PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Incidence of hospitalisation for severe complications of influenza virus infection in Japanese patients between 2012 and 2016: A cross-sectional study using routinely collected administrative data
AUTHORS	Yokomichi, Hiroshi; Mochizuki, Mie; Lee, Joseph; Kojima, Reiji; Yokoyama, Tetsuji; Yamagata, Zentaro

VERSION 1 – REVIEW

REVIEWER	Meredith McMorrow Centers for Disease Control and Prevention, South Africa Country Office
REVIEW RETURNED	10-Aug-2018

GENERAL COMMENTS	This is an interesting manuscript that presents hospitalization rates per 10,000 influenza infections by age groups and common diagnoses. While the data are interesting I think the authors have missed the opportunity to do some more interesting analyses than what are currently presented in this manuscript. First of all, the population from which these data come from is not adequately defined. It states that the data come from 3 million employees and their dependents aged 0-74 years but the total number in each age category are not defined. This prevents calculation of hospitalization rates per 100,000 population which are more standard outputs of influenza research. Second, they have an interesting data set from which they could assess risk factors for severe disease by comparing prevalence of conditions in outpatients vs. inpatients who test positive for influenza. Third, the authors frequently refer to the influenza-positive episodes as "patients". Since we don't know the underlying population we can't determine if these are unique episodes in individual patients or perhaps several episodes per individual. The authors should not refer to these episodes as patients but as influenza-positive patient visits or influenza-positive episodes for clarity. To improve clarity for the reader the primary outcome measure in the abstract should be defined as incidence of hospitalization per 10,000 influenza infections. Likewise in the results section Table 1 should summarize the number of episodes of influenza infection, not patients.

REVIEWER	Hannah Segaloff University of Michigan School of Public Health
REVIEW RETURNED	04-Sep-2018

GENERAL COMMENTS	The authors present a manuscript calculating the incidence of hospitalization due to severe complications of influenza. While their findings are interesting, I have a few suggestions to improve the presentation of the manuscript. Major Comments: I have two major comments to improve this paper. The first is that the specific objective of this manuscript is not immediately clear. The authors write about incidence of hospitalization overall and also about incidence of hospitalization with specific severe diagnoses. The restriction of the data to these patients with these specific outcomes is somewhat confusing. It appears that the authors are trying to restrict to the most severe cases of influenza, but it seems to me that someone could not fall into one of these categories but could still have an extremely severe influenza infection. I would appreciate more explanation as to why only patients in these five diagnosis groups were included. I would also appreciate if the authors were consistent about the primary objective overall, is it to evaluate hospitalizations or hospitalizations specific to these diagnosis groups? I also think that the potential impact of the low sensitivity of the point of care tests is understated in the limitations section. I would appreciate a more thorough discussion of how this could impact the results, particularly based on time from onset of illness to testing (and how this could vary by age or other demographic variables) as well as the impact of this potential misclassification of PPV/NPV depending on the prevalence of influenza at the time of testing. Minor Comments: Abstract: In the objectives, make it clear that you first restricting to hospitalized patients, and then looking for a severe diagnosis among these hospitalized patients rather than looking at all individuals outpatient or inpatient who have the diagnosis and then calculating the incidence of hospitalization. This isn't clear. Introduction: Line 63: It seems like there are many other reasons for hospital admission, why these five? Lines 74-76: An interesting point. Could this still perhaps impact your data if vaccination reduces severity of influenza beyond simply reducing incidence? Lines 78-79: Does encephalitis have a particularly high mortality rate in Japan? The specific reference to Japan in this sentence is confusing to me. Methods: Due to the differences in Japan when compared to other countries a few extra details would be appreciated: Does use of testing tend to vary throughout the year (increase during the influenza season)? Are there certain symptoms (i.e. ILI) that prompt physicians to test in general? How were inpatients/outpatients defined? Would an inpatient in a clinic (<20 beds) count as a hospitalization in this study?

