

# BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email [info.bmjopen@bmj.com](mailto:info.bmjopen@bmj.com)

# BMJ Open

## 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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-024687
Article Type:	Research
Date Submitted by the Author:	12-Jun-2018
Complete List of Authors:	Yokomichi, Hiroshi; University of Yamanashi, Department of Health Sciences Mochizuki, Mie; University of Yamanashi, Department of Pediatrics Lee, Joseph; University of Oxford Kojima, Reiji; University of Yamanashi, Department of Health Sciences Yokoyama, Tetsuji ; National Institute of Public Health, Department of Health Promotion Yamagata, Zentaro; University of Yamanashi
Keywords:	Influenza, Hospitalisation, Pneumonia, Influenza encephalopathy, Influenza encephalitis, Febrile seizure

SCHOLARONE™  
Manuscripts

1 **Incidence of hospitalisation for severe complications of influenza virus infection in**  
2 **Japanese patients between 2012 and 2016: A cross-sectional study using routinely**  
3 **collected administrative data**

4 Hiroshi Yokomichi<sup>1</sup>, Mie Mochizuki<sup>2</sup>, Joseph Jonathan Lee<sup>3</sup>, Reiji Kojima<sup>1</sup>, Tetsuji  
5 Yokoyama<sup>4</sup>, Zentaro Yamagata<sup>1</sup>

6  
7 Author Affiliations

8 <sup>1</sup>Department of Health Sciences, University of Yamanashi

9 <sup>2</sup>Department of Pediatrics, University of Yamanashi

10 <sup>3</sup>Nuffield Department of Primary Care Health Sciences, University of Oxford

11 <sup>4</sup>Department of Health Promotion, National Institute of Public Health

12

13 Correspondence: Hiroshi Yokomichi

14 1110 Shimokato, Chuo City, Yamanashi, 4093898, Japan

1  
2  
3  
4  
5  
6 15 Tel: +81 80 5524 7393  
7  
8

9  
10 16 Fax: +81 55 273 7882  
11

12  
13 17 E-mail: [hyokomichi@yamanashi.ac.jp](mailto:hyokomichi@yamanashi.ac.jp)  
14

15  
16  
17 18  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6 19 **Abstract**

7  
8  
9  
10 20 **Objectives:** To calculate the incidence of hospitalisation in influenza-positive patients  
11  
12  
13 21 with acute respiratory failure, pneumonia, acute respiratory distress syndrome (ARDS),  
14  
15  
16 22 febrile seizures and encephalitis/encephalopathy in Japan where point-of-care tests are  
17  
18 23 routinely used to diagnose influenza.

19  
20  
21  
22 24 **Design:** A cross-sectional study using routinely collected data.  
23  
24

25  
26 25 **Setting:** Japanese clinics and hospitals between 2012 and 2016.  
27  
28

29  
30 26 **Participants:** Japanese patients aged 0-74 years diagnosed with influenza by a rapid  
31  
32  
33 27 test in employment-related health insurance records.  
34  
35

36  
37 28 **Primary outcome measures:** Incidence of hospitalisation.  
38  
39

40  
41 29 **Results:** We included over 16 million patients diagnosed with a rapid test, 1.0% of  
42  
43 30 whom were hospitalised. Of these, 3361 had acute respiratory failure, 27253  
44  
45  
46 31 pneumonias, 18 ARDS, 2603 febrile seizures and 159 encephalitis/encephalopathy. The  
47  
48  
49 32 percentage of hospitalisations by age was 2.96% of patients aged 0–1 years; 0.77% aged  
50  
51  
52 33 2–5; 0.51% aged 6–12; 0.78% aged 13–18; 1.36% aged 19–44; 1.19% aged 45–64; and  
53  
54  
55 34 2.21% aged 65–74. The incidence of hospitalisations from these five complications  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6 35 combined was highest in patients aged 0–1 years (94.3 per 10000) compared with 30.7  
7  
8  
9 36 in those aged 2–5 years and 27.1 in those aged 65–74 years. For pneumonia, incidence  
10  
11 37 was highest for patients aged 0–5 years and 65 years or more. There were statistically  
12  
13  
14 38 significant decreasing trends over the years in the incidence of hospitalisations from  
15  
16  
17 39 pneumonia and febrile seizures.

20  
21 40 **Conclusions:** Japanese administrative data revealed that 1.0% of patients aged under 75  
22  
23  
24 41 years who tested positive for influenza infection were hospitalised. Male patients had a  
25  
26  
27 42 higher incidence of pulmonary complications and febrile seizures. Children aged 0–5  
28  
29  
30 43 years and adults aged 65–74 years were at high risk of being admitted to hospital for  
31  
32  
33 44 pneumonia.

34  
35  
36 45 **Registration:** The ethics committee of the School of Medicine, University of  
37  
38  
39 46 Yamanashi approved this study (approval number: H29-1709).

40  
41  
42  
43 47 **(294 words/300 words)**

44  
45  
46 48

1  
2  
3  
4  
5  
6 49 **Strengths and limitations of this study:**  
7  
8  
9

10 ● This study uses Japanese routinely collected data where uniquely diagnostic tests are  
11  
12 used to identify influenza infections in the population.  
13  
14

15  
16 ● Point-of-care testing for influenza has limited sensitivity, but its high specificity  
17  
18 means that nearly all the participants in this study were infected with influenza.  
19  
20  
21

22  
23 ● Limitations of the data set prevent analysis of mortality and patients over the age of  
24  
25 74 years.  
26  
27  
28

29 56  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 57 INTRODUCTION

58 Influenza is a major burden on health systems worldwide. Every year, an estimated one  
59 billion people [1] including 90 million children younger than 5 years of age are infected  
60 with influenza globally, and 1 million people have influenza-associated acute lower  
61 respiratory tract infection, [2] which causes 290000–600000 deaths.[3]

62 Complications of influenza which cause hospitalisations are a serious public  
63 health concern. Reasons for hospital admission include pneumonia, febrile seizure,  
64 acute respiratory failure, acute respiratory distress syndrome (ARDS) and  
65 encephalitis/encephalopathy.[4 5] We refer to these as ‘severe complications’.

66 Hospitalisation rates from influenza infection have been investigated,[4 6] but most  
67 studies were conducted in Western countries where testing for influenza is not routine.

68 This means that studies have used either limited sample sizes of positively identified  
69 individual hospitalised patients, or extrapolated from influenza surveillance data.[6-8]  
70 Hospital-based studies may be underestimating the risk and the number of infections  
71 and complications in the community.[9] Previous studies have used estimates of the  
72 general population as denominators, rather than assessing the risk of admission amongst  
73 the infected population, combining the risk of infection and the risk of complications.



1  
2  
3  
4  
5  
6 74 This is problematic because programmes targeting high risk groups, such as vaccination  
7  
8  
9 75 or prophylaxis may reduce the number of infections in high risk groups, biasing  
10  
11 76 estimates of the risk of complications if infected.[9] Also, many studies pre-date the  
12  
13  
14 77 option of administering new neuraminidase inhibitors.[10]  
15  
16  
17

18 78 Although it is also seen internationally, influenza encephalitis is a particular  
19  
20  
21 79 concern in Japan owing to a high mortality rate.[11] The prognosis for patients with  
22  
23  
24 80 influenza encephalitis/encephalopathy is very poor; approximately 30% of affected  
25  
26  
27 81 patients die and 20–30% have neurological sequelae.[12] To understand the aetiology  
28  
29  
30 82 and prevalence of this severe outcome, surveillance has been conducted.[13 14] In  
31  
32  
33 83 Japan, influenza-associated encephalopathy is a notifiable disease.[15] Japanese  
34  
35  
36 84 physicians are required to report influenza infection cases with: a) death after coma or  
37  
38  
39 85 hospitalisation with coma for 24 hours or more; and b) a fever of 38°C or higher, central  
40  
41  
42 86 nervous system manifestation or prior influenza infection symptom. This surveillance  
43  
44  
45 87 system has detected 60–100 influenza encephalitis cases annually [16] and 331 cases  
46  
47  
48 88 during the 2009–2010 pandemic;[13] however, underreporting of cases has been  
49  
50  
51 89 acknowledged.[16] Another survey of paediatric departments in 265 hospitals reported  
52  
53  
54 90 263 influenza-associated encephalopathy cases over 3 years.[14] The authors estimate  
55  
56  
57 91 that there would be 200–300 influenza encephalopathy cases per annum in Japan;[17]  
58  
59  
60

1  
2  
3  
4  
5  
6 92 therefore, the incidence of influenza encephalitis/encephalopathy is not accurately  
7  
8  
9 93 known.

10  
11  
12 94 To understand the incidence of severe complications in patients with influenza,  
13  
14  
15 95 an analysis of large-scale real-world data is needed, encompassing hospital and  
16  
17  
18 96 community sites. Previous studies using large data sets of routinely collected medical  
19  
20  
21 97 records have had to rely on clinical diagnoses of influenza-like illness or modelling of  
22  
23  
24 98 influenza and other respiratory virus infections using incomplete laboratory data.[7] In  
25  
26  
27 99 Japan, diagnostic testing for influenza is routine, which presents a unique opportunity to  
28  
29  
30 100 combine the benefits of large data sets with positive diagnoses.[18] We therefore sought  
31  
32  
33 101 to estimate the incidence of hospitalisation with one or more of the above five severe  
34  
35  
36 102 complications amongst diagnosed with influenza infection, using Japanese health  
37  
38  
39 103 insurance claim data.

40  
41  
42 104

## 43 44 45 105 **METHODS**

### 46 47 48 49 106 **Patients and data**

50  
51  
52  
53 107 We analysed administrative data provided by Japan Medical Data Center Ltd. Tokyo,  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6 108 Japan.[19] The data comprised the monthly health insurance claim records between  
7  
8  
9 109 January 2012 and December 2016 of approximately three million employees and their  
10  
11 110 families, representing 2.4% of the Japanese population. Within health insurance  
12  
13  
14 111 coverage in Japan, people can consult physicians in any type of hospital and department,  
15  
16  
17 112 and medical doctors in any speciality can diagnose influenza and prescribe  
18  
19  
20 113 anti-influenza medications. The age of patients in the data set ranged from 0 to 74 years  
21  
22  
23 114 because all Japanese people aged 75 or more (except for individuals who are on public  
24  
25  
26 115 assistance) are covered by another health insurance program with lower out-of-pocket  
27  
28  
29 116 expenses.

30  
31  
32 117 We extracted the data of outpatients and inpatients who consulted physicians  
33  
34  
35 118 with influenza-like illness and were diagnosed with influenza virus infections. In Japan,  
36  
37  
38 119 a test-and-treat strategy is routine. Even if physicians only slightly suspect influenza  
39  
40  
41 120 infection from clinical features, they use an immunochromatogenic assay point-of-care  
42  
43  
44 121 test [POCT] to diagnose influenza, and then administer antivirals to the patient.[20]  
45  
46  
47 122 Therefore, almost all diagnoses in the data were based upon positive results of a  
48  
49  
50 123 POCT.[10 18]

## 51 52 53 124 **Outcomes**

54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6 125 In our population of patients with a diagnosis of influenza infection, we identified those  
7  
8  
9 126 who were hospitalised with a diagnosis of acute respiratory failure, pneumonia, ARDS,  
10  
11 127 febrile seizure, and encephalitis/encephalopathy, according to International  
12  
13 128 Classification of Diseases (ICD-10) codes. In the data, acute respiratory failure was  
14  
15 129 coded as J960, J988, R060, R068 or R092; pneumonia was coded as J10–J18 or J20–  
16  
17 130 J22, acute respiratory distress syndrome (ARDS) as J80, and febrile seizure as R560.  
18  
19  
20 131 We defined influenza encephalitis/encephalopathy in patients who were diagnosed using  
21  
22 132 ICD-10 codes for influenza infection and encephalitis/encephalopathy (G00–G09 or  
23  
24 133 G41) and had been administered steroid pulse or immunoglobulin therapy.[21]  
25  
26  
27  
28  
29  
30  
31

### 32 134 **Statistical analysis**

33  
34  
35

36 135 We collected data for the number of consultations and severe complications according  
37  
38 136 to sex, age, outpatient/inpatient status, number of beds in the facility, and clinical  
39  
40 137 speciality. In Japan, clinical facilities with fewer than 20 beds are denoted a “clinic” by  
41  
42 138 law. Clinics are usually run by a single medical doctor and function as a primary care  
43  
44 139 department. Most clinics have no beds but a subset of clinics have 1–19 beds to  
45  
46 140 accommodate inpatients. In contrast, facilities with 20 beds or more are legally termed a  
47  
48 141 “hospital”. Hospitals have primary care, specialised outpatient, and general and  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6 142 specialised inpatient departments. We plotted histograms of the ages of outpatients and  
7  
8  
9 143 inpatients infected with influenza. Additionally, we determined the number of inpatients  
10  
11  
12 144 with the five severe complications and the proportion of hospitalisations, by age group  
13  
14  
15 145 and age. The primary outcomes were incidence of each of the five complications per  
16  
17 146 10000 influenza infections. We examined this by sex, influenza season and age.  
18  
19  
20 147 Influenza seasons were defined as lasting from September through to the following  
21  
22  
23 148 August. We calculated p values for secular trends of the incidence over influenza  
24  
25  
26 149 seasons. Statistical analyses were performed using SAS statistical software (version 9.4,  
27  
28  
29 150 SAS Institute, Cary, NC, USA). All reported p values were two-sided and we considered  
30  
31 151  $p < 0.05$  indicated a significant difference.  
32  
33  
34

## 35 152 **Patient and public involvement**

36  
37  
38  
39 153 The ethics committee of the School of Medicine, University of Yamanashi approved this  
40  
41  
42 154 study (approval number: H29-1709), in accordance with the ethical guidelines and  
43  
44  
45 155 regulations of the Declaration of Helsinki. The data were properly anonymised by the  
46  
47  
48 156 Japan Medical Data Center in the manner permitted by Japanese guideline of Personal  
49  
50  
51 157 Information Protection Commission, Cabinet Office, Government of Japan for the use  
52  
53  
54 158 of data from medical examinations in medical research without individual participants'  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6 159 consent (Act on the Protection of Personal Information, act no. 57 of 30 May 2003; last  
7  
8  
9 160 version amendment of act no. 65 of 2015).

10  
11  
12  
13 161

## 14 15 16 162 **RESULTS**

### 17 18 19 20 163 **Characteristics of patients diagnosed with influenza**

21  
22  
23  
24 164 Table 1 summarises the number of patients infected with influenza in the study  
25  
26  
27 165 population. Among 16636913 infections, 53.4% of the patients were men, and 1.0%  
28  
29  
30 166 were hospitalised. Approximately a quarter (25.7%) of infections were in children aged  
31  
32  
33 167 6–12 years. Overall 32% of diagnoses were made in the internal medicine department  
34  
35  
36 168 and 23% in paediatrics. Most infections were diagnosed in clinics (n=13572391; 83%).  
37  
38  
39 169 Figures 1 and 2 illustrate the number of outpatients and inpatients with influenza  
40  
41  
42 170 infection, respectively, by age. Influenza was most often diagnosed in outpatients aged  
43  
44  
45 171 0–12 years, with a second small peak in middle-aged patients. In contrast, inpatient  
46  
47  
48 172 cases were commonest among patients aged less than one year. Table 2 shows the  
49  
50  
51 173 number of complicated cases by department, hospital size and type of hospital  
52  
53  
54 174 management. A total of 3361 patients (0.02%) were admitted to hospital with acute  
55  
56  
57 175 respiratory failure, 27253 (0.16%) with pneumonia, 18 (0.0001%) with ARDS, 2603

1  
2  
3  
4  
5  
6 176 (0.02%) with febrile seizures, and 159 (0.001%) with encephalitis/encephalopathy. Most  
7  
8  
9 177 complicated cases were admitted to paediatric departments, with 19012 pneumonia  
10  
11 178 admissions (70% of the total), 1794 with acute respiratory failure (53% of the total),  
12  
13  
14 179 2461 with febrile seizures (95% of the total), and 63 encephalitis (40% of all cases). The  
15  
16  
17 180 number of inpatients with acute respiratory failure, pneumonia, and febrile seizure  
18  
19  
20 181 tended to increase with the number of hospital beds.

### 22 23 24 182 **Hospitalisation rates from severe complications**

25  
26  
27  
28 183 The combined incidence of these five complications was 18.9 per 10000 diagnosed  
29  
30 184 infections. Pneumonia was the commonest complication, with 16.4 per 10000 diagnosed  
31  
32  
33 185 infections, followed by acute respiratory failure (2.0), febrile seizures (1.6),  
34  
35  
36 186 encephalitis/encephalopathy (0.1), and ARDS (0.01). Table 3 shows the incidence of  
37  
38  
39 187 five severe complications by age, sex, and influenza season. Although the incidence of  
40  
41  
42 188 acute respiratory failure, pneumonia, ARDS, and febrile seizures was higher in men,  
43  
44  
45 189 encephalitis/encephalopathy was higher in women. There were decreasing trends over  
46  
47  
48 190 the years in incidence of hospital admissions from pneumonia (p for trend<0.0001),  
49  
50  
51 191 febrile seizure (p for trend<0.0001), and the five severe complications combined (p for  
52  
53  
54 192 trend<0.0001), but not acute respiratory failure (p for trend=0.07),  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6 193 encephalitis/encephalopathy (p for trend=0.19) or ARDS (p for trend=0.98). In each age  
7  
8  
9 194 group, pneumonia was the commonest complication. The incidence of acute respiratory  
10  
11 195 failure, pneumonia, and febrile seizure was highest in patients aged 0–1 years, ARDS  
12  
13  
14 196 was highest in those 65–74 years, and encephalitis/encephalopathy was highest in  
15  
16  
17 197 patients aged 13–18 years.

18  
19  
20  
21 198       Figures 3 and 4 show the number and percentage of inpatients with  
22  
23  
24 199 complications by age group and age over the study period. Young children had most of  
25  
26  
27 200 the severe complications. Across all age groups, pneumonia was by far the most  
28  
29  
30 201 common of the five complications, and the age group with the largest number of cases  
31  
32 202 was children aged 2–5 years. In contrast, the proportion of hospitalisations amongst  
33  
34  
35 203 inpatients was highest in patients aged 0–1 years (2.96%) and second highest in those  
36  
37  
38 204 aged 65–74 years (2.21%).

39  
40  
41  
42 205

## 43 44 45 206 **DISCUSSION**

### 46 47 48 49 207 **Statement of the principal findings**

50  
51  
52  
53 208 We described the epidemiology of hospital admissions and five key severe  
54  
55  
56  
57  
58  
59  
60



209 complications in large cross-sectional data of influenza-positive patients. Influenza  
210 diagnoses were commonest in young children and middle-aged patients (table 1 and  
211 figures 1–2). The incidence and absolute number of hospital admissions with  
212 complications of influenza was highest in young children (figure 2 and table 3). The  
213 most common complication was pneumonia (table 1). The incidence and absolute  
214 number of admissions for pulmonary complications were highest in children (figures 3–  
215 4 and table 3). Patients aged 65–74 years were also at high risk for admission from  
216 complications, but the absolute number of both influenza infections and serious  
217 complications was relatively lower than for children in our data set (figures 3–4 and  
218 table 3). The incidence of admissions for encephalitis/encephalopathy was relatively  
219 high in children aged 0–18 years (table 3).

## 220 **Discussing important differences in results**

221 Male patients suffered more complications than female ones, especially for acute  
222 respiratory failure, pneumonia, and febrile seizures (table 3). This is consistent with  
223 previous studies reporting that during the 2009–2010 pandemic influenza A(H1N1)  
224 season, the incidence of hospitalisation in male children was greater than in female  
225 children in the US (56%),[22] Canada (60%),[23] and Japan (64.3%).[18] Asthma is a

1  
2  
3  
4  
5  
6 226 risk factor for pneumonia in children with influenza [24]. Our finding of an increased  
7  
8  
9 227 risk of pneumonia in males may be because asthma is a more common disease in boys  
10  
11 228 than girls.[25] It is also known that male children develop febrile seizures more often  
12  
13  
14 229 than female children.[26] This was also observed in our data for febrile seizures with  
15  
16  
17 230 influenza infection. Worldwide, women may be at higher risk for severe complications  
18  
19  
20 231 of influenza infection.[27] In Japanese surveillance reports from 2007 to 2010, 153 of  
21  
22  
23 232 263 (58.2%) paediatric patients with encephalopathy were male.[14] In contrast, our  
24  
25  
26 233 data suggest the possibility of a higher risk of encephalitis in women with influenza  
27  
28  
29 234 infection (table 3), although the number of cases is insufficient to draw a strong  
30  
31 235 conclusion.

32  
33  
34  
35 236 Our results by age are consistent with those of previous studies, and add to the  
36  
37  
38 237 understanding of the risk of specific complications amongst those with a diagnosis of  
39  
40  
41 238 influenza. Previous studies, being unable to identify a large number of  
42  
43  
44 239 influenza-positive patients, have used small numbers of influenza positive admissions as  
45  
46  
47 240 cases and general population estimates as the denominators. We found that the risk of  
48  
49  
50 241 hospitalisation was highest in infected infants aged 0–1 years (figures 2–4 and table 3).  
51  
52  
53 242 This is consistent with a US study, which found that the highest hospitalisation rate was  
54  
55  
56 243 among infants aged under one year (1.19 per 10,000 population) during the 2009–2010

1  
2  
3  
4  
5  
6 244 influenza A(H1N1) pandemic;[6] in addition, we are able to show that the risk of  
7  
8  
9 245 admission is as high as 94.3 per 10000 infections. A study from the UK also reported  
10  
11 246 that children aged 0–11 years had the highest influenza related hospitalisation rates  
12  
13  
14 247 (23.53 per 10,000 population), but based upon only 33 confirmed cases of influenza.[8]  
15  
16  
17 248 A systematic review found large gaps in the evidence base (describing the evidence for  
18  
19  
20 249 risk factors for admissions as “limited to absent”).[9] They found contrasting results  
21  
22  
23 250 with children under the age of two years at higher risk of admission to hospital than  
24  
25  
26 251 older children with pandemic H1N1 influenza but the reverse with seasonal  
27  
28  
29 252 influenza.[9] They also found evidence of spectrum bias; studies from hospitals and  
30  
31  
32 253 intensive care units gave lower estimates of risk of death than community-based studies  
33  
34  
35 254 for both the elderly and children compared to young adults. As well as including  
36  
37  
38 255 positively diagnosed patients, our study covers both the community and hospital  
39  
40  
41 256 settings and is of sufficient size to allow estimation for specific causes of admission.

