicators taken as well as methodology used do not provide any insight into prediction. Maybe authors are using prediction in a wrong manner.

The term has been changed to estimating thresholds.

minor comments:

Legend Figure 1: Please use official naming for viruses A(H1N1) instead of AnH1N1.

AnH1N1 has been replaced for A H1N1pdm09

Figure 2 to 4: Authors should show the legend for the different threshold and titles for axes.

Legends have been added to the figures 2-4

FORMATTING CHANGES:

>> Figure 4 has been uploaded.

>> Role of the funding body has been included.

>> Clean version of the manuscript has been uploaded as main manuscript file. Manuscript with tracked changes has been uploaded as supplementary file.