	Results: Table 2: A column of total hospitalizations would help make interpretation of the data easier. Table 3: Similarly to my comment above, indication of the incidence of hospitalization would help with interpretation. Also, it would be clearer if “all five complications” read “Any of the five complications”. Figures 3 and 4: These need much more detailed description in the footnote explaining what the lines and bars represent. As an additional figure, maybe as a supplement, it would be interesting and informative to see the incidence of hospitalization throughout calendar time (maybe by month). This would give more detail to the seasonal differences seen in Table 3. If it is relevant, a discussion about the influenza circulating strains in Japan could also help explain some season specific results. Discussion: For many results, the authors compare their data to data from the 2009 pandemic season. These comparisons should also be bolstered with data from more recent influenza seasons, especially if consistence has been seen across influenza types/subtypes in these results. Lines 230-end of paragraph: The point that the authors are making here about results for men vs women is not clear to me. Lines 245-247: Due to the huge age range in the UK study, I am not sure if this result is necessarily relevant to your results. Lines 265-267: Was this trend seen for overall hospitalizations? Limitations: As mentioned above, I think that a more thorough discussion of the limitation of the low sensitivity of the POCTs is needed. In addition, the impact of clinician driven testing, despite the widespread testing in Japan should be discussed. Does testing vary by age/calendar time?

VERSION 1 – AUTHOR RESPONSE

Responses to comments of reviewer #1

2. First of all, the population from which these data come from is not adequately defined. It states that the data come from 3 million employees and their dependents aged 0-74 years but the total number in each age category are not defined. This prevents calculation of hospitalization rates per 100,000 population which are more standard outputs of influenza research.

We appreciate your suggestion to clarify the studied population and the numbers. The population breakdown by age-category are found in table 1. We apologise that we were unable to know the number of each age category in the insured population as this was not in the dataset. We have also revised the manuscript, describing the studied population and the numbers more clearly.

Line 109: The data source was the monthly health insurance claim records between January 2012 and December 2016 of approximately three million employees and their dependents, representing 2.4% of the Japanese population.

Line 117: From the database, we extracted the data of individuals who consulted physicians with influenza-like illness episodes. We then included only patients with a diagnosis of influenza virus infection.

Line 132: Hospitalisation was recorded in the health insurance claims of inpatients.

Title of table 1: Population Characteristics: Total number (%) of 16636913 Japanese patients with a physician's diagnosis of influenza infection between 2012–2016, in health insurance administrative data.

Table 2. Total number of inpatients with severe influenza complications by department and hospital type amongst 16636913 Japanese influenza cases between 2012–2016.

Category Inpatients Acute respiratory failure Pneumonia ARDS Febrile seizure Encephalitis/ encephalopathy
Number 164394 3361 27253 18 2603 159
Clinical department
Internal medicine 23722 (14.4%) 682 (20.3%) 3633 (13.3%) 6 23 (0.9%) 57 (35.8%)
Paediatrics 47138 (28.7%) 1794 (53.4%) 19012 (69.8%) 2 2461 (94.5%) 63 (39.6%)
Otorhinolaryngology 12825 (7.8%) 43 (1.3%) 217 (0.8%) 0 2 (0.1%) 0
Orthopaedics 7158 (4.4%) 43 (1.3%) 338 (1.2%) 0 6 (0.2%) 0
Dermatology 1100 (0.7%) 3 (0.1%) 45 (0.2%) 0 0 0
Surgery 17138 (10.4%) 189 (5.6%) 720 (2.6%) 3 18 (0.7%) 0
Ophthalmology 2302 (1.4%) 0 23 (0.1%) 0 1 (0.04%) 0
Obstetrics and gynaecology 15155 (9.2%) 88 (2.6%) 330 (1.2%) 0 0 0
Psychiatry 2486 (1.5%) 28 (0.8%) 197 (0.7%) 0 8 (0.3%) 37 (23.3%)
Others or not specified 35370 (21.5%) 486 (14.5%) 2738 (10.0%) 0 84 (3.2%) 2 (1.3%)
No. of hospital beds
0–19 16843 (10.2%) 167 (5.0%) 805 (3.0%) 0 18 (0.7%) 0
20–99 10202 (6.2%) 106 (3.2%) 913 (3.4%) 3 36 (1.4%) 0
100–199 12661 (7.7%) 308 (9.2%) 2394 (8.8%) 0 147 (5.6%) 0
200–299 15701 (9.6%) 358 (10.7%) 2933 (10.8%) 7 220 (8.5%) 26 (16.4%)
300–499 40753 (24.8%) 922 (27.5%) 9179 (33.7%) 0 1003 (38.5%) 57 (35.8%)
500+ 68234 (41.5%) 1500 (44.7%) 11029 (40.5%) 8 1179 (45.3%) 76 (47.8%)
Hospital type
Clinic 16817 (10.2%) 167 (5.0%) 805 (3.0%) 0 18 (0.7%) 0
National or municipal hospital 48243 (29.3%) 985 (29.4%) 10995 (40.3%) 10 1314 (50.5%) 82 (51.6%)
University hospital 21898 (13.3%) 285 (8.5%) 2049 (7.5%) 0 162 (6.2%) 34 (21.4%)
Other hospital 77185 (47.0%) 1919 (57.2%) 13404 (49.2%) 8 1109 (42.6%) 43 (27.0%)
Not specified 251 (0.2%) 5 (0.1%) 0 0 0 0
Abbreviation: ARDS, acute respiratory distress syndrome.