### 42 43 257 **Implications for clinicians and policymakers**

44  
45  
46  
47 258 During the 2009–2010 pandemic, the World Health Organization [28] and the Centers  
48  
49  
50 259 for Disease Control and Prevention [29] issued guidelines for early neuraminidase  
51  
52  
53 260 inhibitor treatment. There are suggestions that administration of this medication within

1  
2  
3  
4  
5  
6 261 48 hours reduces mortality and severe outcomes.[30] A Cochrane review, whilst critical  
7  
8  
9 262 of the quality of trial evidence, found a reduction in secondary infections among  
10  
11 263 children who were prescribed oseltamivir.[31] During the 2000s, four neuraminidase  
12  
13  
14 264 inhibitors became available in Japan: zanamivir in 2000, oseltamivir in 2001, and  
15  
16  
17 265 laninamivir and peramivir in 2010. The decreasing trend with time in the composite  
18  
19  
20 266 incidence of the five severe complications (table 3,  $p < 0.0001$ ) might be attributed to the  
21  
22  
23 267 increasingly widespread use of [10] and more options for neuraminidase inhibitors. A  
24  
25  
26 268 recent meta-analysis of randomised controlled trials reported that in patients with  
27  
28  
29 269 pathogen-ascertained influenza, as is practice in Japan, treatment with oseltamivir  
30  
31 270 reduced hospital admissions by 63%.[32]

32  
33  
34  
35 271 In our study, the incidence of severe outcomes of acute pneumonia and febrile  
36  
37  
38 272 seizures decreased with time (table 3, both  $p$  values  $< 0.0001$ ). This was observed in  
39  
40  
41 273 parallel with increased administration modes of neuraminidase inhibitors. However,  
42  
43  
44 274 there appears to be no trend in the risk of encephalitis/encephalopathy. Because  
45  
46  
47 275 influenza encephalitis appears to be mediated by an acute process during infection,[11]  
48  
49  
50 276 it is important to prevent influenza infection to reduce the incidence of encephalitis. The  
51  
52  
53 277 primary countermeasure to protect individuals from infection is vaccination. In Japan,  
54  
55 278 schoolchildren were vaccinated routinely from 1976 to 1994, when influenza was

1  
2  
3  
4  
5  
6 279 removed from the list of routine vaccinations, and vaccination of high risk groups only  
7  
8  
9 280 was then recommended from 2001.[33] Studies of this natural experiment suggest that  
10  
11 281 the former routine vaccination program for schoolchildren indirectly reduced excess  
12  
13  
14 282 mortality among elderly populations;[34 35] however, the effect upon the incidence of  
15  
16  
17 283 encephalitis is unknown. Because current encephalitis treatments are of limited  
18  
19  
20 284 effectiveness, a vaccination program covering a broad population may be the best way  
21  
22  
23 285 to reduce the morbidity associated with influenza encephalitis.  
24  
25

#### 26 286 **Strengths and weaknesses in relation to other studies**

27  
28  
29  
30 287 A main strength of this study is that the included patients were diagnosed with influenza  
31  
32  
33 288 by testing. The majority of influenza-like illness is usually caused by infections other  
34  
35  
36 289 than influenza.[37] Diagnoses were based on rapid antigen detection with  
37  
38  
39 290 immunochromatogenic assay. Because POCTs for influenza are less invasive and  
40  
41  
42 291 require less time than laboratory tests, they are an essential tool for physicians to  
43  
44  
45 292 evaluate influenza in outpatient and inpatient clinical practice in Japan.[18] Although  
46  
47  
48 293 low sensitivity (59–93%) [38] is a weak point for POCTs, the specificity is 98–  
49  
50  
51 294 100%.[20 39] This means that nearly all individuals with influenza-like illness who  
52  
53  
54 295 have POCT-positive results (the participants in this study) were infected with influenza.  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6 296 This makes routinely collected Japanese data unique. Therefore, we did not greatly  
7  
8  
9 297 overestimate the number of infected patients and thus did not underestimate the risk of  
10  
11  
12 298 complications and hospitalisations.  
13  
14

15 299 There are limitations inherent to the data set used in this study. The  
16  
17  
18 300 administrative data from employees and their families used here do not permit analysis  
19  
20  
21 301 of patients aged 75 years or more. Also, owing to employment patterns in Japan, the  
22  
23  
24 302 number of male patients was slightly higher than female patients (table 1). The sex ratio  
25  
26  
27 303 varies across generations in Japan, with more males in younger populations and women  
28  
29  
30 304 predominating in older populations.[36] However, the incidence of hospitalisation  
31  
32  
33 305 amongst infected patients in both sexes and the studied age groups should not be biased  
34  
35  
36 306 by this imbalance. Second, we were unable to estimate influenza-related mortality in  
37  
38  
39 307 this data set, but the data are sufficient to allow examination of serious complications  
40  
41  
42 308 that are major public health concerns. Although we were unable to define  
43  
44  
45 309 encephalitis/encephalopathy cases virologically, we added the requirement of receiving  
46  
47  
48 310 specific therapy to the definition of encephalitis/encephalopathy cases.[21] This more  
49  
50  
51 311 stringent definition reduces the likelihood that we have overestimated this outcome.  
52  
53  
54 312 Further analysis of influenza-related mortality in Japan is needed, and this should  
55  
56  
57 313 encompass older adults. The effect of neuraminidase inhibitors should be examined  
58  
59  
60

1  
2  
3  
4  
5  
6 314 using observational data, as clinical trials are likely to be underpowered for rare but  
7  
8  
9 315 important complications such as encephalopathy.

10  
11  
12  
13 316 **Conclusions**

14  
15  
16 317 Using Japanese administrative data, 1.0% of patients who tested positive for influenza  
17  
18 318 infection were hospitalised. Male patients had a higher incidence of pulmonary  
19  
20 319 complications and febrile seizures. Children aged 0–5 years and adults aged 65–74  
21  
22 320 years were at high risk of being admitted to hospital for pneumonia, with the highest  
23  
24 321 absolute numbers of hospitalised patients among young children. Further efforts are  
25  
26 322 needed, such as active prescription of neuraminidase inhibitors and vaccination  
27  
28 323 programs, to prevent hospitalisations from severe complications in these age groups.

29  
30  
31  
32  
33  
34 324 **(2894 words)**

35  
36  
37  
38  
39  
40  
41 325

42  
43  
44 326

45  
46  
47 327 **Acknowledgements** The authors are immensely grateful to the Japan Medical Data  
48  
49 328 Center for providing the administrative data. We thank Ms. Analisa Avila, ELS, of  
50  
51  
52 329 Edanz Group for editing a draft of this manuscript.

1  
2  
3  
4  
5  
6 330 **Authors' contributions** All of the authors agreed with the manuscript's results and  
7  
8  
9 331 conclusion and approved the final version of the manuscript. HY conceived the study.  
10  
11 332 HY, MM, JL, RK, TY and ZY contributed to the design of the study and interpretation  
12  
13  
14 333 of the data analyses. HY analysed the data. HY, JL, MM and RK wrote the first draft of  
15  
16  
17 334 the manuscript. JL, RK, MM, ZY and HY contributed to revision of the manuscript. ZY  
18  
19  
20 335 and HY were responsible for data integrity. HY obtained funding.

21  
22  
23 336 **Funding** This work was supported by funding from the Ministry of Education, Culture,  
24  
25  
26 337 Sports, Science, and Technology (MEXT) (KAKENHI grant numbers JP15K08730).

27  
28 338 **Competing interests.** None.

29  
30  
31 339 **Patient consent** Not required.

32  
33  
34 340 **Ethics approval** The ethics committee of the School of Medicine, University of  
35  
36  
37 341 Yamanashi approved this study (approval number: H29-1709).

38  
39  
40 342 **Data sharing statement** The original administrative data are available through a formal  
41  
42  
43 343 request to the Japan Medical Data Center Ltd., subject to fees.

44  
45 344



345 **References**

- 346 1. Ghebrehewet S, MacPherson P, Ho A. Influenza. *BMJ* 2016;355:i6258. doi:  
347 10.1136/bmj.i6258.
- 348 2. Kaiser L, Wat C, Mills T, *et al.* Impact of oseltamivir treatment on influenza-related  
349 lower respiratory tract complications and hospitalisations. *Arch Intern Med*  
350 2003;163:1667-72.
- 351 3. Iuliano AD, Roguski KM, Chang HH, *et al.* Estimates of global seasonal  
352 influenza-associated respiratory mortality: a modelling study. *Lancet* 2017.  
353 doi.org/10.1016/S0140-6736(17)33293-2.
- 354 4. Thompson WW, Shay DK, Weintraub E, *et al.* Influenza-associated hospitalizations  
355 in the United States. *JAMA* 2004;292:1333-40.
- 356 5. Newland JG, Laurich VM, Rosenquist AW, *et al.* Neurologic complications in  
357 children hospitalized with influenza: characteristics, incidence, and risk factors. *J*  
358 *Pediatr* 2006;150:306-10. doi: 10.1016/j.jpeds.2006.11.054.
- 359 6. Louie JK, Acosta M, Winter K, *et al.* Factors associated with death or hospitalization  
360 due to pandemic 2009 influenza A (H1N1) infection in California. *JAMA*  
361 2009;302:1896-902.
- 362 7. Pitman R, Melegaro A, Gelb D, *et al.* Assessing the burden of influenza and other

- 1  
2  
3  
4  
5  
6 363 respiratory infections in England and Wales. *J Infect* 2007;54:530-38.  
7  
8  
9 364 8. Nicholson KG, McNally T, Silverman M, *et al*. Rates of hospitalisation for influenza,  
10  
11 365 respiratory syncytial virus and human metapneumovirus among infants and young  
12  
13  
14 366 children. *Vaccine* 2006;24:102-08.  
15  
16  
17 367 9. Mertz D, Kim TH, Johnstone J, *et al*. Populations at risk for severe or complicated  
18  
19  
20 368 influenza illness: systematic review and meta-analysis. *BMJ* 2013;347:f5061.  
21  
22  
23 369 10. Sugaya N. Widespread use of neuraminidase inhibitors in Japan. *J Infect Chemother*  
24  
25  
26 370 2011;17:595.  
27  
28  
29 371 11. Amin R, Ford-Jones E, Richardson SE, *et al*. Acute childhood encephalitis and  
30  
31 372 encephalopathy associated with influenza: a prospective 11-year review. *Pediatr*  
32  
33  
34 373 *Infect Dis J* 2008;27:390-95.  
35  
36  
37 374 12. Wang GF, Li W, Li K. Acute encephalopathy and encephalitis caused by influenza  
38  
39  
40 375 virus infection. *Curr Opin Neurol* 2010;23:305-11. doi:  
41  
42 376 10.1097/WCO.0b013e328338f6c9.  
43  
44  
45 377 13. Gu Y, Shimada T, Yasui Y, *et al*. National surveillance of influenza-associated  
46  
47  
48 378 encephalopathy in Japan over six years, before and during the 2009–2010 influenza  
49  
50  
51 379 pandemic. *Plos One* 2013;8:e54786.  
52  
53  
54 380 14. Hoshino A, Saitoh M, Oka A, *et al*. Epidemiology of acute encephalopathy in Japan,  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4  
5  
6 381 with emphasis on the association of viruses and syndromes. *Brain Dev*  
7  
8  
9 382 2012;34:337-43.
- 10  
11 383 15. Okumura A, Nakagawa S, Kawashima H, *et al.* Deaths associated with pandemic  
12  
13  
14 384 (H1N1) 2009 among children, Japan, 2009–2010. *Emerg Infect Dis* 2011;17:1993.
- 15  
16  
17 385 16. National Institute of Infectious Diseases and Ministry of Health, Labour and Welfare.  
18  
19  
20 386 Infectious agents surveillance report 36. 2015. Available at  
21  
22  
23 387 <https://www0.niid.go.jp/niid/idsc/iasr/36/429j.pdf>. Japanese. Accessed 12 June  
24  
25  
26 388 2018.
- 27  
28 389 17. Mizuguchi M. Influenza encephalopathy and related neuropsychiatric syndromes.  
29  
30  
31 390 *Influenza Other Resp* 2013;7:67-71.
- 32  
33  
34 391 18. Sugaya N, Shinjoh M, Mitamura K, *et al.* Very low pandemic influenza A (H1N1)  
35  
36  
37 392 2009 mortality associated with early neuraminidase inhibitor treatment in Japan:  
38  
39  
40 393 analysis of 1000 hospitalized children. *J Infect* 2011;63:288-94.
- 41  
42  
43 394 19. Tanaka S, Seto K, Kawakami K. Pharmacoepidemiology in Japan: medical  
44  
45  
46 395 databases and research achievements. *J Pharm Health Care Sci* 2015;1:16.
- 47  
48 396 20. Suzuki M, Yoshimine H, Harada Y, *et al.* Estimating the influenza vaccine  
49  
50  
51 397 effectiveness against medically attended influenza in clinical settings: a  
52  
53  
54 398 hospital-based case-control study with a rapid diagnostic test in Japan. *Plos One*

399 2013;8:e52103.

400 21. Study Group of Influenza Encephalitis, Ministry of Health Labour and Welfare.

401 Guideline of treatment for influenza encephalitis. Revised edition. Japanese.

402 Available at <http://www.tokyo-med.ac.jp/pediat/data/info0925-01.pdf>. Japanese.

403 Accessed 12 June 2018.

404 22. Kumar S, Havens PL, Chusid MJ, *et al*. Clinical and epidemiologic characteristics

405 of children hospitalized with 2009 pandemic H1N1 influenza A infection. *Pediatr*

406 *Infect Dis J* 2010;29:591-94. doi: 10.1097/INF.0b013e3181d73e32.

407 23. O'Riordan S, Barton M, Yau Y, *et al*. Risk factors and outcomes among children

408 admitted to hospital with pandemic H1N1 influenza. *Can Med Assoc J*

409 2010;182:39-44. doi: 10.1503/cmaj.091724.

410 24. Lee JJ, Bankhead C, Smith M, *et al*. Risk factors for influenza-related complications

411 in children during the 2009/10 pandemic: a UK primary care cohort study using

412 linked routinely collected data. *Epidemiol Infect* 2018;1-7. doi:

413 10.1017/S0950268818000353.

414 25. Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and

415 wheezing illness from early childhood to age 33 in a national British cohort. *BMJ*

416 1996;312:1195-99. doi: 10.1136/bmj.312.7040.1195.

- 1  
2  
3  
4  
5  
6 417 26. Tsuboi T. Epidemiology of febrile and afebrile convulsions in children in Japan.  
7  
8 418 Neurology 1984;34:175-75. doi: 10.1212/wnl.34.2.175.  
9  
10  
11 419 27. Klein SL, Hodgson A, Robinson DP. Mechanisms of sex disparities in influenza  
12  
13  
14 420 pathogenesis. J Leukocyte Biol 2012;92:67-73.  
15  
16  
17 421 28. World Health Organization. Rapid advice guidelines for pharmacological  
18  
19  
20 422 management of pandemic influenza (H1N1) 2009 and other influenza viruses. 2010.  
21  
22  
23 423 Available at  
24  
25 424 [http://www.who.int/csr/resources/publications/swineflu/h1n1\\_guidelines\\_pharmace](http://www.who.int/csr/resources/publications/swineflu/h1n1_guidelines_pharmaceutical_mngt.pdf)  
26  
27  
28 425 [utical\\_mngt.pdf](http://www.who.int/csr/resources/publications/swineflu/h1n1_guidelines_pharmaceutical_mngt.pdf). Accessed 12 June 2018.  
29  
30  
31 426 29. Centers for Disease Control and Prevention. Updated interim recommendations for  
32  
33  
34 427 the use of antiviral medications in the treatment and prevention of influenza for the  
35  
36  
37 428 2009–2010 season. Available at  
38  
39  
40 429 <https://www.cdc.gov/h1n1flu/recommendations.htm>. Accessed 12 June 2018.  
41  
42  
43 430 30. Muthuri SG, Myles PR, Venkatesan S, *et al*. Impact of neuraminidase inhibitor  
44  
45  
46 431 treatment on outcomes of public health importance during the 2009–2010 influenza  
47  
48  
49 432 A (H1N1) pandemic: a systematic review and meta-analysis in hospitalized patients.  
50  
51  
52 433 J Infect Dis 2012;207:553-63.  
53  
54 434 31. Jefferson T, Jones MA, Doshi P, *et al*. Neuraminidase inhibitors for preventing and  
55  
56  
57  
58  
59

- 1  
2  
3  
4  
5  
6 435 treating influenza in healthy adults and children. *Cochrane Database Syst Rev*  
7  
8  
9 436 2012;1 Art:CD008965.
- 10  
11 437 32. Dobson J, Whitley RJ, Pocock S, *et al*. Oseltamivir treatment for influenza in adults:  
12  
13  
14 438 a meta-analysis of randomised controlled trials. *Lancet* 2015;385:1729-37.
- 15  
16  
17 439 33. Hirota Y, Kaji M. History of influenza vaccination programs in Japan. *Vaccine*  
18  
19  
20 440 2008;26:6451-54. doi.org/10.1016/j.vaccine.2008.06.042.
- 21  
22  
23 441 34. Reichert TA, Sugaya N, Fedson DS, *et al*. The Japanese experience with vaccinating  
24  
25  
26 442 schoolchildren against influenza. *N Engl J Med* 2001;344:889-96.
- 27  
28 443 35. Charu V, Viboud C, Simonsen L, *et al*. Influenza-related mortality trends in Japanese  
29  
30  
31 444 and American seniors: evidence for the indirect mortality benefits of vaccinating  
32  
33  
34 445 schoolchildren. *Plos One* 2011;6:e26282.
- 35  
36  
37 446 36. Central Intelligence Agency. The world factbook: sex ratio (male/female). 2018.  
38  
39  
40 447 Available at  
41  
42 448 <https://www.cia.gov/library/publications/the-world-factbook/fields/2018.html>.  
43  
44  
45 449 Accessed 12 June 2018.
- 46  
47  
48 450 37. Hayward AC, Fragaszy EB, Bermingham A, *et al*. Comparative community burden  
49  
50  
51 451 and severity of seasonal and pandemic influenza: results of the Flu Watch Cohort  
52  
53  
54 452 Study. *Lancet Resp Med* 2014;2:445-54.
- 55  
56  
57  
58  
59  
60

- 1  
2  
3  
4  
5  
6 453 38. Paules C, Subbarao K. Influenza. *Lancet* 2017;390:697-708. doi:  
7  
8  
9 454 10.1016/S0140-6736(17)30129-0.  
10  
11 455 39. Poehling KA, Zhu Y, Tang Y-W, *et al*. Accuracy and impact of a point-of-care rapid  
12  
13  
14 456 influenza test in young children with respiratory illnesses. *Arch Pediatr Adolescent*  
15  
16  
17 457 *Med* 2006;160:713-18.  
18  
19  
20 458

1  
2  
3  
4  
5 459 **Figure legends**

6 460

7  
8 461 Figure 1. Histogram of the ages of influenza-infected outpatients in the 2012/13,  
9 462 2013/14, 2014/15, and 2015/16 seasons, according to health insurance administrative  
10 463 data.

11  
12 464

13 465 Figure 2. Histogram of the ages of influenza-infected inpatients in the 2012/13, 2013/14,  
14 466 2014/15, and 2015/16 seasons, according to health insurance administrative data.

15  
16 467

17  
18 468 Figure 3. Number of influenza-infected inpatients with severe complications and  
19 469 proportion of hospitalisation, by age group, between 2012 and 2016.

20 470 Abbreviation: ARDS, acute respiratory distress syndrome.

21  
22 471

23 472 Figure 4. Number of influenza-infected inpatients with severe complications and  
24 473 proportion of hospitalisation, by age, between 2012 and 2016.

25 474 Abbreviation: ARDS, acute respiratory distress syndrome.

26  
27 475  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



476 Table 1. Population Characteristics: Number (%) of 16636913 Japanese patients infected with influenza between 2012–2016, in health  
477 insurance administrative data.

Sex, n (%)	Men 8885699 (53.4)	Women 7751214 (46.6)							
Patient status, n (%)	Outpatient 16488970 (99.0)	Inpatient 164394 (1.0)							
Age, years	0–1 823875 (5.1)	2–5 2886462 (17.7)	6–12 4193137 (25.7)	13–18 1480030 (9.1)	19–44 3815970 (23.4)	45–64 2872125 (17.6)	65–74 231120 (1.4)		
No. of hospital beds	0–19 13572391 (83.3)	20–99 392179 (2.4)	100–199 450850 (2.8)	200–299 324418 (2.0)	300–499 616989 (3.8)	500+ 945892 (5.8)			
Clinical department of diagnosis	Internal medicine	Paediatrics	Otorhinolaryngology	Orthopaedics	Dermatology	Surgery	Ophthalmology	Obstetrics &	Psychiatry

								Gynaecol	
								ogy	
No. patients	1187638	827942	310514	308146	250737	206763	165915	156615	99624
(%)	(32.4)	(22.6)	(8.5)	(8.4)	(6.8)	(5.6)	(4.5)	(4.3)	(2.7)

478

For peer review only

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

Category	Acute				Encephalitis/ encephalopathy
	respiratory failure	Pneumonia	ARDS	Febrile seizure	
Overall complications	3361	27253	18	2603	159
Clinical department					
Internal medicine	682 (20.3%)	3633 (13.3%)	6	23 (0.9%)	57 (35.8%)
Paediatrics	1794 (53.4%)	19012 (69.8%)	2	2461 (94.5%)	63 (39.6%)
Otorhinolaryngology	43 (1.3%)	217 (0.8%)	0	2 (0.1%)	0
Orthopaedics	43 (1.3%)	338 (1.2%)	0	6 (0.2%)	0
Dermatology	3 (0.1%)	45 (0.2%)	0	0	0
Surgery	189 (5.6%)	720 (2.6%)	3	18 (0.7%)	0
Ophthalmology	0	23 (0.1%)	0	1 (0.04%)	0
Obstetrics and Gynaecology	88 (2.6%)	330 (1.2%)	0	0	0
Psychiatry	28 (0.8%)	197 (0.7%)	0	8 (0.3%)	37 (23.3%)
Not specified	486 (14.5%)	2738 (10.0%)	0	84 (3.2%)	2 (1.3%)

No. of hospital beds						
0–19	167 (5.0%)	805 (3.0%)	0	18 (0.7%)	0	
20–99	106 (3.2%)	913 (3.4%)	3	36 (1.4%)	0	
100–199	308 (9.2%)	2394 (8.8%)	0	147 (5.6%)	0	
200–299	358 (10.7%)	2933 (10.8%)	7	220 (8.5%)	26 (16.4%)	
300–499	922 (27.5%)	9179 (33.7%)	0	1003 (38.5%)	57 (35.8%)	
500+	1500 (44.7%)	11029 (40.5%)	8	1179 (45.3%)	76 (47.8%)	
Hospital type						
Clinic	167 (5.0%)	805 (3.0%)	0	18 (0.7%)	0	
National or municipal hospital	985 (29.4%)	10995 (40.3%)	10	1314 (50.5%)	82 (51.6%)	
University hospital	285 (8.5%)	2049 (7.5%)	0	162 (6.2%)	34 (21.4%)	
Other hospital	1919 (57.2%)	13404 (49.2%)	8	1109 (42.6%)	43 (27.0%)	
Not specified	5 (0.1%)	0	0	0	0	

481 Abbreviation: ARDS, acute respiratory distress syndrome.

482

483 Table 3. Incidence of hospitalisation with severe complications per 10000 confirmed  
 484 influenza infections.

No. of inpatients per 10,000 influenza infections	All five complications	Acute			Febrile seizure	Encephalitis /encephalop athy
		respiratory failure	Pneumonia	ARDS		
Sex*	p<0.0001	p<0.0001	p<0.0001	p=0.08	p<0.0001	p=0.08
Male	19.1	2.22	17.1	0.015	1.78	0.08
Female	17.1	1.78	15.6	0.006	1.32	0.11
Year†	p<0.0001	p=0.07	p<0.0001	p=0.98	p<0.0001	p=0.19
Jan 2012–Aug 2012	24.9	2.3	22.9	0.025	2.3	0.04
Sep 2012–Aug 2013	19.9	2.2	18.0	0.007	1.7	0.08
Sep 2013–Aug 2014	18.0	2.0	16.0	0.006	1.7	0.13
Sep 2014–Aug 2015	16.9	1.9	15.0	0.017	1.4	0.11
Sep 2015–Aug 2016	17.2	2.1	15.7	0.006	1.4	0.07
Sep 2016–Dec 2016	16.6	2.0	15.2	0.018	1.1	0.14
Age, years						
0–1	94.3	10.1	84.7	0.073	12.1	0.13
2–5	30.7	2.6	27.9	0	4.5	0.09

36

6–12	12.4	1.0	11.5	0	0.7	0.13
13–18	8.7	0.94	7.8	0	0.041	0.14
19–44	10.0	1.5	8.8	0.005	0.018	0.09
45–64	9.5	1.8	8.2	0.021	0	0.05
65–74	27.1	5.6	24.5	0.17	0	0.04

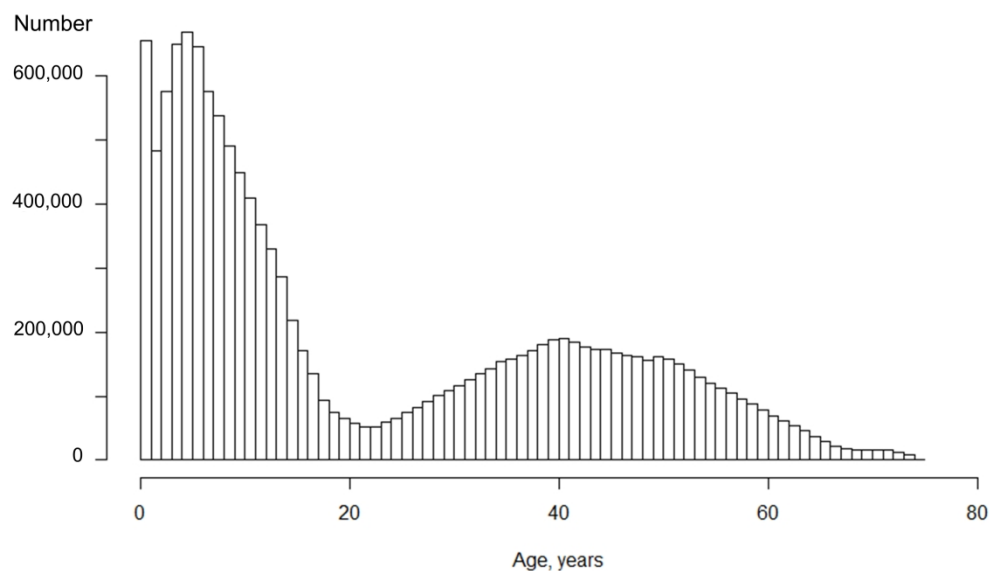
485 Abbreviation: ARDS, acute respiratory distress syndrome.

486 \*p for difference of incidence; †p for trend.

487

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

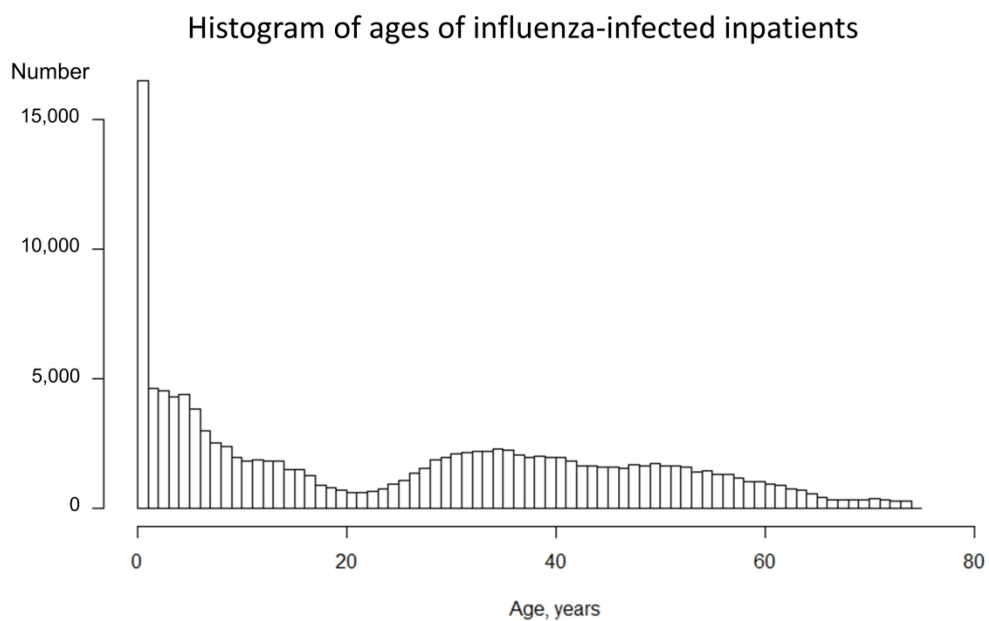
Histogram of ages of influenza-infected outpatients



Histogram of the ages of influenza-infected outpatients in the 2012/13, 2013/14, 2014/15, and 2015/16 seasons, according to health insurance administrative data.

284x189mm (300 x 300 DPI)

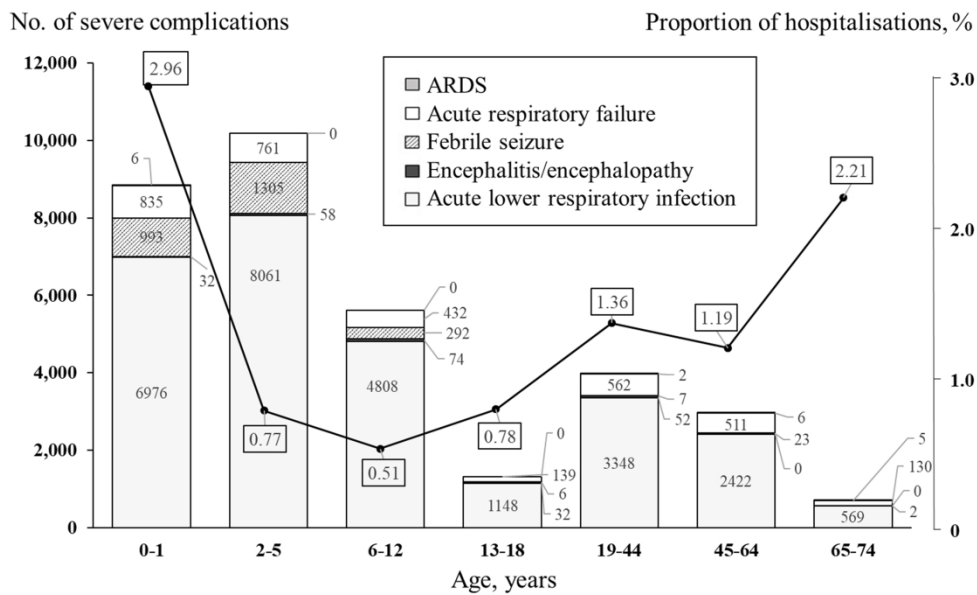
1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



Histogram of the ages of influenza-infected inpatients in the 2012/13, 2013/14, 2014/15, and 2015/16 seasons, according to health insurance administrative data.

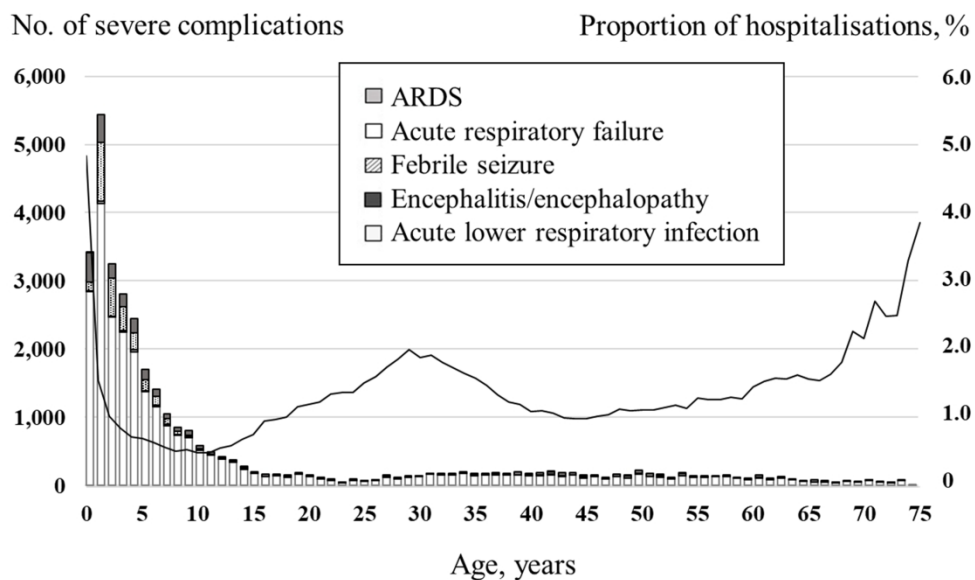
277x181mm (300 x 300 DPI)





Number of influenza-infected inpatients with severe complications and proportion of hospitalisation, by age group, between 2012 and 2016. Abbreviation: ARDS, acute respiratory distress syndrome.

267x167mm (300 x 300 DPI)



Number of influenza-infected inpatients with severe complications and proportion of hospitalisation, by age, between 2012 and 2016. Abbreviation: ARDS, acute respiratory distress syndrome.

258x156mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cross-sectional studies

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3–4
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6–8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	8–9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10–11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9–10
Bias	9	Describe any efforts to address potential sources of bias	10–11
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10–11
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	10–11
		(b) Describe any methods used to examine subgroups and interactions	10–11
		(c) Explain how missing data were addressed	9
		(d) If applicable, describe analytical methods taking account of sampling strategy	9
		(e) Describe any sensitivity analyses	Figures 3 and 4
<b>Results</b>			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12–13
		(b) Give reasons for non-participation at each stage	Not Applicable
		(c) Consider use of a flow diagram	Not Applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Not Applicable
Outcome data	15*	Report numbers of outcome events or summary measures	Table 2
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3 and figures 3–4
		(b) Report category boundaries when continuous variables were categorized	Table 3 and figures 3–4
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not Applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 3 and figures 3–4
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	15–16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19–20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14–17
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## 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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-024687.R1
Article Type:	Research
Date Submitted by the Author:	23-Oct-2018
Complete List of Authors:	Yokomichi, Hiroshi; University of Yamanashi, Department of Health Sciences Mochizuki, Mie; University of Yamanashi, Department of Pediatrics Lee, Joseph; University of Oxford Kojima, Reiji; University of Yamanashi, Department of Health Sciences Yokoyama, Tetsuji ; National Institute of Public Health, Department of Health Promotion Yamagata, Zentaro; University of Yamanashi
<b>Primary Subject Heading</b>:	Infectious diseases
Secondary Subject Heading:	Paediatrics, Respiratory medicine, Epidemiology, Evidence based practice, Health services research
Keywords:	Influenza, Hospitalisation, Pneumonia, Influenza encephalopathy, Influenza encephalitis, Febrile seizure

SCHOLARONE™  
Manuscripts

1 **Incidence of hospitalisation for severe complications of influenza virus infection in**  
2 **Japanese patients between 2012 and 2016: A cross-sectional study using routinely**  
3 **collected administrative data**

4 Hiroshi Yokomichi<sup>1</sup>, Mie Mochizuki<sup>2</sup>, Joseph Jonathan Lee<sup>3</sup>, Reiji Kojima<sup>1</sup>, Tetsuji  
5 Yokoyama<sup>4</sup>, Zentaro Yamagata<sup>1</sup>

6  
7 Author Affiliations

8 <sup>1</sup>Department of Health Sciences, University of Yamanashi

9 <sup>2</sup>Department of Pediatrics, University of Yamanashi

10 <sup>3</sup>Nuffield Department of Primary Care Health Sciences, University of Oxford

11 <sup>4</sup>Department of Health Promotion, National Institute of Public Health

12  
13 Correspondence: Hiroshi Yokomichi

1  
2  
3  
4  
5  
6 14 1110 Shimokato, Chuo City, Yamanashi, 4093898, Japan  
7  
8  
9

10 15 Tel: +81 80 5524 7393  
11  
12

13  
14 16 Fax: +81 55 273 7882  
15  
16

17 17 E-mail: [hyokomichi@yamanashi.ac.jp](mailto:hyokomichi@yamanashi.ac.jp)  
18  
19  
20  
21  
22

23 18  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

19 **Abstract**

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

24 **Design:** A cross-sectional study using routinely collected data.

25 **Setting:** Japanese clinics and hospitals between 2012 and 2016.

26 **Participants:** Japanese patients aged 0-74 years diagnosed with influenza by a rapid test in  
27 employment-related health insurance records.

28 **Primary outcome measures:** Incidence of hospitalisation per 100000 influenza-positive  
29 episodes.

30 **Results:** We included over 16 million influenza-positive episodes, 1.0% of whom were  
31 hospitalised. Of these, 3361 had acute respiratory failure, 27253 pneumonias, 18 ARDS,  
32 2603 febrile seizures and 159 encephalitis/encephalopathy. The percentage of



1  
2  
3  
4  
5  
6  
7 33 hospitalisations by age was 2.96% of patients aged 0–1 years; 0.77% aged 2–5; 0.51% aged  
8  
9  
10 34 6–12; 0.78% aged 13–18; 1.36% aged 19–44; 1.19% aged 45–64; and 2.21% aged 65–74.  
11  
12 35 The incidence of hospitalisations from these five complications combined was highest in  
13  
14  
15 36 influenza-positive patients aged 0–1 years (943 per 100000) compared with 307 in those  
16  
17  
18 37 aged 2–5 years and 271 in those aged 65–74 years. For pneumonia, incidence was highest  
19  
20  
21 38 for influenza-positive patients aged 0–5 years and 65 years or more. There were statistically  
22  
23  
24 39 significant decreasing trends over the years in the incidence of all-cause hospitalisations,  
25  
26  
27 40 pneumonia and febrile seizures.

30  
31 41 **Conclusions:** Japanese administrative data revealed that 1.0% of influenza-positive patients  
32  
33  
34 42 aged under 75 years were hospitalised. Male patients had a higher incidence of pulmonary  
35  
36  
37 43 complications and febrile seizures. Children aged 0–5 years and adults aged 65–74 years  
38  
39  
40 44 were at high risk of being admitted to hospital for pneumonia.

41  
42  
43  
44 45 **Registration:** The ethics committee of the School of Medicine, University of Yamanashi  
45  
46  
47 46 approved this study (approval number: H29-1709).

48  
49  
50  
51 47 **(292 words/300 words)**

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

48

For peer review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56

**Strengths and limitations of this study:**

- This study uses Japanese routinely collected data where uniquely diagnostic tests are used to identify influenza infections in the population.
- Point-of-care testing for influenza has limited sensitivity, but its high specificity means that nearly all the participants in this study were infected with influenza.
- Limitations of the data set prevent analysis of mortality and patients over the age of 74 years.

## 57 INTRODUCTION

58 Influenza is a major burden on health systems worldwide. Every year, an estimated one  
59 billion people [1] including 90 million children younger than 5 years of age are infected  
60 with influenza globally, and 1 million people have influenza-associated acute lower  
61 respiratory tract infection, [2] which causes 290000–600000 deaths.[3]

62 Complications of influenza which cause hospitalisations are a serious public health  
63 concern. In both Western and Asian countries, the majority of influenza-related hospital  
64 admission is due to respiratory or neurologic complications: pneumonia, febrile seizure,  
65 acute respiratory failure, acute respiratory distress syndrome (ARDS) and  
66 encephalitis/encephalopathy.[4-8] We refer to these as ‘severe complications’ here.

67 Hospitalisation rates from influenza infection have been investigated,[4 9] but most studies  
68 were conducted in Western countries where testing for influenza is not routine. This means  
69 that studies have used either limited sample sizes of positively identified individual  
70 hospitalised patients, or extrapolated from influenza surveillance data.[9-11] Hospital-based  
71 studies may have underestimated the risk and the number of infections and complications in  
72 the community.[12] Previous studies have used estimates of the general population as

1  
2  
3  
4  
5  
6 73 denominators, rather than assessing the risk of admission amongst the infected population,  
7  
8  
9 74 combing the risk of infection and the risk of complications. This is problematic because  
10  
11  
12 75 programmes targeting high risk groups, such as vaccination or prophylaxis may reduce the  
13  
14  
15 76 number of infections in high risk groups, biasing estimates of the risk of complications if  
16  
17  
18 77 infected.[12] Also, many studies pre-date the option of administering new neuraminidase  
19  
20  
21 78 inhibitors.[13]  
22  
23  
24

25 79 Although it is also seen internationally,[14-18] influenza encephalitis is a  
26  
27  
28 80 particular concern amongst Japanese physicians owing to a high incidence and mortality  
29  
30  
31 81 rate in Japan.[7 19-23] The prognosis for patients with influenza  
32  
33  
34 82 encephalitis/encephalopathy is very poor; approximately 30% of affected patients die and  
35  
36  
37 83 20–30% have neurological sequelae.[24] To understand the aetiology and prevalence of this  
38  
39  
40 84 severe outcome, surveillance has been conducted.[25 26] In Japan, influenza-associated  
41  
42  
43 85 encephalopathy is a notifiable disease.[27] Japanese physicians are required to report  
44  
45  
46 86 influenza infection cases with: a) death after coma or hospitalisation with coma for 24  
47  
48  
49 87 hours or more; and b) a fever of 38°C or higher, central nervous system manifestation or  
50  
51  
52 88 prior influenza infection symptoms. This surveillance system has detected 60–100  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6 89 influenza encephalitis cases annually [28] and 331 cases during the 2009–2010  
7  
8  
9 90 pandemic;[26] however, underreporting of cases has been acknowledged.[28] Another  
10  
11  
12 91 survey of paediatric departments in 265 hospitals reported 263 influenza-associated  
13  
14  
15 92 encephalopathy cases over 3 years.[25] The authors estimate that there are 200–300  
16  
17  
18 93 influenza encephalopathy cases per annum in Japan;[29] therefore, the incidence of  
19  
20  
21 94 influenza encephalitis/encephalopathy is not accurately known.  
22  
23  
24

25 95 To understand the incidence of severe complications in patients with influenza, an  
26  
27  
28 96 analysis of large-scale real-world data is needed, encompassing hospital and community  
29  
30  
31 97 sites. Previous studies using large data sets of routinely collected medical records have had  
32  
33  
34 98 to rely on clinical diagnoses of influenza-like illness or modelling of influenza and other  
35  
36  
37 99 respiratory virus infections using incomplete laboratory data.[11] In Japan, diagnostic  
38  
39  
40 100 testing for influenza is routine, which presents a unique opportunity to combine the benefits  
41  
42  
43 101 of large data sets with positive diagnoses.[6] We therefore sought to estimate the incidence  
44  
45  
46 102 of hospitalisation with the above five severe complications per influenza infection, using  
47  
48  
49 103 Japanese health insurance claim data.  
50  
51  
52  
53  
54 104

1  
2  
3  
4  
5  
6 105 **METHODS**  
7  
8  
9

10 106 **Patients and data**  
11  
12  
13

14 107 We analysed administrative data provided by Japan Medical Data Center Ltd. (renamed to  
15  
16  
17 108 JMDC) Tokyo, Japan.[30] The data source was the monthly health insurance claim records  
18  
19  
20 109 between January 2012 and December 2016 of approximately three million employees and  
21  
22  
23 110 their dependents, representing 2.4% of the Japanese population. Within health insurance  
24  
25  
26 111 coverage in Japan, people can consult physicians in any type of hospital and department, and  
27  
28  
29 112 medical doctors in any speciality can diagnose influenza and prescribe anti-influenza  
30  
31  
32 113 medications. The age of patients in the data set ranged from 0 to 74 years because all Japanese  
33  
34  
35 114 people aged 75 or more (except for individuals who are on public assistance) are covered by  
36  
37  
38 115 another health insurance program with lower out-of-pocket expenses.  
39  
40  
41  
42

43 116 From the database, we extracted the data of individuals who consulted physicians  
44  
45  
46 117 with influenza-like illness episodes. We then included only patients with a diagnosis of  
47  
48  
49 118 influenza virus infection. In Japan, the use of immunochromatogenic assay point-of-care  
50  
51  
52 119 tests [POCT] in clinical practice has been covered by public health insurance from  
53  
54  
55 120 1999.[23] As recommended in Japanese guidelines,[31] a test-and-treat strategy is  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6 121 routine.[23 32] Even if physicians only slightly suspect influenza infection, they use a  
7  
8  
9 122 POCT to diagnose influenza, and administer antivirals to the positive patients.[31 33 34]  
10  
11  
12 123 Testing would be indicated in fever, sore throat, malaise, non-productive cough or a history  
13  
14  
15 124 of family's infection, for example.[23 35] During the 2009–2010 pandemic influenza  
16  
17  
18 125 A(H1N1) season, physicians performed this test in majority of cases (>90%) and we  
19  
20  
21 126 believe this was likely to be the case during the period of this study because in Japan  
22  
23  
24 127 paediatric patients with an influenza-like illness are required to obtain a medical certificate  
25  
26  
27 128 showing they do not have influenza before return to school.[36]  
28  
29  
30