3. Second, they have an interesting data set from which they could assess risk factors for severe disease by comparing prevalence of conditions in outpatients vs. inpatients who test positive for influenza.

We greatly appreciate your suggestion to explore risk factors for severe complications in the influenza-diagnosed patients. However, the health insurance claim data set does not include detailed characteristics of patients, and we could not analyse risk factors with the exception of sex. We have discussed more about sex as a risk factor for developing encephalopathy/encephalitis.

Line 250: In contrast, our data suggest the possibility of a higher risk of encephalitis/encephalopathy in women with influenza infection (table 3). However, in Japanese surveillance reports from 2007 to 2010, 153 of 263 (58.2%) paediatric patients with encephalopathy were male.[25] Because the means of data collection in previous studies were different, we are unable to conclude in which sex complications are more common. Further study with another large data set is needed to investigate risk factors, including sex, for hospitalisation and incidence of encephalitis/encephalopathy in Asian people.

4. Third, the authors frequently refer to the influenza-positive episodes as "patients". Since we don't know the underlying population we can't determine if these are unique episodes in individual patients or perhaps several episodes per individual. The authors should not refer to these episodes as patients but as influenza-positive patient visits or influenza-positive episodes for clarity. To improve clarity for the reader the primary outcome measure in the abstract should be defined as incidence of hospitalization per 10,000 influenza infections. Likewise in the results section Table 1 should summarize the number of episodes of influenza infection, not patients.

Thank you very much for your kindness to improve the clarity of the subjects. We have revised the descriptions and the unit for hospitalisation incidence.

Part of Abstract:
Primary outcome measures: Incidence of hospitalisation per 100000 influenza-positive episodes.
Results: We included over 16 million influenza-positive episodes, 1.0% of whom were hospitalised. Of these, 3361 had acute respiratory failure, 27253 pneumonias, 18 ARDS, 2603 febrile seizures and 159 encephalitis/encephalopathy. The percentage of hospitalisations by age was 2.96% of patients aged 0–1 years; 0.77% aged 2–5; 0.51% aged 6–12; 0.78% aged 13–18; 1.36% aged 19–44; 1.19% aged 45–64; and 2.21% aged 65–74. The incidence of hospitalisations from these five complications combined was highest in influenza-positive patients aged 0–1 years (943 per 100000) compared with 307 in those aged 2–5 years and 271 in those aged 65–74 years. For pneumonia, incidence was highest for influenza-positive patients aged 0–5 years and 65 years or more. There were statistically significant decreasing trends over the years in the incidence of all-cause hospitalisations, pneumonia and febrile seizures.
Conclusions: Japanese administrative data revealed that 1.0% of influenza-positive patients aged under 75 years were hospitalised. Male patients had a higher incidence of pulmonary complications and febrile seizures. Children aged 0–5 years and adults aged 65–74 years were at high risk of being admitted to hospital for pneumonia.

Responses to comments of reviewer #2

5. The first is that the specific objective of this manuscript is not immediately clear. The authors write about incidence of hospitalization overall and also about incidence of hospitalization with specific severe diagnoses. The restriction of the data to these patients with these specific outcomes is somewhat confusing. It appears that the authors are trying to restrict to the most severe cases of influenza, but it seems to me that someone could not fall into one of these categories but could still have an extremely severe influenza infection. I would appreciate more explanation as to why only patients in these five diagnosis groups were included. I would also appreciate if the authors were consistent about the primary objective overall, is it to evaluate hospitalizations or hospitalizations specific to these diagnosis groups?