### 31 **Outcomes**

32  
33  
34  
35  
36 130 Hospitalisation was recorded in the health insurance claims of inpatients. In patients with a  
37  
38  
39 131 diagnosis of influenza infection, we identified those who were hospitalised with a diagnosis  
40  
41  
42 132 of acute respiratory failure, pneumonia, ARDS, febrile seizure, and  
43  
44  
45 133 encephalitis/encephalopathy, according to International Classification of Diseases (ICD-10)  
46  
47  
48 134 codes in their records. The primary outcomes were the incidence of each of the five severe  
49  
50  
51 135 complications per 100000 influenza infections. Acute respiratory failure was coded as J960,  
52  
53  
54 136 J988, R060, R068 or R092; pneumonia was coded as J10–J18 or J20–J22, acute respiratory  
55  
56  
57  
58  
59  
60



1  
2  
3  
4  
5  
6  
7 137 distress syndrome (ARDS) as J80, and febrile seizures as R560. We defined influenza  
8  
9 138 encephalitis/encephalopathy as patients who were diagnosed using ICD-10 codes for  
10  
11  
12 139 influenza infection and encephalitis/encephalopathy (G00–G09 or G41) and had been  
13  
14  
15 140 administered steroid pulse or immunoglobulin therapy.[37]  
16  
17  
18

### 19 141 **Statistical analysis**

20  
21  
22  
23  
24 142 We examined the number of diagnosed influenza infections and severe complications by sex,  
25  
26  
27 143 age, outpatient/inpatient status, number of beds in the facility, and clinical speciality. In Japan,  
28  
29  
30 144 clinical facilities with fewer than 20 beds are denoted a “clinic” by law. Clinics are usually  
31  
32  
33 145 run by a single medical doctor and function as a primary care department. Most clinics have  
34  
35  
36 146 no beds but a very small subset of clinics have 1–19 beds to accommodate inpatients. In  
37  
38  
39 147 contrast, facilities with 20 beds or more are legally termed a “hospital”. Hospitals have  
40  
41  
42 148 primary care, specialised outpatient, and general and specialised inpatient departments. In  
43  
44  
45 149 this study, hospitalised influenza-positive patients were inpatients in both “clinic” and  
46  
47  
48 150 “hospital” settings. We plotted histograms of the ages of outpatients and inpatients infected  
49  
50  
51 151 with influenza. We determined the incidence of inpatients with the five severe complications  
52  
53  
54 152 by dividing the number of complications by the number of infections. We stratified this by  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6 153 sex, influenza season and age. We also examined the numbers of the influenza-infected  
7  
8  
9 154 patients and the proportions of inpatients over calendar time at the request of a reviewer.  
10  
11  
12 155 Influenza seasons were defined as lasting from September through to the following August.  
13  
14  
15 156 We calculated p values for secular trends of incidence over influenza seasons. Statistical  
16  
17  
18 157 analyses were performed using SAS statistical software (version 9.4, SAS Institute, Cary,  
19  
20  
21 158 NC, USA). All reported p values were two-sided and we considered  $p < 0.05$  indicated a  
22  
23  
24 159 significant difference.  
25  
26  
27

## 28 160 **Patient and public involvement**

29  
30  
31  
32  
33 161 The ethics committee of the School of Medicine, University of Yamanashi approved this  
34  
35  
36 162 study (approval number: H29-1709), in accordance with the ethical guidelines and  
37  
38  
39 163 regulations of the Declaration of Helsinki. The data were properly anonymised by the JMDC  
40  
41  
42 164 in the manner permitted by Japanese guideline of Personal Information Protection  
43  
44  
45 165 Commission, Cabinet Office, Government of Japan for the use of data from medical  
46  
47  
48 166 examinations in medical research without individual participants' consent (Act on the  
49  
50  
51 167 Protection of Personal Information, act no. 57 of 30 May 2003; last version amendment of  
52  
53  
54 168 act no. 65 of 2015).  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6 169 Patients were not actively involved in developing the research question and  
7  
8  
9 170 protocol including outcome measures. The participants will be provided the final study  
10  
11  
12 171 results by clinical research information services and homepage of the University of  
13  
14  
15 172 Yamanashi.  
16  
17  
18  
19  
20 173

## 23 174 **RESULTS**

### 27 175 **Characteristics of patients diagnosed with influenza**

28  
29  
30  
31  
32 176 Table 1 summarises the number of patients with diagnoses of influenza infection in the study  
33  
34  
35 177 population. Among 16636913 infections, 53.4% of the patients were men, and 1.0% were  
36  
37  
38 178 hospitalised. Approximately a quarter (25.7%) of infections were in children aged 6–12 years.  
39  
40  
41 179 Overall 32% of diagnoses were made in the internal medicine department and 23% in  
42  
43  
44 180 paediatrics. Most infections were diagnosed in clinics (n=13572391; 83%). Figures 1 and 2  
45  
46  
47 181 illustrate the number of outpatients and inpatients with influenza infection, respectively, by  
48  
49  
50 182 age. Influenza was most often diagnosed in outpatients aged 0–12 years, with a second small  
51  
52  
53 183 peak in middle-aged patients. In contrast, inpatient cases were commonest among patients  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7 184 aged less than one year. Table 2 shows the number of complicated cases by department,  
8  
9  
10 185 hospital size and type of hospital management. A total of 3361 patients (0.02%) were  
11  
12 186 admitted to hospital with acute respiratory failure, 27253 (0.16%) with pneumonia, 18  
13  
14  
15 187 (0.0001%) with ARDS, 2603 (0.02%) with febrile seizures, and 159 (0.001%) with  
16  
17  
18 188 encephalitis/encephalopathy. Most complicated cases were admitted to paediatric  
19  
20  
21 189 departments, with 19012 pneumonia admissions (70% of the total), 1794 with acute  
22  
23  
24 190 respiratory failure (53% of the total), 2461 with febrile seizures (95% of the total), and 63  
25  
26  
27 191 encephalitis (40% of all cases). The number of inpatients with acute respiratory failure,  
28  
29  
30 192 pneumonia, and febrile seizure tended to increase with the number of hospital beds.  
31  
32  
33

### 34 193 **Hospitalisation rates from severe complications**

35  
36  
37  
38  
39 194 The combined incidence of the five complications was 189 per 100000 diagnosed infections.  
40  
41  
42 195 Pneumonia was the commonest complication, with 164 per 100000 diagnosed infections,  
43  
44  
45 196 followed by acute respiratory failure (20.2), febrile seizures (15.7),  
46  
47  
48 197 encephalitis/encephalopathy (0.9), and ARDS (0.10). Table 3 shows the incidence of five  
49  
50  
51 198 severe complications by age, sex, and influenza season. Although the incidence of acute  
52  
53  
54 199 respiratory failure, pneumonia, ARDS, and febrile seizures was higher in men,  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7 200 encephalitis/encephalopathy was higher in women. There were decreasing trends over the  
8  
9  
10 201 years in incidence of hospital admissions from pneumonia (p for trend<0.0001), febrile  
11  
12 202 seizure (p for trend<0.0001), and the five severe complications combined (p for  
13  
14  
15 203 trend<0.0001), but not acute respiratory failure (p for trend=0.07),  
16  
17  
18 204 encephalitis/encephalopathy (p for trend=0.19) or ARDS (p for trend=0.98). In each age  
19  
20  
21 205 group, pneumonia was the commonest complication. The incidence of acute respiratory  
22  
23  
24 206 failure, pneumonia, and febrile seizure was highest in patients aged 0–1 years, ARDS was  
25  
26  
27 207 highest in those 65–74 years, and encephalitis/encephalopathy was highest in patients aged  
28  
29  
30 208 13–18 years.

31  
32  
33  
34 209       Figures 3 and 4 show the number and percentage of inpatients with complications  
35  
36  
37 210 by age group and age over the study period. Young children had most of the severe  
38  
39  
40 211 complications. Across all age groups, pneumonia was by far the most common of the five  
41  
42  
43 212 complications, and the age group with the largest number of cases was children aged 2–5  
44  
45  
46 213 years. In contrast, the proportion of infections hospitalised was highest in patients aged 0–1  
47  
48  
49 214 years (2.96%) and second highest in those aged 65–74 years (2.21%).

50  
51  
52 215       Figure 5 shows the numbers of influenza-infected patients and the proportion who  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6 216 were inpatients by calendar month between 2012 and 2016. Every year the number of  
7  
8  
9 217 infections increased from winter to spring while the proportion admitted peaked in summer.  
10  
11  
12 218 The number of infections was similar between 2014 and 2016. The proportion hospitalised  
13  
14  
15 219 gradually decreased between 2012 and 2016.  
16  
17  
18  
19  
20 220

## 21 DISCUSSION

### 22 **Principal findings**

23  
24  
25  
26  
27  
28 222 We described the epidemiology of hospital admissions and five key severe complications in  
29  
30  
31  
32 223 large cross-sectional data of influenza-positive patient visits. Influenza diagnoses were  
33  
34  
35 224 commonest in young children and middle-aged patients (table 1 and figures 1–2). The  
36  
37  
38 225 incidence and absolute number of hospital admissions with complications of influenza was  
39  
40  
41 226 highest in young children (figure 2 and table 3). The most common complication was  
42  
43  
44 227 pneumonia (table 1). The incidence and absolute number of admissions for pulmonary  
45  
46  
47 228 complications were highest in children (figures 3–4 and table 3). Patients aged 65–74 years  
48  
49  
50 229 were also at high risk for admission from complications, but the absolute number of both  
51  
52  
53 230  
54  
55  
56  
57  
58  
59  
60

231 influenza infections and serious complications was lower than for children in our data set  
232 (figures 3–4 and table 3). The incidence of admissions for encephalitis/encephalopathy was  
233 relatively high in children aged 0–18 years (table 3). There was a decreasing trend in the  
234 proportions of infections hospitalised for any reason, and with any of the five complications,  
235 pneumonia, or febrile seizures between 2012 and 2016 (table 3 and figure 5).

### 236 **Comparison with previous research**

237 Male patients suffered more complications than female ones, especially for acute  
238 respiratory failure, pneumonia, and febrile seizures (table 3). This is consistent with  
239 previous studies reporting that during the 2009–2010 pandemic influenza A(H1N1) season,  
240 the incidence of hospitalisation in male children was greater than in female children in the  
241 US (56%),[38] Canada (60%),[39] and Japan (64.3%).[6] Asthma is a risk factor for  
242 pneumonia in children with influenza.[40] Our finding of an increased risk of pneumonia in  
243 males may be because asthma is a more common disease in boys than girls.[41] It is also  
244 known that boys get febrile seizures more often than girls.[42] This was also observed in  
245 our data for febrile seizures with influenza infection. In contrast, our data suggest the  
246 possibility of a higher risk of encephalitis/encephalopathy in women with influenza

1  
2  
3  
4  
5  
6 247 infection (table 3). However, in Japanese surveillance reports from 2007 to 2010, 153 of  
7  
8  
9 248 263 (58.2%) paediatric patients with encephalopathy were male.[25] Because the means of  
10  
11  
12 249 data collection in previous studies were different, we are unable to conclude in which sex  
13  
14  
15 250 complications are more common. Further study with another large data set is needed to  
16  
17  
18 251 investigate risk factors, including sex, for hospitalisation and incidence of  
19  
20  
21 252 encephalitis/encephalopathy in Asian people.  
22  
23  
24

25  
26 253 Our results by age are consistent with those of previous studies, and add to  
27  
28 254 understanding the risk of specific complications amongst those with a diagnosis of influenza.  
29  
30  
31 255 Previous studies, being unable to identify a large number of influenza-positive patients, have  
32  
33  
34 256 used small numbers of influenza positive admissions as cases and general population  
35  
36  
37 257 estimates as the denominators. This combines the risk of infection and the risk of  
38  
39  
40 258 complications. We found that the risk of hospitalisation was highest in infected infants aged  
41  
42  
43 259 0–1 years (figures 2–4 and table 3). This is consistent with a US study, which found that the  
44  
45  
46 260 highest hospitalisation rate was among infants aged under one year (11.9 per 100000  
47  
48  
49 261 population) during the 2009–2010 influenza A(H1N1) pandemic;[9] in addition, we are able  
50  
51  
52 262 to show that the risk of admission is as high as 943 per 100000 infections. A study from the  
53  
54  
55  
56  
57  
58  
59  
60



1  
2  
3  
4  
5  
6 263 UK also reported that children aged 6 months to 4 years had the high influenza related  
7  
8  
9 264 hospitalisation rates between 2001 and 2007 (3360 per 100000 population).[8]  
10  
11  
12

13 265 A systematic review found large gaps in the evidence base (describing the evidence  
14  
15  
16 266 for risk factors for admissions as “limited to absent”).[12] They found contrasting results  
17  
18  
19 267 with children under the age of two years at higher risk of admission to hospital than older  
20  
21  
22 268 children with pandemic H1N1 influenza but the reverse with seasonal influenza.[12] They  
23  
24  
25 269 also found evidence of spectrum bias; studies from hospitals and intensive care units gave  
26  
27  
28 270 lower estimates of risk of death than community-based studies for both the elderly and  
29  
30  
31 271 children compared to young adults. As well as including positively diagnosed patients, our  
32  
33  
34 272 study covers both the community and hospital settings and is of sufficient size to allow  
35  
36  
37 273 estimation for specific causes of admission. In addition, because vaccination reduces the  
38  
39  
40 274 hospitalisation rate,[43-45] vaccination programmes in other countries that target high risk  
41  
42  
43 275 groups may bias hospitalisation rate estimates for these patients. In Japan all individuals have  
44  
45  
46 276 had to pay a fee to receive influenza vaccine irrespective of their risk profile since 1994,  
47  
48  
49 277 when free vaccination for primary and secondary school students was stopped.[46] This  
50  
51  
52 278 means that high-risk groups in Japan are less resistant to severe disease than in other countries,  
53  
54  
55  
56  
57  
58  
59  
60

279 reducing this bias in our hospitalisation rates.

## 280 **Implications for clinicians and policymakers**

281 During the 2009–2010 pandemic, the World Health Organization [47] and the Centers for  
282 Disease Control and Prevention [48] issued guidelines for early neuraminidase inhibitor  
283 treatment. There are suggestions that administration of this medication within 48 hours  
284 reduces mortality and severe outcomes.[49] A Cochrane review, whilst critical of the quality  
285 of trial evidence, found a reduction in secondary infections among children who were  
286 prescribed oseltamivir.[50] During the 2000s, four neuraminidase inhibitors became  
287 available in Japan: zanamivir in 2000, oseltamivir in 2001, and laninamivir and peramivir in  
288 2010.[23] The Japanese Association for Infectious Diseases also recommended post-  
289 exposure prophylaxis of zanamivir and oseltamivir in hospitals and geriatric facilities in 2012.  
290 Reportedly, seven to eight million patients per annum were prescribed with neuraminidase  
291 inhibitors from 2011 to 2015; more than half of all patients infected with influenza received  
292 these medicines.[23] The decreasing trend with time in the hospitalisation and the composite  
293 incidence of the five severe complications (table 3,  $p < 0.0001$ ) might be attributed to the  
294 increasingly widespread use of [13 33] and more options for neuraminidase inhibitors.[6 23]

1  
2  
3  
4  
5  
6  
7 295 This decreasing trend was not altered in the 2014/15 season when influenza A(H3N2) spread  
8  
9 296 internationally including in Japan.[51] A recent meta-analysis of randomised controlled trials  
10  
11  
12 297 reported that in patients with pathogen-ascertained influenza, as is practice in Japan,  
13  
14  
15 298 treatment with oseltamivir reduced hospital admissions by 63%.[52]  
16  
17  
18

19 299 In our study, the incidence of hospitalisations, acute pneumonia and febrile seizures  
20  
21  
22 300 decreased with time (table 3, all p values <0.0001). This was observed in parallel with  
23  
24  
25 301 increased administration of neuraminidase inhibitors. However, there appears to be no trend  
26  
27  
28 302 in the risk of encephalitis/encephalopathy. Because influenza encephalitis appears to be  
29  
30  
31 303 mediated by an acute process during infection,[14] it is important to prevent influenza  
32  
33  
34 304 infection to reduce the incidence of encephalitis. The primary countermeasure to protect  
35  
36  
37 305 individuals from infection is vaccination. National vaccine policies may have impacted upon  
38  
39  
40 306 variation in the hospitalisation incidence between countries. In Japan, schoolchildren were  
41  
42  
43 307 vaccinated routinely from 1976 to 1993, when influenza was removed from the list of free  
44  
45  
46 308 routine vaccinations, and vaccination of high risk groups was only recommended from 2001,  
47  
48  
49 309 albeit for a fee which has limited uptake.[53] Studies of this natural experiment suggest that  
50  
51  
52 310 the former routine vaccination program for schoolchildren indirectly reduced excess  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6 311 mortality among the elderly.[46 54] The previous results suggest indirect effect of the  
7  
8  
9 312 vaccines upon reducing severe complication risk amongst children; however, the effect upon  
10  
11  
12 313 the incidence of encephalitis is unknown. Because current encephalitis treatments are of  
13  
14  
15 314 limited effectiveness, a vaccination program covering a broad population may be the best  
16  
17  
18 315 way to reduce the morbidity associated with influenza encephalitis.  
19  
20  
21

### 22 316 **Strengths and weaknesses**

23  
24  
25  
26  
27 317 A main strength of this study is that the included patients were diagnosed with influenza by  
28  
29  
30 318 testing. The majority of influenza-like illness is usually caused by infections other than  
31  
32  
33 319 influenza.[55] Diagnoses were based on rapid antigen detection with immunochromatogenic  
34  
35  
36 320 assay. Because POCTs for influenza are less invasive and require less time than laboratory  
37  
38  
39 321 tests, they are an essential tool for physicians to evaluate influenza in outpatient and inpatient  
40  
41  
42 322 clinical practice in Japan.[6] Although low sensitivity (59–93%) [56] is a weak point for  
43  
44  
45 323 POCTs, the specificity is 98–100%.[34 57] This means that nearly all individuals with  
46  
47  
48 324 influenza-like illness who have POCT-positive results (the participants in this study) were  
49  
50  
51 325 infected with influenza. This makes routinely collected Japanese data unique. Additionally,  
52  
53  
54 326 all Japanese people who are hospitalised with severe complications of influenza infection  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7 327 should be present in universal health insurance data. Therefore, we did not greatly  
8  
9 328 overestimate the number of infected patients or underestimate severe complications, and thus  
10  
11  
12 329 did not underestimate the risk of complications and hospitalisations.  
13  
14

15  
16 330 There are limitations inherent to the data set used in this study. Firstly, POCTs for  
17  
18  
19 331 influenza are known to have variable sensitivity. In the 2010s, 20 or more POCT kits were  
20  
21  
22 332 available in Japan.[58] Sensitivity would have been influenced by the following factors: (1)  
23  
24  
25 333 time from the onset of illness;[59 60] (2) patient age;[60 61] (3) influenza type A/B/C;[61]  
26  
27  
28 334 (4) operator technique;[60] (5) number of times patients were tested. (1) Reportedly, the  
29  
30  
31 335 sensitivity is lower 0–24 hours from symptom onset and higher in days 2–4.[59 60] Parents  
32  
33  
34 336 tend to bring children to paediatricians at an earlier stage of the infection while infected  
35  
36  
37 337 employed adults tend to consult physicians in mid- or later stages. This would bias sensitivity  
38  
39  
40 338 toward comparatively low in children compared to adults. (2) In contrast children are known  
41  
42  
43 339 to have higher viral load and longer shedding and consequently POCTs have higher  
44  
45  
46 340 sensitivity in children.[60 61] (3) POCT sensitivity is higher in influenza A than in B.[61] In  
47  
48  
49 341 Japan, influenza type A spreads early in winter, type B late in winter, and type C in all seasons.  
50  
51  
52 342 Therefore, the sensitivity might have been relatively low between Jan 2012–Aug 2012 and  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6 343 higher between Sep 2016–Dec 2016 (table 3). (4) In almost all Japanese medical care  
7  
8  
9 344 facilities, physicians conduct POCT for individuals with influenza-like illness.[31 32]  
10  
11  
12 345 Because physicians are trained to appropriately sample specimen material, operator bias  
13  
14  
15 346 within our Japanese data would be small. (5) In Japan, physicians are permitted to conduct  
16  
17  
18 347 POCTs up to twice per patient in a calendar month within health insurance coverage. Even  
19  
20  
21 348 if the first POCT had failed to detect influenza-positive patients, the second POCT might  
22  
23  
24 349 identify the infection. Thus the sensitivity in Japanese clinical practice would be higher than  
25  
26  
27 350 the nominal sensitivity. Overall, the sensitivity of POCTs can vary unpredictably according  
28  
29  
30 351 to the circumstances. Our denominator (influenza-positive episodes) may be underestimated  
31  
32  
33 352 in low sensitivity situations and to a smaller degree in high sensitivity situations. In contrast,  
34  
35  
36 353 we would expect almost all of the numerator population (hospitalised patients with severe  
37  
38  
39 354 symptoms) would have been positively diagnosed. Thus, the estimated incidence of  
40  
41  
42 355 hospitalisation amongst influenza-positive patients may have been overestimated.  
43  
44  
45

46 356 Second, the administrative data from employees and their families used here do not  
47  
48  
49 357 permit analysis of patients aged 75 years or more. Also, due to employment patterns in Japan,  
50  
51  
52 358 the number of male patients was slightly higher than female patients (table 1). The sex ratio  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7 359 varies across generations in Japan, with more males in younger populations and women  
8  
9 360 predominating in older populations.[62] However, the incidence of hospitalisation amongst  
10  
11 361 infected patients in both sexes and the studied age groups should not be biased by this  
12  
13  
14  
15 362 imbalance. Third, we were unable to estimate influenza-related mortality in this data set, but  
16  
17  
18 363 the data are sufficient to allow examination of serious complications that are major public  
19  
20  
21 364 health concerns. Although we were unable to define encephalitis/encephalopathy cases  
22  
23  
24 365 virologically, we added the requirement of receiving specific therapy to the definition of  
25  
26  
27 366 encephalitis/encephalopathy cases.[37] This more stringent definition reduces the likelihood  
28  
29  
30 367 that we have overestimated this outcome. Further analyses of influenza-related mortality in  
31  
32  
33 368 Japan are needed, and this should encompass older adults. The effect of neuraminidase  
34  
35  
36 369 inhibitors should be examined using observational data, as clinical trials are likely to be  
37  
38  
39 370 underpowered for rare but important complications such as encephalopathy.  
40  
41  
42

## 43 371 **Conclusions**

44  
45  
46  
47  
48 372 Using Japanese administrative data, 1.0% of patients who tested positive for influenza  
49  
50  
51 373 infection were hospitalised. Male patients had a higher incidence of pulmonary  
52  
53  
54 374 complications and febrile seizures. Children aged 0–5 years and adults aged 65–74 years  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6 375 were at high risk of being admitted to hospital for pneumonia, with the highest absolute  
7  
8  
9 376 numbers of hospitalised patients among young children. Further efforts are needed, such as  
10  
11  
12 377 active prescription of neuraminidase inhibitors and vaccination programs, to prevent  
13  
14  
15 378 hospitalisations from severe complications in these age groups.  
16  
17  
18

19 379 **(3854 words)**  
20  
21  
22  
23  
24 380

25  
26  
27 381 **Acknowledgements** The authors are immensely grateful to the Japan Medical Data Center  
28  
29 382 for providing the administrative data. We thank Ms. Analisa Avila, ELS, of Edanz Group  
30  
31 383 for editing a draft of this manuscript.  
32  
33  
34

35 384 **Authors' contributions** All of the authors agreed with the manuscript's results and  
36  
37 385 conclusion and approved the final version of the manuscript. HY conceived the study. HY,  
38  
39 386 MM, JL, RK, TY and ZY contributed to the design of the study and interpretation of the  
40  
41 387 data analyses. HY analysed the data. HY, JL, MM and RK wrote the first draft of the  
42  
43 388 manuscript. JL, RK, MM, ZY and HY contributed to revision of the manuscript. ZY and  
44  
45 389 HY were responsible for data integrity. HY obtained funding.  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



1  
2  
3  
4  
5  
6  
7 390 **Funding** This work was supported by funding from the Ministry of Education, Culture,  
8  
9 391 Sports, Science, and Technology (MEXT) (KAKENHI grant numbers JP15K08730).