Thank you for your suggestion to clarify the primary objective and the primary outcomes. We are exploring the incidence of hospitalisations due to the five specific complications amongst influenza-positive patients (not influenza-like illness patients). We have added descriptions and references.

Line 63: In both Western and Asian countries, the majority of influenza-related hospital admission is due to respiratory or neurologic complications: pneumonia, febrile seizure, acute respiratory failure, acute respiratory distress syndrome (ARDS) and encephalitis/encephalopathy.[4-8]

Line 136: The primary outcomes were the incidence of each of the five severe complications per 100000 influenza infections.

Line 153: We determined the incidence of inpatients with the five severe complications by dividing the number of complications by the number of infections. We stratified this by sex, influenza season and age.

6. I also think that the potential impact of the low sensitivity of the point of care tests is understated in the limitations section. I would appreciate a more thorough discussion of how this could impact the results, particularly based on time from onset of illness to testing (and how this could vary by age or other demographic variables) as well as the impact of this potential misclassification of PPV/NPV depending on the prevalence of influenza at the time of testing.
7. Limitations: As mentioned above, I think that a more thorough discussion of the limitation of the low sensitivity of the POCTs is needed. In addition, the impact of clinician driven testing, despite the widespread testing in Japan should be discussed. Does testing vary by age/calendar time?
8. Methods: Does use of testing tend to vary throughout the year (increase during the influenza season)? Are there certain symptoms (i.e. ILI) that prompt physicians to test in general?

We appreciate your insightful suggestion to consider the limitation of the low sensitivity of point of care testing. We agree with you in that sensitivity of POCT would be influenced by time from the onset of illness, patient age, influenza type A/B/C, operator technique, number of times patients were tested; however, the direction of bias would vary. We have added a sentence explaining more about POCT use and a paragraph of discussing this limitation. We could not find evidence of a trend in rapid test use between 2012–2016. Instead, we have added a reference from the 2009/2010 season.

Line 120: In Japan, the use of immunochromatogenic assay point-of-care tests [POCT] in clinical practice has been covered by public health insurance from 1999.[23] As recommended in Japanese guidelines,[31] a test-and-treat strategy is routine.[23 32] Even if physicians only slightly suspect influenza infection, they use a POCT to diagnose influenza, and administer antivirals to the positive patients.[31 33 34] Testing would be indicated in fever, sore throat, malaise, non-productive cough or a history of family's infection, for example.[23 35] During the 2009–2010 pandemic influenza A(H1N1) season, physicians performed this test in majority of cases (>90%) and we believe this was likely to be the case during the period of this study because in Japan paediatric patients with an influenza-like illness are required to obtain a medical certificate showing they do not have influenza before return to school.[36]

Line 341: Firstly, POCTs for influenza are known to have variable sensitivity. In the 2010s, 20 or more POCT kits were available in Japan.[58] Sensitivity would have been influenced by the following factors: (1) time from the onset of illness;[59 60] (2) patient age;[60 61] (3) influenza type A/B/C;[61] (4) operator technique;[60] (5) number of times patients were tested. (1) Reportedly, the sensitivity is lower 0–24 hours from symptom onset and higher in days 2–4.[59 60] Parents tend to bring children to paediatricians at an earlier stage of the infection while infected employed adults tend to consult physicians in mid- or later stages. This would bias sensitivity toward comparatively low in children

compared to adults. (2) In contrast children are known to have higher viral load and longer shedding and consequently POCTs have higher sensitivity in children.[60 61] (3) POCT sensitivity is higher in influenza A than in B.[61] In Japan, influenza type A spreads early in winter, type B late in winter, and type C in all seasons. Therefore, the sensitivity might have been relatively low between Jan 2012–Aug 2012 and higher between Sep 2016–Dec 2016 (table 3). (4) In almost all Japanese medical care facilities, physicians conduct POCT for individuals with influenza-like illness.[31 32] Because physicians are trained to appropriately sample specimen material, operator bias within our Japanese data would be small. (5) In Japan, physicians are permitted to conduct POCTs up to twice per patient in a calendar month within health insurance coverage. Even if the first POCT had failed to detect influenza-positive patients, the second POCT might identify the infection. Thus the sensitivity in Japanese clinical practice would be higher than the nominal sensitivity. Overall, the sensitivity of POCTs can vary unpredictably according to the circumstances. Our denominator (influenza-positive episodes) may be underestimated in low sensitivity situations and to a smaller degree in high sensitivity situations. In contrast, we would expect almost all of the numerator population (hospitalised patients with severe symptoms) would have been positively diagnosed. Thus, the estimated incidence of hospitalisation amongst influenza-positive patients may have been overestimated.

9. Abstract: In the objectives, make it clear that you first restricting to hospitalized patients, and then looking for a severe diagnosis among these hospitalized patients rather than looking at all individual outpatient or inpatient who have the diagnosis and then calculating the incidence of hospitalization. This isn't clear.

Thank you very much for your comment to clarify the objective. We have clarified the objective as requested.

Line 20:
Objectives: To calculate the incidence of hospitalisation due to acute respiratory failure, pneumonia, acute respiratory distress syndrome (ARDS), febrile seizures and encephalitis/encephalopathy amongst influenza-positive patients in Japan where point-of-care tests are routinely used to diagnose influenza.

10. Introduction: Line 63: It seems like there are many other reasons for hospital admission, why these five?

Thank you for allowing us to clarify why we looked at these five complications. Previous studies showed hospital admissions with influenza-related complications were mainly due to respiratory and neurologic complications, and these were severe or common complications identifiable in the dataset. We have added an explanation as requested.

Line 63: In both Western and Asian countries, the majority of influenza-related hospital admission is due to respiratory or neurologic complications: pneumonia, febrile seizure, acute respiratory failure, acute respiratory distress syndrome (ARDS) and encephalitis/encephalopathy.[4-8]

11. Lines 74-76: An interesting point. Could this still perhaps impact your data if vaccination reduces severity of influenza beyond simply reducing incidence?

Thank you for your suggestion to refer to the impact of vaccination upon the results. We think that although vaccination may reduce hospitalisation rates, there is no targeting of free vaccine to high risk groups in Japan, and so the impact of vaccination upon hospitalisation incidence would be limited. We have clarified this point in the Discussion section.

Line 280: In addition, because vaccination reduces the hospitalisation rate,[43-45] vaccination programmes in other countries that target high risk groups may bias hospitalisation rate estimates for these patients. In Japan all individuals have had to pay a fee to receive influenza vaccine irrespective of their risk profile since 1994, when free vaccination for primary and secondary school students was stopped.[46] This means that high-risk groups in Japan are less resistant to severe disease than in other countries, reducing this bias in our hospitalisation rates.

12. Lines 78-79: Does encephalitis have a particularly high mortality rate in Japan? The specific reference to Japan in this sentence is confusing to me.

Thank you for the comment to improve the description. We think that the incidence and mortality of influenza encephalitis in Japanese influenza infection is high and therefore the physicians are more concerned about the complication. We have added the explanation and related references.

Line 79: Although it is also seen internationally,[14-18] influenza encephalitis is a particular concern amongst Japanese physicians owing to a high incidence and mortality rate in Japan.[7 19-23]

13. How were inpatients/outpatients defined? Would an inpatient in a clinic (<20 beds) count as a hospitalization in this study?

We apologise the confusing explanation about the definition of hospitalisation. We have modified the description.

Line 133: Hospitalisation was recorded in the health insurance claims of inpatients.
Line 152: In this study, hospitalised influenza-positive patients were inpatients in both “clinic” and “hospital” settings.

14. Results: Table 2: A column of total hospitalizations would help make interpretation of the data easier.

We appreciate your suggestion to describe the numbers of hospitalisation to improve the readability. We have revised table 2 accordingly.

Table 2. Total number of inpatients with severe influenza complications by department and hospital type amongst 16636913 Japanese influenza cases between 2012–2016.