10  
11  
12 392 **Competing interests.** None.

13  
14  
15 393 **Patient consent** Not required.

16  
17  
18 394 **Ethics approval** The ethics committee of the School of Medicine, University of  
19  
20  
21 395 Yamanashi approved this study (approval number: H29-1709).

22  
23  
24 396 **Data sharing statement** The original administrative data are available through a formal  
25  
26  
27 397 request to the JMDC, subject to fees.

28  
29  
30  
31 398

399 **References**

- 400 1. Ghebrehewet S, MacPherson P, Ho A. Influenza. *BMJ* 2016;355:i6258.
- 401 2. Kaiser L, Wat C, Mills T, *et al.* Impact of oseltamivir treatment on influenza-related  
402 lower respiratory tract complications and hospitalisations. *Arch Intern Med*  
403 2003;163:1667–72.
- 404 3. Iuliano AD, Roguski KM, Chang HH, *et al.* Estimates of global seasonal influenza-  
405 associated respiratory mortality: a modelling study. *Lancet* 2017;391:1285–1300.
- 406 4. Thompson WW, Shay DK, Weintraub E, *et al.* Influenza-associated hospitalizations in  
407 the United States. *JAMA* 2004;292:1333–40.
- 408 5. Newland JG, Laurich VM, Rosenquist AW, *et al.* Neurologic complications in children  
409 hospitalized with influenza: characteristics, incidence, and risk factors. *J Pediatr*  
410 2006;150:306–10.
- 411 6. Sugaya N, Shinjoh M, Mitamura K, *et al.* Very low pandemic influenza A (H1N1) 2009  
412 mortality associated with early neuraminidase inhibitor treatment in Japan: analysis of  
413 1000 hospitalized children. *J Infect* 2011;63:288–94
- 414 7. Influenza Working Group of the Japan Pediatric Society. Secondary treatment guideline  
415 of 2013/2014 influenza infection. 2014. Japanese.

- 1  
2  
3  
4  
5  
6 416 [https://www.jpeds.or.jp/uploads/files/2013\\_2014\\_influenza\\_all.pdf](https://www.jpeds.or.jp/uploads/files/2013_2014_influenza_all.pdf). Accessed 23 October  
7  
8  
9 417 2018.  
10  
11  
12 418 8. Cromer D, van Hoek AJ, Jit M, *et al*. The burden of influenza in England by age and  
13  
14  
15 419 clinical risk group: a statistical analysis to inform vaccine policy. *J Infect* 2014;68:363–  
16  
17  
18 420 71.  
19  
20  
21 421 9. Louie JK, Acosta M, Winter K, *et al*. Factors associated with death or hospitalization due  
22  
23  
24 422 to pandemic 2009 influenza A (H1N1) infection in California. *JAMA* 2009;302:1896–902.  
25  
26  
27 423 10. Nicholson KG, McNally T, Silverman M, *et al*. Rates of hospitalisation for influenza,  
28  
29  
30 424 respiratory syncytial virus and human metapneumovirus among infants and young  
31  
32  
33 425 children. *Vaccine* 2006;24:102–08.  
34  
35  
36 426 11. Pitman R, Melegaro A, Gelb D, *et al*. Assessing the burden of influenza and other  
37  
38  
39 427 respiratory infections in England and Wales. *J Infect* 2007;54:530–38.  
40  
41  
42 428 12. Mertz D, Kim TH, Johnstone J, *et al*. Populations at risk for severe or complicated  
43  
44  
45 429 influenza illness: systematic review and meta-analysis. *BMJ* 2013;347:f5061.  
46  
47  
48 430 13. Sugaya N. Widespread use of neuraminidase inhibitors in Japan. *J Infect Chemother*  
49  
50  
51 431 2011;17:595.  
52  
53  
54 432 14. Amin R, Ford-Jones E, Richardson SE, *et al*. Acute childhood encephalitis and  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4  
5  
6 433 encephalopathy associated with influenza: a prospective 11-year review. *Pediatr Infect*  
7  
8  
9 434 *Dis J* 2008;27:390–95.
- 10  
11  
12 435 15. Ekstrand JJ, Herbener A, Rawlings J, *et al.* Heightened neurologic complications in  
13  
14  
15 436 children with pandemic H1N1 influenza. *Ann Neurol* 2010;68:762–66.
- 16  
17  
18 437 16. Evans A, Agadi S, Siegel J, *et al.* Neurologic complications associated with novel  
19  
20  
21 438 influenza A (H1N1) virus infection in children-Dallas, Texas, May 2009. *MMWR-Morb.*  
22  
23  
24 439 *Mortal. Wkly. Rep* 2009;58:773–78.
- 25  
26  
27 440 17. Rellosa N, Bloch KC, Shane AL, *et al.* Neurologic manifestations of pediatric novel  
28  
29  
30 441 H1N1 influenza infection. *Pediatr Infect Dis J* 2011;30:165–67.
- 31  
32  
33 442 18. Baltagi SA, Shoykhet M, Felmet K, *et al.* Neurological sequelae of 2009 influenza A  
34  
35  
36 443 (H1N1) in children: a case series observed during a pandemic. *Pediatr Crit Care Med*  
37  
38  
39 444 2010;11:179–84.
- 40  
41  
42 445 19. Kasai T, Togashi T, Morishima T. Encephalopathy associated with influenza epidemics.  
43  
44  
45 446 *Lancet* 2000;355:1558–59.
- 46  
47  
48 447 20. Morishima T, Togashi T, Yokota S, *et al.* Encephalitis and encephalopathy associated  
49  
50  
51 448 with an influenza epidemic in Japan. *Clin Infect Dis* 2002;35:512–17.
- 52  
53  
54 449 21. Sugaya N. Influenza-associated encephalopathy in Japan. *Semin Pediatr Infect Dis*  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4  
5  
6 450 2002;13:79–84.  
7  
8  
9 451 22. Akihisa O, Satoshi N, Hisashi K, *et al.* Deaths associated with pandemic (H1N1) 2009  
10  
11  
12 452 among children, Japan, 2009–2010. *Emerg Infect Dis J* 2011;17:1993–2000.  
13  
14  
15 453 23. Zaraket H, Saito R. Japanese surveillance systems and treatment for influenza. *Curr*  
16  
17  
18 454 *Treat Options Infect Dis* 2016;8:311–28  
19  
20  
21 455 24. Wang GF, Li W, Li K. Acute encephalopathy and encephalitis caused by influenza  
22  
23  
24 456 virus infection. *Curr Opin Neurol* 2010;23:305–11  
25  
26  
27 457 25. Hoshino A, Saitoh M, Oka A, *et al.* Epidemiology of acute encephalopathy in Japan,  
28  
29  
30 458 with emphasis on the association of viruses and syndromes. *Brain Dev* 2012;34:337–43.  
31  
32  
33 459 26. Gu Y, Shimada T, Yasui Y, *et al.* National surveillance of influenza-associated  
34  
35  
36 460 encephalopathy in Japan over six years, before and during the 2009–2010 influenza  
37  
38  
39 461 pandemic. *Plos One* 2013;8:e54786.  
40  
41  
42 462 27. Okumura A, Nakagawa S, Kawashima H, *et al.* Deaths associated with pandemic  
43  
44  
45 463 (H1N1) 2009 among children, Japan, 2009–2010. *Emerg Infect Dis* 2011;17:1993–2000.  
46  
47  
48 464 28. National Institute of Infectious Diseases and Ministry of Health, Labour and Welfare.  
49  
50  
51 465 Infectious agents surveillance report 36. 2015. Japanese. Available at  
52  
53  
54 466 <https://www0.niid.go.jp/niid/idsc/iasr/36/429j.pdf>. Accessed 23 October 2018.  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4  
5  
6 467 29. Mizuguchi M. Influenza encephalopathy and related neuropsychiatric syndromes.  
7  
8  
9 468 *Influenza Other Resp* 2013;7:67–71.  
10  
11  
12 469 30. Tanaka S, Seto K, Kawakami K. Pharmacoepidemiology in Japan: medical databases  
13  
14  
15 470 and research achievements. *J Pharm Health Care Sci* 2015;1:16.  
16  
17  
18 471 31. Uehara S, Sunakawa K, Eguchi H, *et al.* Japanese guidelines for the management of  
19  
20  
21 472 respiratory infectious diseases in children 2007 with focus on pneumonia. *Pediatr Int*  
22  
23  
24 473 2011;53:264–76.  
25  
26  
27 474 32. Ito M, Watanabe M, Nakagawa N, *et al.* Rapid detection and typing of influenza A and  
28  
29  
30 475 B by loop-mediated isothermal amplification: comparison with immunochromatography  
31  
32  
33 476 and virus isolation. *J Virol Methods* 2006;135:272–75.  
34  
35  
36 477 33. Sugaya N, Mitamura K, Yamazaki M, *et al.* Lower clinical effectiveness of oseltamivir  
37  
38  
39 478 against influenza B contrasted with influenza a infection in children. *Clin Infect Dis*  
40  
41  
42 479 2007;44:197–202.  
43  
44  
45 480 34. Suzuki M, Yoshimine H, Harada Y, *et al.* Estimating the influenza vaccine  
46  
47  
48 481 effectiveness against medically attended influenza in clinical settings: a hospital-based  
49  
50  
51 482 case-control study with a rapid diagnostic test in Japan. *Plos One* 2013;8:e52103.  
52  
53  
54 483 35. Watanabe M, Nakagawa N, Ito M, *et al.* Sensitivity of rapid immunoassay for influenza  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4  
5  
6 484 A and B in the early phase of the disease. *Pediatr Int* 2009;51:211–15.  
7  
8  
9 485 36. Komiya N, Gu Y, Kamiya H, *et al*. Clinical features of cases of influenza A (H1N1) v  
10  
11  
12 486 in Osaka prefecture, Japan, May 2009. *Eurosurveillance* 2009;14:19272.  
13  
14  
15 487 37. Study Group of Influenza Encephalitis. Ministry of Health, Labour and Welfare.  
16  
17  
18 488 Guideline of treatment for influenza encephalitis. revised edition. 2011. Japanese.  
19  
20  
21 489 <https://www.mhlw.go.jp/kinkyu/kenkou/influenza/hourei/2009/09/dl/info0925-01.pdf>.  
22  
23  
24 490 Accessed 23 October 2018.  
25  
26  
27 491 38. Kumar S, Havens PL, Chusid MJ, *et al*. Clinical and epidemiologic characteristics of  
28  
29  
30 492 children hospitalized with 2009 pandemic H1N1 influenza A infection. *Pediatr Infect Dis*  
31  
32  
33 493 *J* 2010;29:591–94.  
34  
35  
36 494 39. O'Riordan S, Barton M, Yau Y, *et al*. Risk factors and outcomes among children  
37  
38  
39 495 admitted to hospital with pandemic H1N1 influenza. *Can Med Assoc J* 2010;182:39–44.  
40  
41  
42 496 40. Lee JJ, Bankhead C, Smith M, *et al*. Risk factors for influenza-related complications in  
43  
44  
45 497 children during the 2009/10 pandemic: a UK primary care cohort study using linked  
46  
47  
48 498 routinely collected data. *Epidemiol Infect* 2018:1–7.  
49  
50  
51 499 41. Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and  
52  
53  
54 500 wheezing illness from early childhood to age 33 in a national British cohort. *BMJ*

- 1  
2  
3  
4  
5  
6 501 1996;312:1195–99.  
7  
8  
9 502 42. Tsuboi T. Epidemiology of febrile and afebrile convulsions in children in Japan.  
10  
11  
12 503 *Neurology* 1984;34:175–75.  
13  
14  
15 504 43. Talbot HK, Zhu Y, Chen Q, *et al.* Effectiveness of influenza vaccine for preventing  
16  
17  
18 505 laboratory-confirmed influenza hospitalizations in adults, 2011–2012 influenza season.  
19  
20  
21 506 *Clin Infect Dis* 2013;56:1774–77.  
22  
23  
24 507 44. Yokomichi H, Kurihara S, Yokoyama T, *et al.* The pandemic influenza A (H1N1) 2009  
25  
26  
27 508 vaccine does not increase the mortality rate of idiopathic interstitial pneumonia: a  
28  
29  
30 509 matched case-control study. *Plos One* 2014;9:e88927.  
31  
32  
33 510 45. Yokomichi H, Kurihara S, Yokoyama T, *et al.* Safety of the influenza A (H1N1)2009  
34  
35  
36 511 vaccine in chronic obstructive pulmonary disease: a matched case-control study. *J*  
37  
38  
39 512 *Vaccines Vaccination* 2012;3:1000148.  
40  
41  
42 513 46. Reichert TA, Sugaya N, Fedson DS, *et al.* The Japanese experience with vaccinating  
43  
44  
45 514 schoolchildren against influenza. *N Engl J Med* 2001;344:889–96.  
46  
47  
48 515 47. World Health Organization. Rapid advice guidelines for pharmacological management  
49  
50  
51 516 of pandemic influenza (H1N1) 2009 and other influenza viruses. 2010. Available at  
52  
53  
54 517 [http://www.who.int/csr/resources/publications/swineflu/h1n1\\_guidelines\\_pharmaceutical\\_](http://www.who.int/csr/resources/publications/swineflu/h1n1_guidelines_pharmaceutical_)  
55  
56  
57  
58  
59  
60



- 1  
2  
3  
4  
5  
6 518 mngt.pdf. Accessed 23 October 2018.  
7  
8  
9 519 48. Centers for Disease Control and Prevention. Updated interim recommendations for the  
10  
11  
12 520 use of antiviral medications in the treatment and prevention of influenza for the 2009–  
13  
14  
15 521 2010 season. Available at <https://www.cdc.gov/h1n1flu/recommendations.htm>. Accessed  
16  
17  
18 522 23 October 2018.  
19  
20  
21 523 49. Muthuri SG, Myles PR, Venkatesan S, *et al*. Impact of neuraminidase inhibitor  
22  
23  
24 524 treatment on outcomes of public health importance during the 2009–2010 influenza A  
25  
26  
27 525 (H1N1) pandemic: a systematic review and meta-analysis in hospitalized patients. *J Infect*  
28  
29  
30 526 *Dis* 2012;207:553–63.  
31  
32  
33 527 50. Jefferson T, Jones MA, Doshi P, *et al*. Neuraminidase inhibitors for preventing and  
34  
35  
36 528 treating influenza in healthy adults and children. *Cochrane Database Syst Rev* 2012;1  
37  
38  
39 529 Art:CD008965.  
40  
41  
42 530 51. Pebody R, Warburton F, Andrews N, *et al*. Effectiveness of seasonal influenza vaccine  
43  
44  
45 531 in preventing laboratory-confirmed influenza in primary care in the United Kingdom:  
46  
47  
48 532 2014/15 end of season results. *Eurosurveillance* 2015;20:30013.  
49  
50  
51 533 52. Dobson J, Whitley RJ, Pocock S, *et al*. Oseltamivir treatment for influenza in adults: a  
52  
53  
54 534 meta-analysis of randomised controlled trials. *Lancet* 2015;385:1729–37.  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4  
5  
6 535 53. Hirota Y, Kaji M. History of influenza vaccination programs in Japan. *Vaccine*  
7  
8  
9 536 2008;26:6451–54.  
10  
11  
12 537 54. Charu V, Viboud C, Simonsen L, *et al.* Influenza-related mortality trends in Japanese  
13  
14  
15 538 and American seniors: evidence for the indirect mortality benefits of vaccinating  
16  
17  
18 539 schoolchildren. *Plos One* 2011;6:e26282.  
19  
20  
21 540 55. Hayward AC, Fragaszy EB, Bermingham A, *et al.* Comparative community burden and  
22  
23  
24 541 severity of seasonal and pandemic influenza: results of the Flu Watch cohort study.  
25  
26  
27 542 *Lancet Resp Med* 2014;2:445–54.  
28  
29  
30 543 56. Paules C, Subbarao K. Influenza. *Lancet* 2017;390:697–708.  
31  
32  
33 544 57. Poehling KA, Zhu Y, Tang Y-W, *et al.* Accuracy and impact of a point-of-care rapid  
34  
35  
36 545 influenza test in young children with respiratory illnesses. *Arch Pediatr Adolescent Med*  
37  
38  
39 546 2006;160:713–18.  
40  
41  
42 547 58. Sakai-Tagawa Y, Ozawa M, Tamura D, *et al.* Sensitivity of influenza rapid diagnostic  
43  
44  
45 548 tests to H5N1 and 2009 pandemic H1N1 viruses. *J Clin Microbiol* 2010;48:2872–77.  
46  
47  
48 549 59. Hata A, Asada J, Mizumoto H, *et al.* Appropriate use of rapid diagnostic testing for  
49  
50  
51 550 influenza. *J Jpn Assoc Infect Dis* 2004;78:846-52.  
52  
53  
54 551 60. Landry ML. Diagnostic tests for influenza infection. *Curr Opin Pediatr* 2011;23:91–97.  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4  
5  
6 552 61. Chartrand C, Leeflang MM, Minion J, *et al.* Accuracy of rapid influenza diagnostic  
7  
8  
9 553 tests: a meta-analysis. *Ann Intern Med* 2012;156:500–11.  
10  
11  
12 554 62. Central Intelligence Agency. The world factbook: sex ratio (male/female). 2018.  
13  
14  
15 555 Available at <https://www.cia.gov/library/publications/the-world->  
16  
17  
18 556 [factbook/fields/2018.html](https://www.cia.gov/library/publications/the-world-factbook/fields/2018.html). Accessed 23 October 2018.  
19  
20  
21 557  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6 558 **Figure legends**

7 559

8  
9 560 Figure 1. Histogram of the ages of influenza-infected outpatients in the 2012/13, 2013/14,  
10 561 2014/15, and 2015/16 seasons, according to health insurance administrative data.

11 562

12  
13 563 Figure 2. Histogram of the ages of influenza-infected inpatients in the 2012/13, 2013/14,  
14 564 2014/15, and 2015/16 seasons, according to health insurance administrative data.

15 565

16  
17 566 Figure 3. Number of influenza-infected inpatients with severe complications and proportion  
18 567 of infections and hospitalisation in a health insurance claim database, by age group, between  
19 568 2012 and 2016.

20  
21 569 Bars represent the number of each severe complication; the line represents the proportion of infections resulting  
22 570 in hospitalisation in each age group. Abbreviation: ARDS, acute respiratory distress syndrome.

23 571

24  
25 572 Figure 4. Number of influenza-infected inpatients with severe complications and proportion  
26 573 of infection and hospitalisation in a health insurance claim database, by age, between 2012  
27 574 and 2016.

28  
29 575 Bars represent the number of each severe complication; the line represents the proportion of infections with  
30 576 hospitalisation. Abbreviation: ARDS, acute respiratory distress syndrome.

31 577

32  
33 578 Figure 5. Number of influenza-infected inpatients and proportion of hospitalisation in  
34 579 health insurance claim database between 2012 and 2016.

35  
36 580 Black line represents number of inpatients; red line proportion of infections hospitalised.

37 581  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

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

Sex, n (%)	Men	Women							
	8885699	7751214							
	(53.4)	(46.6)							
Patient status, n (%)	Outpatient	Inpatient							
	16488970	164394							
	(99.0)	(1.0)							
Age, years	0–1	2–5	6–12	13–18	19–44	45–64	65–74		
n (%)	823875	2886462	4193137	1480030	3815970	2872125	231125		
	(5.1)	(17.7)	(25.7)	(9.1)	(23.4)	(17.6)	(1.4)		
No. of hospital beds	0–19	20–99	100–199	200–299	300–499	500+			
No. patients (%)	13572391	392179	450850	324418	616989	945892			
	(83.3)	(2.4)	(2.8)	(2.0)	(3.8)	(5.8)			
Clinical department of diagnosis	Internal medicine	Paediatrics	Otorhinolaryngology	Orthopaedics	Dermatology	Surgery	Ophthalmology	Obstetrics & Gynaecology	Psychiatry

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47

No. patients	1187638	827942	310514	308146	250737	206763	165914	156615	99624
(%)	(32.4)	(22.6)	(8.5)	(8.4)	(6.8)	(5.6)	(4.5)	(4.3)	(2.7)

584  
585  
586

For peer review only

136/bmjopen-2018-024687 on 17 January 2019. Downloaded from <http://bmjopen.bmj.com/> on July 7, 2023 by guest. Protected by copyright.