Category	Inpatients	Acute respiratory failure	Pneumonia	ARDS	Febrile seizure	Encephalitis/ encephalopathy
Number	164394	3361	27253	18	2603	159
Clinical department						
Internal medicine	23722 (14.4%)	682 (20.3%)	3633 (13.3%)	6	23 (0.9%)	57 (35.8%)
Paediatrics	47138 (28.7%)	1794 (53.4%)	19012 (69.8%)	2	2461 (94.5%)	63 (39.6%)
Otorhinolaryngology	12825 (7.8%)	43 (1.3%)	217 (0.8%)	0	2 (0.1%)	0
Orthopaedics	7158 (4.4%)	43 (1.3%)	338 (1.2%)	0	6 (0.2%)	0
Dermatology	1100 (0.7%)	3 (0.1%)	45 (0.2%)	0	0	0
Surgery	17138 (10.4%)	189 (5.6%)	720 (2.6%)	3	18 (0.7%)	0
Ophthalmology	2302 (1.4%)	0	23 (0.1%)	0	1 (0.04%)	0
Obstetrics and gynaecology	15155 (9.2%)	88 (2.6%)	330 (1.2%)	0	0	0
Psychiatry	2486 (1.5%)	28 (0.8%)	197 (0.7%)	0	8 (0.3%)	37 (23.3%)
Others or not specified	35370 (21.5%)	486 (14.5%)	2738 (10.0%)	0	84 (3.2%)	2 (1.3%)
No. of hospital beds						
0–19	16843 (10.2%)	167 (5.0%)	805 (3.0%)	0	18 (0.7%)	0
20–99	10202 (6.2%)	106 (3.2%)	913 (3.4%)	3	36 (1.4%)	0

100–199 12661 (7.7%) 308 (9.2%) 2394 (8.8%) 0 147 (5.6%) 0
200–299 15701 (9.6%) 358 (10.7%) 2933 (10.8%) 7 220 (8.5%) 26 (16.4%)
300–499 40753 (24.8%) 922 (27.5%) 9179 (33.7%) 0 1003 (38.5%) 57 (35.8%)
500+ 68234 (41.5%) 1500 (44.7%) 11029 (40.5%) 8 1179 (45.3%) 76 (47.8%)
Hospital type
Clinic 16817 (10.2%) 167 (5.0%) 805 (3.0%) 0 18 (0.7%) 0
National or municipal hospital 48243 (29.3%) 985 (29.4%) 10995 (40.3%) 10 1314 (50.5%) 82 (51.6%)
University hospital 21898 (13.3%) 285 (8.5%) 2049 (7.5%) 0 162 (6.2%) 34 (21.4%)
Other hospital 77185 (47.0%) 1919 (57.2%) 13404 (49.2%) 8 1109 (42.6%) 43 (27.0%)
Not specified 251 (0.2%) 5 (0.1%) 0 0 0 0
Abbreviation: ARDS, acute respiratory distress syndrome.

15. Table 3: Similarly to my comment above, indication of the incidence of hospitalization would help with interpretation. Also, it would be clearer if “all five complications” read “Any of the five complications”.

Thank you very much for your suggestion to describe the incidence of hospitalisation to improve the readability. We have revised table 3.

Table 3. Incidence of hospitalisation with severe complications per 100000 confirmed influenza infections.
No. of inpatients per 100,000 influenza infections Hospitalisation Any of five complications Acute respiratory failure Pneumonia ARDS Febrile seizure Encephalitis/encephalopathy
Sex* p<0.0001 p<0.0001 p<0.0001 p<0.0001 p=0.08 p<0.0001 p=0.08
Male (n=8885794) 970 191 22.2 171 0.15 17.8 0.8
Female (n=7751279) 1011 171 17.8 156 0.06 13.2 1.1
Year† p<0.0001 p<0.0001 p=0.07 p<0.0001 p=0.98 p<0.0001 p=0.19
Jan 2012–Aug 2012 (n=1611699) 1114 249 23 229 0.25 23 0.4
Sep 2012–Aug 2013 (n=2912806) 1079 199 22 180 0.07 17 0.8
Sep 2013–Aug 2014 (n=3532559) 1023 180 20 160 0.06 17 1.3
Sep 2014–Aug 2015 (n=3628976) 965 169 19 150 0.17 14 1.1
Sep 2015–Aug 2016 (n=3530057) 951 172 21 157 0.06 14 0.7
Sep 2016–Dec 2016 (n=1103073) 946 166 20 152 0.18 11 1.4
Age, years
0–1 (n=823875) 2551 943 101 847 0.73 121 1.3
2–5 (n=2886462) 776 307 26 279 0 45 0.9
6–12 (n=4193137) 526 124 10 115 0 7 1.3
13–18 (n=1480030) 734 87 9.4 78 0 0.41 1.4
19–44 (n=3815970) 1337 100 15 88 0.05 0.18 0.9
45–64 (n=2872125) 1141 95 18 82 0.21 0 0.5
65–74 (n=231120) 1919 271 56 245 1.7 0 0.4
Abbreviation: ARDS, acute respiratory distress syndrome.
*p for difference of incidence; †p for trend.

Line 239: There was a decreasing trend in the proportions of infections hospitalised for any reason, and with any of the five complications, pneumonia, or febrile seizures between 2012 and 2016 (table 3 and figure 5).

16. Figures 3 and 4: These need much more detailed description in the footnote explaining what the lines and bars represent.

Thank you for your suggestion to clearly illustrate the figures. We have added the explanations.

Figure 3. Number of influenza-infected inpatients with severe complications and proportion of infections and hospitalisation in a health insurance claim database, by age group, between 2012 and 2016.
Bars represent the number of each severe complication; the line represents the proportion of infections resulting in hospitalisation in each age group. Abbreviation: ARDS, acute respiratory distress syndrome.

Figure 4. Number of influenza-infected inpatients with severe complications and proportion of infection and hospitalisation in a health insurance claim database, by age, between 2012 and 2016.
Bars represent the number of each severe complication; the line represents the proportion of infections with hospitalisation. Abbreviation: ARDS, acute respiratory distress syndrome.

17. As an additional figure, maybe as a supplement, it would be interesting and informative to see the incidence of hospitalization throughout calendar time (maybe by month). This would give more detail to the seasonal differences seen in Table 3. If it is relevant, a discussion about the influenza circulating strains in Japan could also help explain some season specific results.

As requested by the reviewer's suggestion, we have constructed another figure to illustrate the proportion of inpatients over calendar time and have added it to the manuscript as figure 5.

Figure 5. Number of influenza-infected inpatients and proportion of hospitalisation in health insurance claim database between 2012 and 2016.
Black line represents number of inpatients; red line proportion of infections hospitalised.

Line 156: We also examined the numbers of the influenza-infected patients and the proportions of inpatients over calendar time at the request of a reviewer.

Line 216: Figure 5 shows the numbers of influenza-infected patients and the proportion who were inpatients by calendar month between 2012 and 2016. Every year the number of infections increased from winter to spring while the proportion admitted peaked in summer. The number of infections was similar between 2014 and 2016. The proportion hospitalised gradually decreased between 2012 and 2016.

Line 239: There was a decreasing trend in the proportions of infections hospitalised for any reason, and with any of the five complications, pneumonia, or febrile seizures between 2012 and 2016 (table 3 and figure 5).

Line 303: This decreasing trend was not altered in the 2014/15 season when influenza A(H3N2) spread internationally including in Japan.[51]

18. Discussion: For many results, the authors compare their data to data from the 2009 pandemic season. These comparisons should also be bolstered with data from more recent influenza seasons, especially if consistence has been seen across influenza types/subtypes in these results.

We appreciate your suggestion to improve the discussion. Although we sought Japanese publications about hospitalisation rates from 2010/2011 to 2017/2018 seasons, we were unable to find them. We also think that amongst countries where healthcare is delivered differently, it would be difficult to simply compare hospitalisation rates. We apologise for the difficulty improving the manuscript on the point.

19. Lines 230-end of paragraph: The point that the authors are making here about results for men vs women is not clear to me.

Thank you for your suggestion. We have deleted the corresponding sentence (line 251–) and have added a future study question about if hospitalisation rate due to specific reasons may change according to sex.

Line 251: In contrast, our data suggest the possibility of a higher risk of encephalitis/encephalopathy in women with influenza infection (table 3). However, in Japanese surveillance reports from 2007 to 2010, 153 of 263 (58.2%) paediatric patients with encephalopathy were male.[25] Because the means of data collection in previous studies were different, we are unable to conclude in which sex complications are more common. Further study with another large data set is needed to investigate risk factors, including sex, for hospitalisation and incidence of encephalitis/encephalopathy in Asian people.