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			Febrile seizure	Encephalitis/ encephalopathy
		respiratory failure	Pneumonia	ARDS		
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

1							
2							
3		10202	106			36	
4	20–99	(6.2%)	(3.2%)	913 (3.4%)	3	(1.4%)	0
5							
6		12661	308	2394		147	
7	100–199	(7.7%)	(9.2%)	(8.8%)	0	(5.6%)	0
8							
9		15701	358	2933		220	
10	200–299	(9.6%)	(10.7%)	(10.8%)	7	(8.5%)	26 (16.4%)
11							
12		40753	922	9179		1003	
13	300–499	(24.8%)	(27.5%)	(33.7%)	0	(38.5%)	57 (35.8%)
14							
15		68234	1500	11029		1179	
16	500+	(41.5%)	(44.7%)	(40.5%)	8	(45.3%)	76 (47.8%)
17							
18	Hospital type						
19							
20		16817	167			18	
21	Clinic	(10.2%)	(5.0%)	805 (3.0%)	0	(0.7%)	0
22							
23	National or	48243	985	10995		1314	
24	municipal hospital	(29.3%)	(29.4%)	(40.3%)	10	(50.5%)	82 (51.6%)
25							
26		21898	285	2049		162	
27	University hospital	(13.3%)	(8.5%)	(7.5%)	0	(6.2%)	34 (21.4%)
28							
29		77185	1919	13404		1109	
30	Other hospital	(47.0%)	(57.2%)	(49.2%)	8	(42.6%)	43 (27.0%)
31							
32		251	5 (0.1%)	0		0	
33	Not specified	(0.2%)			0		0
34							

Abbreviation: ARDS, acute respiratory distress syndrome.



Table 3. Incidence of hospitalisation with severe complications per 100000 confirmed influenza infections.

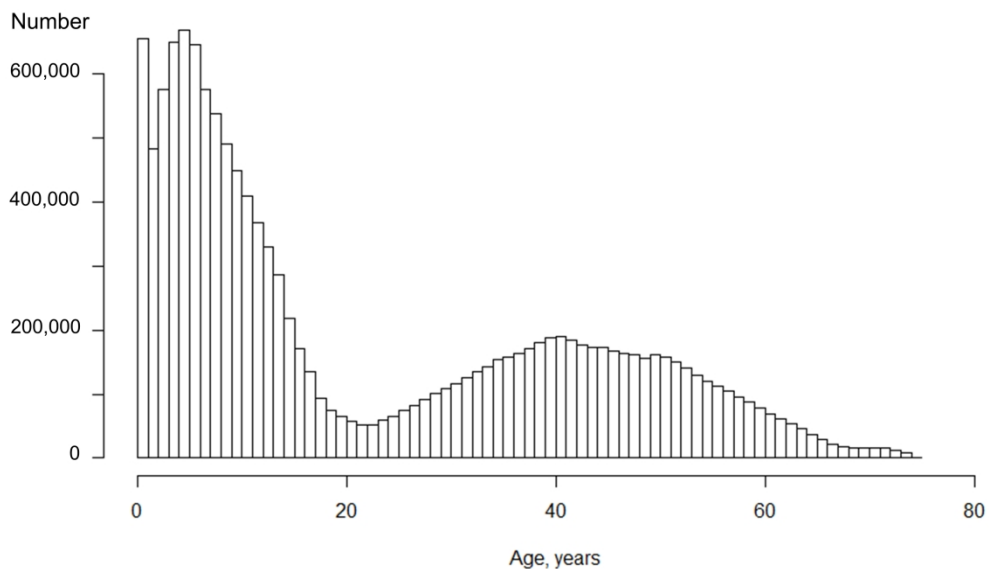
No. of inpatients per 100,000 influenza infections	Hospitalisation	Any of five complications	Acute respiratory failure	Pneumonia	ARDS	Febrile seizure	Encephalitis/encephalopathy
Sex*	p<0.0001	p<0.0001	p<0.0001	p<0.0001	p=0.08	p<0.0001	p=0.08
Male (n=8885794)	970	191	22.2	171	0.15	17.8	0.8
Female (n=7751279)	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.

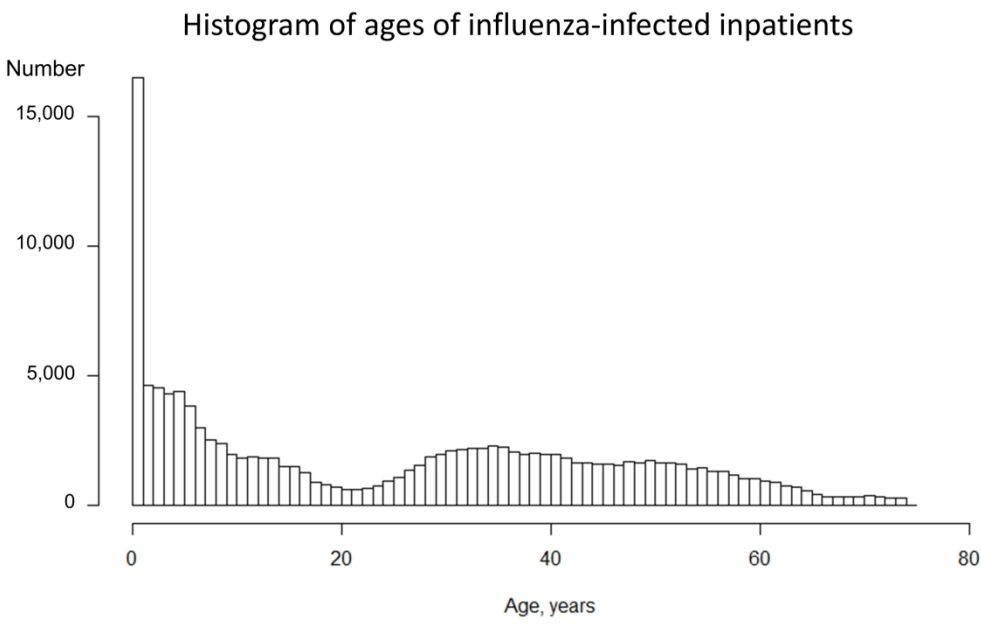
Histogram of ages of influenza-infected outpatients



Histogram of the ages of influenza-infected outpatients in the 2012/13, 2013/14, 2014/15, and 2015/16 seasons, according to health insurance administrative data.

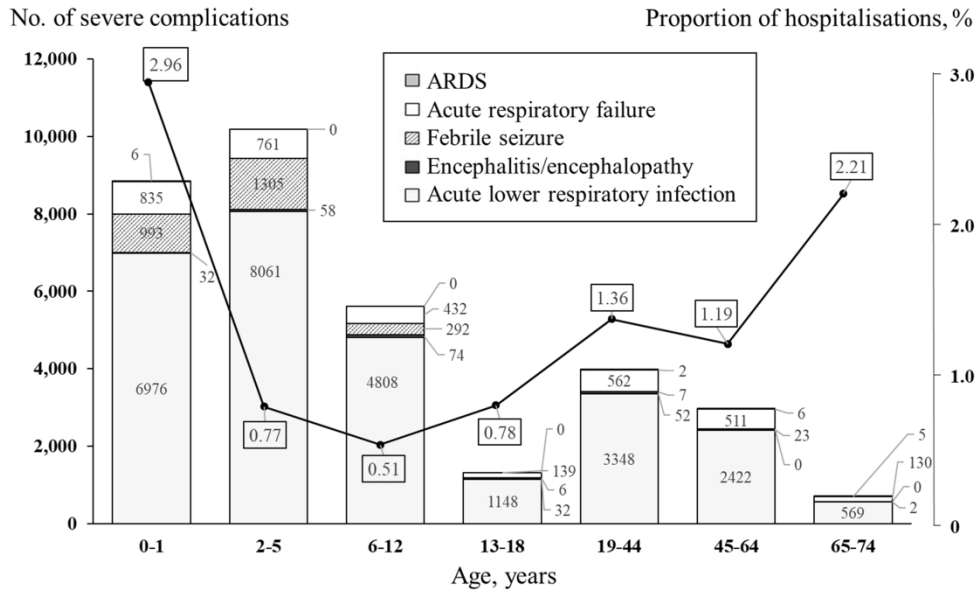
284x189mm (300 x 300 DPI)

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



Histogram of the ages of influenza-infected inpatients in the 2012/13, 2013/14, 2014/15, and 2015/16 seasons, according to health insurance administrative data.

277x181mm (300 x 300 DPI)



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.

267x167mm (300 x 300 DPI)

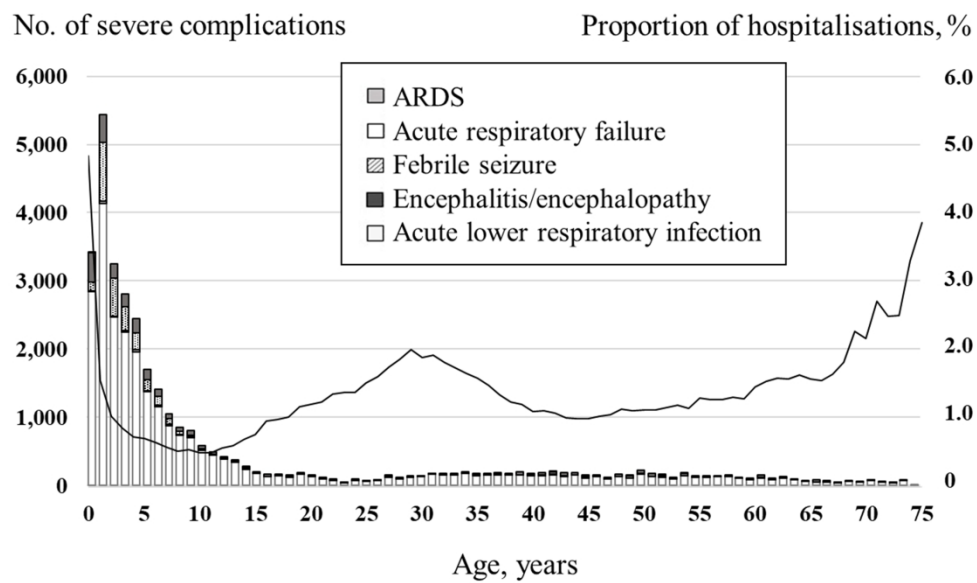
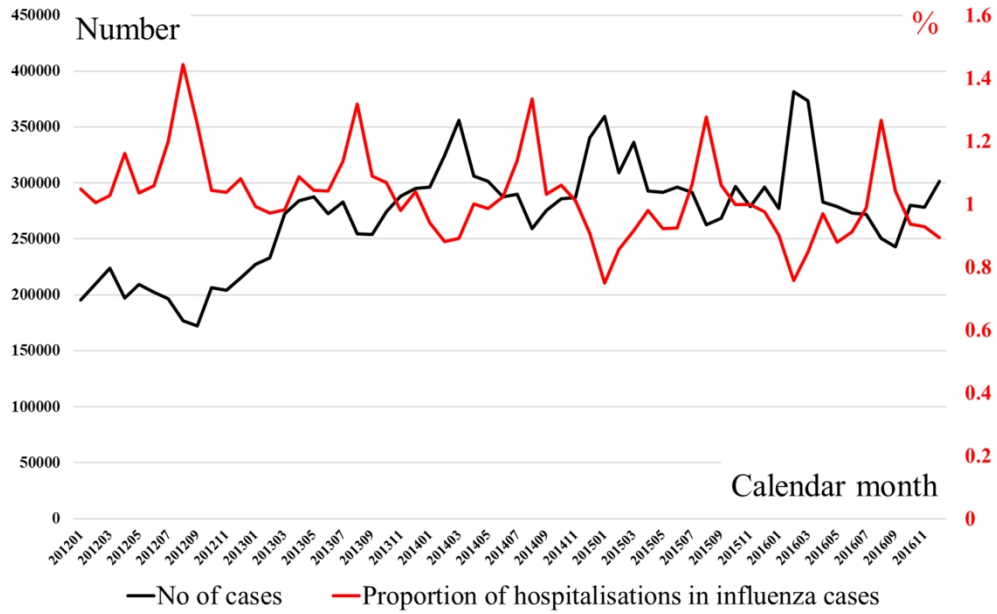


Figure 4. Number of influenza-infected inpatients with severe complications and proportion of infection and hospitalisation in a health insurance claim database, by age, between 2012 and 2016. Bars represent the number of each severe complication; the line represents the proportion of infections with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

258x156mm (300 x 300 DPI)



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.

539x340mm (300 x 300 DPI)

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies***

Section/Topic	Item #	Recommendation	Reported on page #
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3–4
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6–8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	9–10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10–11
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	11
Bias	9	Describe any efforts to address potential sources of bias	10–11
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10–11
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	11
		(b) Describe any methods used to examine subgroups and interactions	11
		(c) Explain how missing data were addressed	9
		(d) If applicable, describe analytical methods taking account of sampling strategy	9
		(e) Describe any sensitivity analyses	Figures 3–5
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility,	13



		confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	Not Applicable
		(c) Consider use of a flow diagram	Not Applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Not Applicable
Outcome data	15*	Report numbers of outcome events or summary measures	Table 2
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3 and figures 3–5
		(b) Report category boundaries when continuous variables were categorized	Table 3 and figures 3–5
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not Applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 3 and figures 3–5
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	22–24
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16–21
Generalisability	21	Discuss the generalisability (external validity) of the study results	21–22
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	26

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## 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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-024687.R2
Article Type:	Research
Date Submitted by the Author:	01-Dec-2018
Complete List of Authors:	Yokomichi, Hiroshi; University of Yamanashi, Department of Health Sciences Mochizuki, Mie; University of Yamanashi, Department of Pediatrics Lee, Joseph; University of Oxford Kojima, Reiji; University of Yamanashi, Department of Health Sciences Yokoyama, Tetsuji ; National Institute of Public Health, Department of Health Promotion Yamagata, Zentaro; University of Yamanashi
<b>Primary Subject Heading</b>:	Infectious diseases
Secondary Subject Heading:	Paediatrics, Respiratory medicine, Epidemiology, Evidence based practice, Health services research
Keywords:	Influenza, Hospitalisation, Pneumonia, Influenza encephalopathy, Influenza encephalitis, Febrile seizure

SCHOLARONE™  
Manuscripts

1  
2  
3  
4  
5  
6  
7 **1 Incidence of hospitalisation for severe complications of influenza virus infection in**  
8  
9 **2 Japanese patients between 2012 and 2016: A cross-sectional study using routinely**  
10  
11  
12 **3 collected administrative data**

13  
14  
15  
16  
17 4 Hiroshi Yokomichi<sup>1</sup>, Mie Mochizuki<sup>2</sup>, Joseph Jonathan Lee<sup>3</sup>, Reiji Kojima<sup>1</sup>, Tetsuji  
18  
19 5 Yokoyama<sup>4</sup>, Zentaro Yamagata<sup>1</sup>

20  
21  
22  
23  
24 6

25  
26  
27  
28 7 Author Affiliations

29  
30  
31  
32 8 <sup>1</sup>Department of Health Sciences, University of Yamanashi

33  
34  
35  
36 9 <sup>2</sup>Department of Pediatrics, University of Yamanashi

37  
38  
39  
40 10 <sup>3</sup>Nuffield Department of Primary Care Health Sciences, University of Oxford

41  
42  
43  
44 11 <sup>4</sup>Department of Health Promotion, National Institute of Public Health

45  
46  
47  
48  
49 12

50  
51  
52  
53 13 Correspondence: Hiroshi Yokomichi

54  
55  
56  
57 14 1110 Shimokato, Chuo City, Yamanashi, 4093898, Japan  
58  
59  
60

1  
2  
3  
4  
5  
6 15 Tel: +81 80 5524 7393  
7  
8  
9

10 16 Fax: +81 55 273 7882  
11  
12  
13

14 17 E-mail: [hyokomichi@yamanashi.ac.jp](mailto:hyokomichi@yamanashi.ac.jp)  
15  
16

17  
18  
19 18  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

1  
2  
3  
4  
5  
6 19 **Abstract**  
7  
8  
9

10 **Objectives:** To calculate the incidence of hospitalisation due to acute respiratory  
11  
12  
13 failure, pneumonia, acute respiratory distress syndrome (ARDS), febrile seizures and  
14  
15  
16 encephalitis/encephalopathy amongst influenza-positive patients in Japan where point-  
17  
18  
19 of-care tests are routinely used to diagnose influenza.  
20  
21  
22

23  
24 **Design:** A cross-sectional study using routinely collected data.  
25  
26  
27

28 **Setting:** Japanese clinics and hospitals between 2012 and 2016.  
29  
30  
31

32 **Participants:** Japanese patients aged 0-74 years diagnosed with influenza by a rapid  
33  
34  
35 test in employment-related health insurance records.  
36  
37  
38

39 **Primary outcome measures:** Incidence of hospitalisation per 100000 influenza-  
40  
41  
42 positive episodes.  
43  
44  
45

46 **Results:** We included over 16 million influenza-positive episodes, 1.0% of whom were  
47  
48  
49 hospitalised. Of these, 3361 had acute respiratory failure, 27253 pneumonias, 18 ARDS,  
50  
51  
52 2603 febrile seizures and 159 encephalitis/encephalopathy. The percentage of  
53  
54  
55 hospitalisations by age was 2.96% of patients aged 0–1 years; 0.77% aged 2–5; 0.51%  
56  
57  
58 aged 6–12; 0.78% aged 13–18; 1.36% aged 19–44; 1.19% aged 45–64; and 2.21% aged  
59  
60

1  
2  
3  
4  
5  
6  
7 35 65–74. The incidence of hospitalisations from these five complications combined was  
8  
9  
10 36 highest in influenza-positive patients aged 0–1 years (943 per 100000) compared with  
11  
12 37 307 in those aged 2–5 years and 271 in those aged 65–74 years. For pneumonia,  
13  
14  
15 38 incidence was highest for influenza-positive patients aged 0–5 years and 65 years or  
16  
17  
18 39 more. There were statistically significant decreasing trends over the years in the  
19  
20  
21 40 incidence of all-cause hospitalisations, pneumonia and febrile seizures.  
22  
23  
24

25 41 **Conclusions:** Japanese administrative data revealed that 1.0% of influenza-positive  
26  
27  
28 42 patients aged under 75 years were hospitalised. Male patients had a higher incidence of  
29  
30  
31 43 pulmonary complications and febrile seizures. Children aged 0–5 years and adults aged  
32  
33  
34 44 65–74 years were at high risk of being admitted to hospital for pneumonia.  
35  
36  
37

38 45 **Registration:** The ethics committee of the School of Medicine, University of  
39  
40  
41 46 Yamanashi approved this study (approval number: H29-1709).  
42  
43  
44

45  
46 47 **(292 words/300 words)**  
47  
48  
49

50 48  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56

**Strengths and limitations of this study:**

● This study uses Japanese routinely collected data where uniquely diagnostic tests are used to identify influenza infections in the population.

● Point-of-care testing for influenza has limited sensitivity, but its high specificity means that nearly all the participants in this study were infected with influenza.

● Limitations of the data set prevent analysis of mortality and patients over the age of 74 years.

## 57 INTRODUCTION

58 Influenza is a major burden on health systems worldwide. Every year, an estimated one  
59 billion people [1] including 90 million children younger than 5 years of age are infected  
60 with influenza globally, and 1 million people have influenza-associated acute lower  
61 respiratory tract infection, [2] which causes 290000–600000 deaths.[3]

62 Complications of influenza which cause hospitalisations are a serious public  
63 health concern. In both Western and Asian countries, the majority of influenza-related  
64 hospital admission is due to respiratory or neurologic complications: pneumonia, febrile  
65 seizure, acute respiratory failure, acute respiratory distress syndrome (ARDS) and  
66 encephalitis/encephalopathy.[4-8] We refer to these as ‘severe complications’ here.  
67 Hospitalisation rates from influenza infection have been investigated,[4 9] but most  
68 studies were conducted in Western countries where testing for influenza is not routine.  
69 This means that studies have used either limited sample sizes of positively identified  
70 individual hospitalised patients, or extrapolated from influenza surveillance data.[9-11]  
71 Hospital-based studies may have underestimated the risk and the number of infections  
72 and complications in the community.[12] Previous studies have used estimates of the  
73 general population as denominators, rather than assessing the risk of admission amongst



1  
2  
3  
4  
5  
6 74 the infected population, combining the risk of infection and the risk of complications.  
7  
8  
9 75 This is problematic because programmes targeting high risk groups, such as vaccination  
10  
11  
12 76 or prophylaxis may reduce the number of infections in high risk groups, biasing  
13  
14  
15 77 estimates of the risk of complications if infected.[12] Also, many studies pre-date the  
16  
17  
18 78 option of administering new neuraminidase inhibitors.[13]  
19  
20  
21

22 79 Although it is also seen internationally,[14-18] influenza encephalitis is a  
23  
24  
25 80 particular concern amongst Japanese physicians owing to a high incidence and mortality  
26  
27  
28 81 rate in Japan.[7 19-23] The prognosis for patients with influenza  
29  
30  
31 82 encephalitis/encephalopathy is very poor; approximately 30% of affected patients die  
32  
33  
34 83 and 20–30% have neurological sequelae.[24] To understand the aetiology and  
35  
36  
37 84 prevalence of this severe outcome, surveillance has been conducted.[25 26] In Japan,  
38  
39  
40 85 influenza-associated encephalopathy is a notifiable disease.[27] Japanese physicians are  
41  
42  
43 86 required to report influenza infection cases with: a) death after coma or hospitalisation  
44  
45  
46 87 with coma for 24 hours or more; and b) a fever of 38°C or higher, central nervous  
47  
48  
49 88 system manifestation or prior influenza infection symptoms. This surveillance system  
50  
51  
52 89 has detected 60–100 influenza encephalitis cases annually [28] and 331 cases during the  
53  
54  
55 90 2009–2010 pandemic;[26] however, underreporting of cases has been  
56  
57  
58 91 acknowledged.[28] Another survey of paediatric departments in 265 hospitals reported  
59  
60

1  
2  
3  
4  
5  
6 92 263 influenza-associated encephalopathy cases over 3 years.[25] The authors estimate  
7  
8  
9 93 that there are 200–300 influenza encephalopathy cases per annum in Japan;[29]  
10  
11  
12 94 therefore, the incidence of influenza encephalitis/encephalopathy is not accurately  
13  
14  
15 95 known.  
16  
17  
18  
19

20 96 To understand the incidence of severe complications in patients with influenza,  
21  
22 97 an analysis of large-scale real-world data is needed, encompassing hospital and  
23  
24  
25 98 community sites. Previous studies using large data sets of routinely collected medical  
26  
27  
28 99 records have had to rely on clinical diagnoses of influenza-like illness or modelling of  
29  
30  
31 100 influenza and other respiratory virus infections using incomplete laboratory data.[11] In  
32  
33  
34 101 Japan, diagnostic testing for influenza is routine, which presents a unique opportunity to  
35  
36  
37 102 combine the benefits of large data sets with positive diagnoses.[6] We therefore sought  
38  
39  
40 103 to estimate the incidence of hospitalisation with the above five severe complications per  
41  
42  
43 104 influenza infection, using Japanese health insurance claim data.  
44  
45  
46  
47  
48 105

## 51 106 **METHODS**

### 52 53 54 55 56 107 **Patients and data** 57 58 59 60

1  
2  
3  
4  
5  
6 108 We analysed administrative data provided by Japan Medical Data Center Ltd. (renamed  
7  
8  
9 109 to JMDC) Tokyo, Japan.[30] The data source was the monthly health insurance claim  
10  
11  
12 110 records between January 2012 and December 2016 of approximately three million  
13  
14  
15 111 employees and their dependents, representing 2.4% of the Japanese population. Within  
16  
17  
18 112 health insurance coverage in Japan, people can consult physicians in any type of hospital  
19  
20  
21 113 and department, and medical doctors in any speciality can diagnose influenza and  
22  
23  
24 114 prescribe anti-influenza medications. The age of patients in the data set ranged from 0 to  
25  
26  
27 115 74 years because all Japanese people aged 75 or more (except for individuals who are on  
28  
29  
30 116 public assistance) are covered by another health insurance program with lower out-of-  
31  
32  
33 117 pocket expenses.