20. Lines 245-247: Due to the huge age range in the UK study, I am not sure if this result is necessarily relevant to your results.

Thank you for your suggestion to improve the discussion. We have replaced the UK reference with: (Cromer D, van Hoek AJ, Jit M, Edmunds WJ, Fleming D, Miller E. The burden of influenza in England by age and clinical risk group: A statistical analysis to inform vaccine policy. Journal of Infection 2014;68(4):363-71).

Line 268: A study from the UK also reported that children aged 6 months to 4 years had the high influenza related hospitalisation rates between 2001 and 2007 (3360 per 100000 population).[8]

21. Lines 265-267: Was this trend seen for overall hospitalizations?

Thank you for your suggestion. The trend was seen for overall hospitalisation as in the revised table 3 and a new figure 5. We have added a this to the text.

Line 223: The number of infections was similar between 2014 and 2016. The proportion hospitalised gradually decreased between 2012 and 2016.

Line 339: There was a decreasing trend in the proportions of infections hospitalised for any reason, and with any of the five complications, pneumonia, or febrile seizures between 2012 and 2016 (table 3 and figure 5).

Line 300: The decreasing trend with time in the hospitalisation and the composite incidence of the five severe complications (table 3, $p<0.0001$) might be attributed to the increasingly widespread use of [13 33] and more options for neuraminidase inhibitors.[6 23]

We hope we have addressed the main points raised by the editor and the reviewers. We would like to add the new figure showing the proportion of infected patients admitted over time to the main manuscript because it may be useful for clinicians (figure 5). Once again, we are extremely grateful for the insightful suggestions and hope that the manuscript is now acceptable for publication in BMJ Open.

VERSION 2 – REVIEW

REVIEWER	Hannah Segaloff University of Michigan School of Public Health, United States
REVIEW RETURNED	07-Nov-2018

GENERAL COMMENTS	The authors have addressed all of my comments sufficiently and produced a very interesting paper. One note, it appears that a few lines are duplicated on page 17 lines 343-345.

VERSION 2 – AUTHOR RESPONSE

Responses to comments of reviewer #2

2. One note, it appears that a few lines are duplicated on page 17 lines 343-345.

We appreciate your suggestion to modify the duplicated sentences. We sought to shrink the section accordingly. Would you let us know if the revision fell short of your request, please?

Line 343:

Sensitivity would have been influenced by the following factors. (1) Time from the onset of illness. Reportedly, the sensitivity is lower 0–24 hours from symptom onset and higher in days 2–4.[59 60] Parents tend to bring children to paediatricians at an earlier stage of the infection while infected employed adults tend to consult physicians in mid- or later stages. This would bias sensitivity toward comparatively low in children compared to adults. (2) Patient age. In contrast children are known to have higher viral load and longer shedding and consequently POCTs have higher sensitivity in children.[60 61] (3) Influenza type A/B/C. POCT sensitivity is higher in influenza A than in B.[61] In Japan, influenza type A spreads early in winter, type B late in winter, and type C in all seasons. Therefore, the sensitivity might have been relatively low between Jan 2012–Aug 2012 and higher between Sep 2016–Dec 2016 (table 3). (4) Operator technique.[60] In almost all Japanese medical care facilities, physicians conduct POCT for individuals with influenza-like illness.[31 32] Because physicians are trained to appropriately sample specimen material, operator bias within our Japanese data would be small. (5) Number of times patients were tested. In Japan, physicians are permitted to conduct POCTs up to twice per patient in a calendar month within health insurance coverage. Even if the first POCT had failed to detect influenza-positive patients, the second POCT might identify the infection. Thus the sensitivity in Japanese clinical practice would be higher than the nominal sensitivity. Overall, the sensitivity of POCTs can vary unpredictably according to the circumstances. Our denominator (influenza-positive episodes) may be underestimated in low sensitivity situations and to a smaller degree in high sensitivity situations. In contrast, we would expect almost all of the numerator population (hospitalised patients with severe symptoms) would have been positively diagnosed. Thus, the estimated incidence of hospitalisation amongst influenza-positive patients may have been overestimated.