34  
35  
36  
37 118 From the database, we extracted the data of individuals who consulted  
38  
39  
40 119 physicians with influenza-like illness episodes. We then included only patients with a  
41  
42  
43 120 diagnosis of influenza virus infection. In Japan, the use of immunochromatogenic assay  
44  
45  
46 121 point-of-care tests [POCT] in clinical practice has been covered by public health  
47  
48  
49 122 insurance from 1999.[23] As recommended in Japanese guidelines,[31] a test-and-treat  
50  
51  
52 123 strategy is routine.[23 32] Even if physicians only slightly suspect influenza infection,  
53  
54  
55 124 they use a POCT to diagnose influenza, and administer antivirals to the positive  
56  
57  
58 125 patients.[31 33 34] Testing would be indicated in fever, sore throat, malaise, non-

1  
2  
3  
4  
5  
6 126 productive cough or a history of family's infection, for example.[23 35] During the  
7  
8  
9 127 2009–2010 pandemic influenza A(H1N1) season, physicians performed this test in  
10  
11  
12 128 majority of cases (>90%) and we believe this was likely to be the case during the period  
13  
14  
15 129 of this study because in Japan paediatric patients with an influenza-like illness are  
16  
17  
18 130 required to obtain a medical certificate showing they do not have influenza before return  
19  
20  
21 131 to school.[36]  
22  
23  
24

## 132 **Outcomes**

133 Hospitalisation was recorded in the health insurance claims of inpatients. In patients with  
134 a diagnosis of influenza infection, we identified those who were hospitalised with a  
135 diagnosis of acute respiratory failure, pneumonia, ARDS, febrile seizure, and  
136 encephalitis/encephalopathy, according to International Classification of Diseases (ICD-  
137 10) codes in their records. The primary outcomes were the incidence of each of the five  
138 severe complications per 100000 influenza infections. Acute respiratory failure was  
139 coded as J960, J988, R060, R068 or R092; pneumonia was coded as J10–J18 or J20–J22,  
140 acute respiratory distress syndrome (ARDS) as J80, and febrile seizures as R560. We  
141 defined influenza encephalitis/encephalopathy as patients who were diagnosed using  
142 ICD-10 codes for influenza infection and encephalitis/encephalopathy (G00–G09 or G41)

1  
2  
3  
4  
5  
6 143 and had been administered steroid pulse or immunoglobulin therapy.[37]  
7  
8  
9

10 144 **Statistical analysis**  
11  
12  
13  
14

15 145 We examined the number of diagnosed influenza infections and severe complications by  
16  
17 146 sex, age, outpatient/inpatient status, number of beds in the facility, and clinical speciality.  
18  
19

20 147 In Japan, clinical facilities with fewer than 20 beds are denoted a “clinic” by law. Clinics  
21  
22 148 are usually run by a single medical doctor and function as a primary care department.  
23  
24

25 149 Most clinics have no beds but a very small subset of clinics have 1–19 beds to  
26  
27 150 accommodate inpatients. In contrast, facilities with 20 beds or more are legally termed a  
28  
29

30 151 “hospital”. Hospitals have primary care, specialised outpatient, and general and  
31  
32 152 specialised inpatient departments. In this study, hospitalised influenza-positive patients  
33  
34

35 153 were inpatients in both “clinic” and “hospital” settings. We plotted histograms of the ages  
36  
37 154 of outpatients and inpatients infected with influenza. We determined the incidence of  
38  
39

40 155 inpatients with the five severe complications by dividing the number of complications by  
41  
42 156 the number of infections. We stratified this by sex, influenza season and age. We also  
43  
44

45 157 examined the numbers of the influenza-infected patients and the proportions of inpatients  
46  
47 158 over calendar time at the request of a reviewer. Influenza seasons were defined as lasting  
48  
49

50 159 from September through to the following August. We calculated p values for secular  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6 160 trends of incidence over influenza seasons. Statistical analyses were performed using SAS  
7  
8  
9 161 statistical software (version 9.4, SAS Institute, Cary, NC, USA). All reported p values  
10  
11  
12 162 were two-sided and we considered  $p < 0.05$  indicated a significant difference.  
13  
14  
15

### 16 163 **Ethical approval**

17  
18  
19  
20  
21 164 The ethics committee of the School of Medicine, University of Yamanashi approved this  
22  
23  
24 165 study (approval number: H29-1709), in accordance with the ethical guidelines and  
25  
26  
27 166 regulations of the Declaration of Helsinki. The data were properly anonymised by the  
28  
29  
30 167 JMDC in the manner permitted by Japanese guideline of Personal Information Protection  
31  
32  
33 168 Commission, Cabinet Office, Government of Japan for the use of data from medical  
34  
35  
36 169 examinations in medical research without individual participants' consent (Act on the  
37  
38  
39 170 Protection of Personal Information, act no. 57 of 30 May 2003; last version amendment  
40  
41  
42 171 of act no. 65 of 2015).  
43  
44  
45

### 46 172 **Patient and public involvement**

47  
48  
49  
50 173 Patients were not actively involved in developing the research question and protocol  
51  
52  
53 174 including outcome measures. The participants will be provided the final study results by  
54  
55  
56 175 clinical research information services and homepage of the University of Yamanashi.  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7 176  
8  
910 177 **RESULTS**  
11  
1213  
14  
15 178 **Characteristics of patients diagnosed with influenza**  
16

17  
18 179 Table 1 summarises the number of patients with diagnoses of influenza infection in the  
19  
20  
21  
22 180 study population. Among 16636913 infections, 53.4% of the patients were men, and 1.0%  
23  
24  
25 181 were hospitalised. Approximately a quarter (25.7%) of infections were in children aged  
26  
27  
28 182 6–12 years. Overall 32% of diagnoses were made in the internal medicine department and  
29  
30  
31 183 23% in paediatrics. Most infections were diagnosed in clinics (n=13572391; 83%).  
32  
33  
34 184 Figures 1 and 2 illustrate the number of outpatients and inpatients with influenza infection,  
35  
36  
37 185 respectively, by age. Influenza was most often diagnosed in outpatients aged 0–12 years,  
38  
39  
40 186 with a second small peak in middle-aged patients. In contrast, inpatient cases were  
41  
42  
43 187 commonest among patients aged less than one year. Table 2 shows the number of  
44  
45  
46 188 complicated cases by department, hospital size and type of hospital management. A total  
47  
48  
49 189 of 3361 patients (0.02%) were admitted to hospital with acute respiratory failure, 27253  
50  
51  
52 190 (0.16%) with pneumonia, 18 (0.0001%) with ARDS, 2603 (0.02%) with febrile seizures,  
53  
54  
55 191 and 159 (0.001%) with encephalitis/encephalopathy. Most complicated cases were  
56  
57  
58 192 admitted to paediatric departments, with 19012 pneumonia admissions (70% of the total),  
59  
60

1  
2  
3  
4  
5  
6 193 1794 with acute respiratory failure (53% of the total), 2461 with febrile seizures (95% of  
7  
8  
9 194 the total), and 63 encephalitis (40% of all cases). The number of inpatients with acute  
10  
11  
12 195 respiratory failure, pneumonia, and febrile seizure tended to increase with the number of  
13  
14  
15 196 hospital beds.

### 197 **Hospitalisation rates from severe complications**

198 The combined incidence of the five complications was 189 per 100000 diagnosed  
199 infections. Pneumonia was the commonest complication, with 164 per 100000 diagnosed  
200 infections, followed by acute respiratory failure (20.2), febrile seizures (15.7),  
201 encephalitis/encephalopathy (0.9), and ARDS (0.10). Table 3 shows the incidence of five  
202 severe complications by age, sex, and influenza season. Although the incidence of acute  
203 respiratory failure, pneumonia, ARDS, and febrile seizures was higher in men,  
204 encephalitis/encephalopathy was higher in women. There were decreasing trends over the  
205 years in incidence of hospital admissions from pneumonia (p for trend<0.0001), febrile  
206 seizure (p for trend<0.0001), and the five severe complications combined (p for  
207 trend<0.0001), but not acute respiratory failure (p for trend=0.07),  
208 encephalitis/encephalopathy (p for trend=0.19) or ARDS (p for trend=0.98). In each age  
209 group, pneumonia was the commonest complication. The incidence of acute respiratory



1  
2  
3  
4  
5  
6 210 failure, pneumonia, and febrile seizure was highest in patients aged 0–1 years, ARDS was  
7  
8  
9 211 highest in those 65–74 years, and encephalitis/encephalopathy was highest in patients  
10  
11  
12 212 aged 13–18 years.  
13  
14  
15

16 213 Figures 3 and 4 show the number and percentage of inpatients with  
17  
18  
19 214 complications by age group and age over the study period. Young children had most of  
20  
21  
22 215 the severe complications. Across all age groups, pneumonia was by far the most  
23  
24  
25 216 common of the five complications, and the age group with the largest number of cases  
26  
27  
28 217 was children aged 2–5 years. In contrast, the proportion of infections hospitalised was  
29  
30  
31 218 highest in patients aged 0–1 years (2.96%) and second highest in those aged 65–74  
32  
33  
34 219 years (2.21%).  
35  
36

37 220 Figure 5 shows the numbers of influenza-infected patients and the proportion  
38  
39  
40 221 who were inpatients by calendar month between 2012 and 2016. Every year the number  
41  
42  
43 222 of infections increased from winter to spring while the proportion admitted peaked in  
44  
45  
46 223 summer. The number of infections was similar between 2014 and 2016. The proportion  
47  
48  
49 224 hospitalised gradually decreased between 2012 and 2016.  
50  
51

52  
53 225

54  
55  
56  
57 226 **DISCUSSION**  
58  
59  
60

## 227 **Principal findings**

228 We described the epidemiology of hospital admissions and five key severe complications  
229 in large cross-sectional data of influenza-positive patient visits. Influenza diagnoses were  
230 commonest in young children and middle-aged patients (table 1 and figures 1–2). The  
231 incidence and absolute number of hospital admissions with complications of influenza  
232 was highest in young children (figure 2 and table 3). The most common complication was  
233 pneumonia (table 1). The incidence and absolute number of admissions for pulmonary  
234 complications were highest in children (figures 3–4 and table 3). Patients aged 65–74  
235 years were also at high risk for admission from complications, but the absolute number  
236 of both influenza infections and serious complications was lower than for children in our  
237 data set (figures 3–4 and table 3). The incidence of admissions for  
238 encephalitis/encephalopathy was relatively high in children aged 0–18 years (table 3).  
239 There was a decreasing trend in the proportions of infections hospitalised for any reason,  
240 and with any of the five complications, pneumonia, or febrile seizures between 2012 and  
241 2016 (table 3 and figure 5).

## 242 **Comparison with previous research**

243 Male patients suffered more complications than female ones, especially for acute

1  
2  
3  
4  
5  
6 244 respiratory failure, pneumonia, and febrile seizures (table 3). This is consistent with  
7  
8  
9 245 previous studies reporting that during the 2009–2010 pandemic influenza A(H1N1)  
10  
11  
12 246 season, the incidence of hospitalisation in male children was greater than in female  
13  
14  
15 247 children in the US (56%),[38] Canada (60%),[39] and Japan (64.3%).[6] Asthma is a  
16  
17  
18 248 risk factor for pneumonia in children with influenza.[40] Our finding of an increased  
19  
20  
21 249 risk of pneumonia in males may be because asthma is a more common disease in boys  
22  
23  
24 250 than girls.[41] It is also known that boys get febrile seizures more often than girls.[42]  
25  
26  
27 251 This was also observed in our data for febrile seizures with influenza infection. In  
28  
29  
30 252 contrast, our data suggest the possibility of a higher risk of encephalitis/encephalopathy  
31  
32  
33 253 in women with influenza infection (table 3). However, in Japanese surveillance reports  
34  
35  
36 254 from 2007 to 2010, 153 of 263 (58.2%) paediatric patients with encephalopathy were  
37  
38  
39 255 male.[25] Because the means of data collection in previous studies were different, we  
40  
41  
42 256 are unable to conclude in which sex complications are more common. Further study  
43  
44  
45 257 with another large data set is needed to investigate risk factors, including sex, for  
46  
47  
48 258 hospitalisation and incidence of encephalitis/encephalopathy in Asian people.  
49  
50

51  
52 259 Our results by age are consistent with those of previous studies, and add to  
53  
54  
55 260 understanding the risk of specific complications amongst those with a diagnosis of  
56  
57  
58 261 influenza. Previous studies, being unable to identify a large number of influenza-positive  
59  
60

1  
2  
3  
4  
5  
6 262 patients, have used small numbers of influenza positive admissions as cases and general  
7  
8  
9 263 population estimates as the denominators. This combines the risk of infection and the risk  
10  
11  
12 264 of complications. We found that the risk of hospitalisation was highest in infected infants  
13  
14  
15 265 aged 0–1 years (figures 2–4 and table 3). This is consistent with a US study, which found  
16  
17  
18 266 that the highest hospitalisation rate was among infants aged under one year (11.9 per  
19  
20  
21 267 100000 population) during the 2009–2010 influenza A(H1N1) pandemic;[9] in addition,  
22  
23  
24 268 we are able to show that the risk of admission is as high as 943 per 100000 infections. A  
25  
26  
27 269 study from the UK also reported that children aged 6 months to 4 years had the high  
28  
29  
30 270 influenza related hospitalisation rates between 2001 and 2007 (3360 per 100000  
31  
32  
33 271 population).[8]

34  
35  
36  
37 272 A systematic review found large gaps in the evidence base (describing the  
38  
39  
40 273 evidence for risk factors for admissions as “limited to absent”).[12] They found  
41  
42  
43 274 contrasting results with children under the age of two years at higher risk of admission to  
44  
45  
46 275 hospital than older children with pandemic H1N1 influenza but the reverse with seasonal  
47  
48  
49 276 influenza.[12] They also found evidence of spectrum bias; studies from hospitals and  
50  
51  
52 277 intensive care units gave lower estimates of risk of death than community-based studies  
53  
54  
55 278 for both the elderly and children compared to young adults. As well as including  
56  
57  
58 279 positively diagnosed patients, our study covers both the community and hospital settings  
59  
60

1  
2  
3  
4  
5  
6 280 and is of sufficient size to allow estimation for specific causes of admission. In addition,  
7  
8  
9 281 because vaccination reduces the hospitalisation rate,[43-45] vaccination programmes in  
10  
11  
12 282 other countries that target high risk groups may bias hospitalisation rate estimates for  
13  
14  
15 283 these patients. In Japan all individuals have had to pay a fee to receive influenza vaccine  
16  
17  
18 284 irrespective of their risk profile since 1994, when free vaccination for primary and  
19  
20  
21 285 secondary school students was stopped.[46] This means that high-risk groups in Japan  
22  
23  
24 286 are less resistant to severe disease than in other countries, reducing this bias in our  
25  
26  
27 287 hospitalisation rates.

### 288 **Implications for clinicians and policymakers**

289 During the 2009–2010 pandemic, the World Health Organization [47] and the Centers for  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39 290 Disease Control and Prevention [48] issued guidelines for early neuraminidase inhibitor  
40  
41  
42 291 treatment. There are suggestions that administration of this medication within 48 hours  
43  
44  
45 292 reduces mortality and severe outcomes.[49] A Cochrane review, whilst critical of the  
46  
47  
48 293 quality of trial evidence, found a reduction in secondary infections among children who  
49  
50  
51 294 were prescribed oseltamivir.[50] During the 2000s, four neuraminidase inhibitors became  
52  
53  
54 295 available in Japan: zanamivir in 2000, oseltamivir in 2001, and laninamivir and peramivir  
55  
56  
57 296 in 2010.[23] The Japanese Association for Infectious Diseases also recommended post-

1  
2  
3  
4  
5  
6 297 exposure prophylaxis of zanamivir and oseltamivir in hospitals and geriatric facilities in  
7  
8  
9 298 2012. Reportedly, seven to eight million patients per annum were prescribed with  
10  
11  
12 299 neuraminidase inhibitors from 2011 to 2015; more than half of all patients infected with  
13  
14  
15 300 influenza received these medicines.[23] The decreasing trend with time in the  
16  
17  
18 301 hospitalisation and the composite incidence of the five severe complications (table 3,  
19  
20  
21 302  $p < 0.0001$ ) might be attributed to the increasingly widespread use of [13 33] and more  
22  
23  
24 303 options for neuraminidase inhibitors.[6 23] This decreasing trend was not altered in the  
25  
26  
27 304 2014/15 season when influenza A(H3N2) spread internationally including in Japan.[51]  
28  
29  
30 305 A recent meta-analysis of randomised controlled trials reported that in patients with  
31  
32  
33 306 pathogen-ascertained influenza, as is practice in Japan, treatment with oseltamivir  
34  
35  
36 307 reduced hospital admissions by 63%.[52]

38  
39  
40 308 In our study, the incidence of hospitalisations, acute pneumonia and febrile  
41  
42  
43 309 seizures decreased with time (table 3, all  $p$  values  $< 0.0001$ ). This was observed in parallel  
44  
45  
46 310 with increased administration of neuraminidase inhibitors. However, there appears to be  
47  
48  
49 311 no trend in the risk of encephalitis/encephalopathy. Because influenza encephalitis  
50  
51  
52 312 appears to be mediated by an acute process during infection,[14] it is important to prevent  
53  
54  
55 313 influenza infection to reduce the incidence of encephalitis. The primary countermeasure  
56  
57  
58 314 to protect individuals from infection is vaccination. National vaccine policies may have  
59  
60

1  
2  
3  
4  
5  
6 315 impacted upon variation in the hospitalisation incidence between countries. In Japan,  
7  
8  
9 316 schoolchildren were vaccinated routinely from 1976 to 1993, when influenza was  
10  
11  
12 317 removed from the list of free routine vaccinations, and vaccination of high risk groups  
13  
14  
15 318 was only recommended from 2001, albeit for a fee which has limited uptake.[53] Studies  
16  
17  
18 319 of this natural experiment suggest that the former routine vaccination program for  
19  
20  
21 320 schoolchildren indirectly reduced excess mortality among the elderly.[46 54] The  
22  
23  
24 321 previous results suggest indirect effect of the vaccines upon reducing severe complication  
25  
26  
27 322 risk amongst children; however, the effect upon the incidence of encephalitis is unknown.  
28  
29  
30 323 Because current encephalitis treatments are of limited effectiveness, a vaccination  
31  
32  
33 324 program covering a broad population may be the best way to reduce the morbidity  
34  
35  
36 325 associated with influenza encephalitis.  
37  
38  
39

#### 40 326 **Strengths and weaknesses**

41  
42  
43  
44  
45 327 A main strength of this study is that the included patients were diagnosed with influenza  
46  
47  
48 328 by testing. The majority of influenza-like illness is usually caused by infections other than  
49  
50  
51 329 influenza.[55] Diagnoses were based on rapid antigen detection with  
52  
53  
54 330 immunochromatogenic assay. Because POCTs for influenza are less invasive and require  
55  
56  
57 331 less time than laboratory tests, they are an essential tool for physicians to evaluate  
58  
59  
60

1  
2  
3  
4  
5  
6 332 influenza in outpatient and inpatient clinical practice in Japan.[6] Although low  
7  
8  
9 333 sensitivity (59–93%) [56] is a weak point for POCTs, the specificity is 98–100%.[34 57]  
10  
11  
12 334 This means that nearly all individuals with influenza-like illness who have POCT-positive  
13  
14  
15 335 results (the participants in this study) were infected with influenza. This makes routinely  
16  
17  
18 336 collected Japanese data unique. Additionally, all Japanese people who are hospitalised  
19  
20  
21 337 with severe complications of influenza infection should be present in universal health  
22  
23  
24 338 insurance data. Therefore, we did not greatly overestimate the number of infected patients  
25  
26  
27 339 or underestimate severe complications, and thus did not underestimate the risk of  
28  
29  
30 340 complications and hospitalisations.  
31  
32  
33

34  
35 341 There are limitations inherent to the data set used in this study. Firstly, POCTs  
36  
37 342 for influenza are known to have variable sensitivity. In the 2010s, 20 or more POCT kits  
38  
39  
40 343 were available in Japan.[58] Sensitivity would have been influenced by the following  
41  
42  
43 344 factors. (1) Time from the onset of illness. Reportedly, the sensitivity is lower 0–24 hours  
44  
45  
46 345 from symptom onset and higher in days 2–4.[59 60] Parents tend to bring children to  
47  
48  
49 346 paediatricians at an earlier stage of the infection while infected employed adults tend to  
50  
51  
52 347 consult physicians in mid- or later stages. This would bias sensitivity toward  
53  
54  
55 348 comparatively low in children compared to adults. (2) Patient age. In contrast children  
56  
57  
58 349 are known to have higher viral load and longer shedding and consequently POCTs have  
59  
60



1  
2  
3  
4  
5  
6 350 higher sensitivity in children.[60 61] (3) Influenza type A/B/C. POCT sensitivity is higher  
7  
8  
9 351 in influenza A than in B.[61] In Japan, influenza type A spreads early in winter, type B  
10  
11  
12 352 late in winter, and type C in all seasons. Therefore, the sensitivity might have been  
13  
14  
15 353 relatively low between Jan 2012–Aug 2012 and higher between Sep 2016–Dec 2016  
16  
17  
18 354 (table 3). (4) Operator technique.[60] In almost all Japanese medical care facilities,  
19  
20  
21 355 physicians conduct POCT for individuals with influenza-like illness.[31 32] Because  
22  
23  
24 356 physicians are trained to appropriately sample specimen material, operator bias within  
25  
26  
27 357 our Japanese data would be small. (5) Number of times patients were tested. In Japan,  
28  
29  
30 358 physicians are permitted to conduct POCTs up to twice per patient in a calendar month  
31  
32  
33 359 within health insurance coverage. Even if the first POCT had failed to detect influenza-  
34  
35  
36 360 positive patients, the second POCT might identify the infection. Thus the sensitivity in  
37  
38  
39 361 Japanese clinical practice would be higher than the nominal sensitivity. Overall, the  
40  
41  
42 362 sensitivity of POCTs can vary unpredictably according to the circumstances. Our  
43  
44  
45 363 denominator (influenza-positive episodes) may be underestimated in low sensitivity  
46  
47  
48 364 situations and to a smaller degree in high sensitivity situations. In contrast, we would  
49  
50  
51 365 expect almost all of the numerator population (hospitalised patients with severe  
52  
53  
54 366 symptoms) would have been positively diagnosed. Thus, the estimated incidence of  
55  
56  
57 367 hospitalisation amongst influenza-positive patients may have been overestimated.  
58  
59  
60

1  
2  
3  
4  
5  
6 368 Second, the administrative data from employees and their families used here do  
7  
8  
9 369 not permit analysis of patients aged 75 years or more. Also, due to employment patterns  
10  
11  
12 370 in Japan, the number of male patients was slightly higher than female patients (table 1).  
13  
14  
15 371 The sex ratio varies across generations in Japan, with more males in younger populations  
16  
17  
18 372 and women predominating in older populations.[62] However, the incidence of  
19  
20  
21 373 hospitalisation amongst infected patients in both sexes and the studied age groups should  
22  
23  
24 374 not be biased by this imbalance. Third, we were unable to estimate influenza-related  
25  
26  
27 375 mortality in this data set, but the data are sufficient to allow examination of serious  
28  
29  
30 376 complications that are major public health concerns. Although we were unable to define  
31  
32  
33 377 encephalitis/encephalopathy cases virologically, we added the requirement of receiving  
34  
35  
36 378 specific therapy to the definition of encephalitis/encephalopathy cases.[37] This more  
37  
38  
39 379 stringent definition reduces the likelihood that we have overestimated this outcome.  
40  
41  
42 380 Further analyses of influenza-related mortality in Japan are needed, and this should  
43  
44  
45 381 encompass older adults. The effect of neuraminidase inhibitors should be examined using  
46  
47  
48 382 observational data, as clinical trials are likely to be underpowered for rare but important  
49  
50  
51 383 complications such as encephalopathy.

52  
53  
54  
55 384 **Conclusions**  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6 385 Using Japanese administrative data, 1.0% of patients who tested positive for influenza  
7  
8  
9 386 infection were hospitalised. Male patients had a higher incidence of pulmonary  
10  
11  
12 387 complications and febrile seizures. Children aged 0–5 years and adults aged 65–74  
13  
14  
15 388 years were at high risk of being admitted to hospital for pneumonia, with the highest  
16  
17  
18 389 absolute numbers of hospitalised patients among young children. Further efforts are  
19  
20  
21 390 needed, such as active prescription of neuraminidase inhibitors and vaccination  
22  
23  
24 391 programs, to prevent hospitalisations from severe complications in these age groups.  
25  
26  
27

28 392 **(3849 words)**  
29  
30  
31  
32  
33 393

34  
35 394 **Acknowledgements** The authors are immensely grateful to the Japan Medical Data  
36  
37  
38 395 Center for providing the administrative data. We thank Ms. Analisa Avila, ELS, of  
39  
40  
41 396 Edanz Group for editing a draft of this manuscript.  
42  
43

44 397 **Authors' contributions** All of the authors agreed with the manuscript's results and  
45  
46  
47 398 conclusion and approved the final version of the manuscript. HY conceived the study.  
48  
49  
50 399 HY, MM, JL, RK, TY and ZY contributed to the design of the study and interpretation  
51  
52  
53 400 of the data analyses. HY analysed the data. HY, JL, MM and RK wrote the first draft of  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6 401 the manuscript. JL, RK, MM, ZY and HY contributed to revision of the manuscript. ZY

7  
8  
9 402 and HY were responsible for data integrity. HY obtained funding.

10  
11  
12 403 **Funding** This work was supported by funding from the Ministry of Education, Culture,

13  
14  
15 404 Sports, Science, and Technology (MEXT) (KAKENHI grant numbers JP15K08730 and

16  
17  
18 405 JP18K17376).

19  
20  
21 406 **Competing interests.** None.

22  
23  
24 407 **Patient consent** Not required.

25  
26  
27 408 **Ethics approval** The ethics committee of the School of Medicine, University of

28  
29  
30 409 Yamanashi approved this study (approval number: H29-1709).

31  
32  
33 410 **Data sharing statement** The original administrative data are available through a formal

34  
35  
36 411 request to the Japan Medical Data Center Ltd., subject to fees.

37  
38  
39 412

413 **References**

- 414 1. Ghebrehewet S, MacPherson P, Ho A. Influenza. *BMJ* 2016;355:i6258.
- 415 2. Kaiser L, Wat C, Mills T, *et al.* Impact of oseltamivir treatment on influenza-related  
416 lower respiratory tract complications and hospitalisations. *Arch Intern Med*  
417 2003;163:1667–72.
- 418 3. Iuliano AD, Roguski KM, Chang HH, *et al.* Estimates of global seasonal influenza-  
419 associated respiratory mortality: a modelling study. *Lancet* 2017;391:1285–1300.
- 420 4. Thompson WW, Shay DK, Weintraub E, *et al.* Influenza-associated hospitalizations  
421 in the United States. *JAMA* 2004;292:1333–40.
- 422 5. Newland JG, Laurich VM, Rosenquist AW, *et al.* Neurologic complications in  
423 children hospitalized with influenza: characteristics, incidence, and risk factors. *J*  
424 *Pediatr* 2006;150:306–10.
- 425 6. Sugaya N, Shinjoh M, Mitamura K, *et al.* Very low pandemic influenza A (H1N1)  
426 2009 mortality associated with early neuraminidase inhibitor treatment in Japan:  
427 analysis of 1000 hospitalized children. *J Infect* 2011;63:288–94.

- 1  
2  
3  
4  
5  
6  
7 428 7. Influenza Working Group of the Japan Pediatric Society. Secondary treatment  
8  
9  
10 429 guideline of 2013/2014 influenza infection. 2014. Japanese.  
11  
12 430 [https://www.jpeds.or.jp/uploads/files/2013\\_2014\\_influenza\\_all.pdf](https://www.jpeds.or.jp/uploads/files/2013_2014_influenza_all.pdf). Accessed 1  
13  
14  
15 431 December 2018.  
16  
17  
18  
19 432 8. Cromer D, van Hoek AJ, Jit M, *et al*. The burden of influenza in England by age and  
20  
21  
22 433 clinical risk group: a statistical analysis to inform vaccine policy. *J Infect*  
23  
24  
25 434 2014;68:363–71.  
26  
27  
28  
29 435 9. Louie JK, Acosta M, Winter K, *et al*. Factors associated with death or hospitalization  
30  
31  
32 436 due to pandemic 2009 influenza A (H1N1) infection in California. *JAMA*  
33  
34  
35 437 2009;302:1896–902.  
36  
37  
38  
39 438 10. Nicholson KG, McNally T, Silverman M, *et al*. Rates of hospitalisation for  
40  
41  
42 439 influenza, respiratory syncytial virus and human metapneumovirus among infants  
43  
44  
45 440 and young children. *Vaccine* 2006;24:102–08.  
46  
47  
48  
49 441 11. Pitman R, Melegaro A, Gelb D, *et al*. Assessing the burden of influenza and other  
50  
51  
52 442 respiratory infections in England and Wales. *J Infect* 2007;54:530–38.  
53  
54  
55  
56 443 12. Mertz D, Kim TH, Johnstone J, *et al*. Populations at risk for severe or complicated  
57  
58  
59  
60

- 1  
2  
3  
4  
5  
6 444 influenza illness: systematic review and meta-analysis. *BMJ* 2013;347:f5061.  
7  
8  
9  
10  
11 445 13. Sugaya N. Widespread use of neuraminidase inhibitors in Japan. *J Infect Chemother*  
12  
13 446 2011;17:595.  
14  
15  
16  
17 447 14. Amin R, Ford-Jones E, Richardson SE, *et al.* Acute childhood encephalitis and  
18  
19  
20 448 encephalopathy associated with influenza: a prospective 11-year review. *Pediatr*  
21  
22  
23 449 *Infect Dis J* 2008;27:390–95.  
24  
25  
26  
27  
28 450 15. Ekstrand JJ, Herbener A, Rawlings J, *et al.* Heightened neurologic complications in  
29  
30  
31 451 children with pandemic H1N1 influenza. *Ann Neurol* 2010;68:762–66.  
32  
33  
34  
35 452 16. Evans A, Agadi S, Siegel J, *et al.* Neurologic complications associated with novel  
36  
37  
38 453 influenza A (H1N1) virus infection in children-Dallas, Texas, May 2009. *MMWR-*  
39  
40  
41 454 *Morb. Mortal. Wkly. Rep* 2009;58:773–78.  
42  
43  
44  
45 455 17. Rellosa N, Bloch KC, Shane AL, *et al.* Neurologic manifestations of pediatric novel  
46  
47  
48 456 H1N1 influenza infection. *Pediatr Infect Dis J* 2011;30:165–67.  
49  
50  
51  
52 457 18. Baltagi SA, Shoykhet M, Felmet K, *et al.* Neurological sequelae of 2009 influenza  
53  
54  
55 458 A (H1N1) in children: a case series observed during a pandemic. *Pediatr Crit Care*  
56  
57  
58 459 *Med* 2010;11:179–84.  
59  
60

- 1  
2  
3  
4  
5  
6 460 19. Kasai T, Togashi T, Morishima T. Encephalopathy associated with influenza  
7  
8  
9 461 epidemics. *Lancet* 2000;355:1558–59.  
10  
11  
12  
13 462 20. Morishima T, Togashi T, Yokota S, *et al.* Encephalitis and encephalopathy  
14  
15  
16 463 associated with an influenza epidemic in Japan. *Clin Infect Dis* 2002;35:512–17.  
17  
18  
19  
20  
21 464 21. Sugaya N. Influenza-associated encephalopathy in Japan. *Semin Pediatr Infect Dis*  
22  
23 465 2002;13:79–84.  
24  
25  
26  
27  
28 466 22. Akihisa O, Satoshi N, Hisashi K, *et al.* Deaths associated with pandemic (H1N1)  
29  
30  
31 467 2009 among children, Japan, 2009–2010. *Emerg Infect Dis J* 2011;17:1993–2000.  
32  
33  
34  
35 468 23. Zaraket H, Saito R. Japanese surveillance systems and treatment for influenza. *Curr*  
36  
37 469 *Treat Options Infect Dis* 2016;8:311–28.  
38  
39  
40  
41  
42 470 24. Wang GF, Li W, Li K. Acute encephalopathy and encephalitis caused by influenza  
43  
44 471 virus infection. *Curr Opin Neurol* 2010;23:305–11.  
45  
46  
47  
48  
49 472 25. Hoshino A, Saitoh M, Oka A, *et al.* Epidemiology of acute encephalopathy in Japan,  
50  
51 473 with emphasis on the association of viruses and syndromes. *Brain Dev* 2012;34:337–  
52  
53 474 43.  
54  
55  
56  
57  
58  
59  
60



- 1  
2  
3  
4  
5  
6 475 26. Gu Y, Shimada T, Yasui Y, *et al.* National surveillance of influenza-associated  
7  
8  
9 476 encephalopathy in Japan over six years, before and during the 2009–2010 influenza  
10  
11  
12 477 pandemic. *Plos One* 2013;8:e54786.  
13  
14  
15  
16 478 27. Okumura A, Nakagawa S, Kawashima H, *et al.* Deaths associated with pandemic  
17  
18  
19 479 (H1N1) 2009 among children, Japan, 2009–2010. *Emerg Infect Dis* 2011;17:1993–  
20  
21  
22 480 2000.  
23  
24  
25  
26 481 28. National Institute of Infectious Diseases and Ministry of Health, Labour and Welfare.  
27  
28  
29 482 Infectious agents surveillance report 36. 2015. Japanese. Available at  
30  
31  
32 483 <https://www0.niid.go.jp/niid/idsc/iasr/36/429j.pdf>. Accessed 1 December 2018.  
33  
34  
35  
36 484 29. Mizuguchi M. Influenza encephalopathy and related neuropsychiatric syndromes.  
37  
38  
39 485 *Influenza Other Resp* 2013;7:67–71.  
40  
41  
42  
43  
44 486 30. Tanaka S, Seto K, Kawakami K. Pharmacoepidemiology in Japan: medical  
45  
46  
47 487 databases and research achievements. *J Pharm Health Care Sci* 2015;1:16.  
48  
49  
50  
51 488 31. Uehara S, Sunakawa K, Eguchi H, *et al.* Japanese guidelines for the management of  
52  
53  
54 489 respiratory infectious diseases in children 2007 with focus on pneumonia. *Pediatr Int*  
55  
56  
57 490 2011;53:264–76.  
58  
59  
60

- 1  
2  
3  
4  
5  
6  
7 491 32. Ito M, Watanabe M, Nakagawa N, *et al.* Rapid detection and typing of influenza A  
8  
9 492 and B by loop-mediated isothermal amplification: comparison with  
10  
11  
12 493 immunochromatography and virus isolation. *J Virol Methods* 2006;135:272–75.  
13  
14  
15  
16 494 33. Sugaya N, Mitamura K, Yamazaki M, *et al.* Lower clinical effectiveness of  
17  
18  
19 495 oseltamivir against influenza B contrasted with influenza A infection in children. *Clin*  
20  
21  
22 496 *Infect Dis* 2007;44:197–202.  
23  
24  
25  
26 497 34. Suzuki M, Yoshimine H, Harada Y, *et al.* Estimating the influenza vaccine  
27  
28  
29 498 effectiveness against medically attended influenza in clinical settings: a hospital-  
30  
31  
32 499 based case-control study with a rapid diagnostic test in Japan. *Plos One*  
33  
34  
35 500 2013;8:e52103.  
36  
37  
38  
39 501 35. Watanabe M, Nakagawa N, Ito M, *et al.* Sensitivity of rapid immunoassay for  
40  
41  
42 502 influenza A and B in the early phase of the disease. *Pediatr Int* 2009;51:211–15.  
43  
44  
45  
46 503 36. Komiya N, Gu Y, Kamiya H, *et al.* Clinical features of cases of influenza A (H1N1)  
47  
48  
49 504 v in Osaka prefecture, Japan, May 2009. *Eurosurveillance* 2009;14:19272.  
50  
51  
52  
53  
54 505 37. Study Group of Influenza Encephalitis. Ministry of Health, Labour and Welfare.  
55  
56  
57 506 Guideline of treatment for influenza encephalitis. revised edition. 2011. Japanese.  
58  
59  
60

- 1  
2  
3  
4  
5  
6 507 <https://www.mhlw.go.jp/kinkyu/kenkou/influenza/hourei/2009/09/dl/info0925->  
7  
8  
9 508 01.pdf. Accessed 1 December 2018.  
10  
11  
12  
13 509 38. Kumar S, Havens PL, Chusid MJ, *et al.* Clinical and epidemiologic characteristics  
14  
15  
16 510 of children hospitalized with 2009 pandemic H1N1 influenza A infection. *Pediatr*  
17  
18  
19 511 *Infect Dis J* 2010;29:591–94.  
20  
21  
22  
23 512 39. O’Riordan S, Barton M, Yau Y, *et al.* Risk factors and outcomes among children  
24  
25  
26 513 admitted to hospital with pandemic H1N1 influenza. *Can Med Assoc J* 2010;182:39–  
27  
28  
29 514 44.  
30  
31  
32  
33 515 40. Lee JJ, Bankhead C, Smith M, *et al.* Risk factors for influenza-related complications  
34  
35  
36 516 in children during the 2009/10 pandemic: a UK primary care cohort study using  
37  
38  
39 517 linked routinely collected data. *Epidemiol Infect* 2018:1–7.  
40  
41  
42  
43 518 41. Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and  
44  
45  
46 519 wheezing illness from early childhood to age 33 in a national British cohort. *BMJ*  
47  
48  
49 520 1996;312:1195–99.  
50  
51  
52  
53 521 42. Tsuboi T. Epidemiology of febrile and afebrile convulsions in children in Japan.  
54  
55  
56 522 *Neurology* 1984;34:175–75.  
57  
58  
59  
60

- 1  
2  
3  
4  
5  
6 523 43. Talbot HK, Zhu Y, Chen Q, *et al.* Effectiveness of influenza vaccine for preventing  
7  
8  
9 524 laboratory-confirmed influenza hospitalizations in adults, 2011–2012 influenza  
10  
11  
12 525 season. *Clin Infect Dis* 2013;56:1774–77.  
13  
14  
15  
16 526 44. Yokomichi H, Kurihara S, Yokoyama T, *et al.* The pandemic influenza A (H1N1)  
17  
18  
19 527 2009 vaccine does not increase the mortality rate of idiopathic interstitial pneumonia:  
20  
21  
22 528 a matched case-control study. *Plos One* 2014;9:e88927.  
23  
24  
25  
26 529 45. Yokomichi H, Kurihara S, Yokoyama T, *et al.* Safety of the influenza A  
27  
28  
29 530 (H1N1)2009 vaccine in chronic obstructive pulmonary disease: a matched case-  
30  
31  
32 531 control study. *J Vaccines Vaccination* 2012;3:1000148.  
33  
34  
35  
36 532 46. Reichert TA, Sugaya N, Fedson DS, *et al.* The Japanese experience with vaccinating  
37  
38  
39 533 schoolchildren against influenza. *N Engl J Med* 2001;344:889–96.  
40  
41  
42  
43 534 47. World Health Organization. Rapid advice guidelines for pharmacological  
44  
45  
46 535 management of pandemic influenza (H1N1) 2009 and other influenza viruses. 2010.  
47  
48  
49 536 Available at  
50  
51  
52 537 [http://www.who.int/csr/resources/publications/swineflu/h1n1\\_guidelines\\_pharmaceu](http://www.who.int/csr/resources/publications/swineflu/h1n1_guidelines_pharmaceu)  
53  
54  
55 538 [tical\\_mngt.pdf](http://www.who.int/csr/resources/publications/swineflu/h1n1_guidelines_pharmaceutical_mngt.pdf). Accessed 1 December 2018.  
56  
57  
58  
59  
60

- 1  
2  
3  
4  
5  
6 539 48. Centers for Disease Control and Prevention. Updated interim recommendations for  
7  
8  
9 540 the use of antiviral medications in the treatment and prevention of influenza for the  
10  
11  
12 541 2009–2010 season. Available at <https://www.cdc.gov/h1n1flu/recommendations.htm>.  
13  
14  
15 542 Accessed 1 December 2018.  
16  
17  
18  
19 543 49. Muthuri SG, Myles PR, Venkatesan S, *et al*. Impact of neuraminidase inhibitor  
20  
21  
22 544 treatment on outcomes of public health importance during the 2009–2010 influenza  
23  
24  
25 545 A (H1N1) pandemic: a systematic review and meta-analysis in hospitalized patients.  
26  
27  
28 546 *J Infect Dis* 2012;207:553–63.  
29  
30  
31  
32 547 50. Jefferson T, Jones MA, Doshi P, *et al*. Neuraminidase inhibitors for preventing and  
33  
34  
35 548 treating influenza in healthy adults and children. *Cochrane Database Syst Rev*  
36  
37  
38 549 2012;1 Art:CD008965.  
39  
40  
41  
42 550 51. Pebody R, Warburton F, Andrews N, *et al*. Effectiveness of seasonal influenza  
43  
44  
45 551 vaccine in preventing laboratory-confirmed influenza in primary care in the United  
46  
47  
48 552 Kingdom: 2014/15 end of season results. *Eurosurveillance* 2015;20:30013.  
49  
50  
51  
52 553 52. Dobson J, Whitley RJ, Pocock S, *et al*. Oseltamivir treatment for influenza in adults:  
53  
54  
55 554 a meta-analysis of randomised controlled trials. *Lancet* 2015;385:1729–37.  
56  
57  
58  
59  
60

- 1  
2  
3  
4  
5  
6 555 53. Hirota Y, Kaji M. History of influenza vaccination programs in Japan. *Vaccine*  
7  
8  
9 556 2008;26:6451–54.  
10  
11  
12  
13 557 54. Charu V, Viboud C, Simonsen L, *et al.* Influenza-related mortality trends in  
14  
15  
16 558 Japanese and American seniors: evidence for the indirect mortality benefits of  
17  
18  
19 559 vaccinating schoolchildren. *Plos One* 2011;6:e26282.  
20  
21  
22  
23 560 55. Hayward AC, Fragaszy EB, Bermingham A, *et al.* Comparative community burden  
24  
25  
26 561 and severity of seasonal and pandemic influenza: results of the Flu Watch cohort  
27  
28  
29 562 study. *Lancet Resp Med* 2014;2:445–54.  
30  
31  
32  
33 563 56. Paules C, Subbarao K. Influenza. *Lancet* 2017;390:697–708.  
34  
35  
36  
37  
38 564 57. Poehling KA, Zhu Y, Tang Y-W, *et al.* Accuracy and impact of a point-of-care rapid  
39  
40  
41 565 influenza test in young children with respiratory illnesses. *Arch Pediatr Adolescent*  
42  
43  
44 566 *Med* 2006;160:713–18.  
45  
46  
47  
48 567 58. Sakai-Tagawa Y, Ozawa M, Tamura D, *et al.* Sensitivity of influenza rapid  
49  
50  
51 568 diagnostic tests to H5N1 and 2009 pandemic H1N1 viruses. *J Clin Microbiol*  
52  
53  
54 569 2010;48:2872–77.  
55  
56  
57  
58 570 59. Hata A, Asada J, Mizumoto H, *et al.* Appropriate use of rapid diagnostic testing for  
59  
60

- 1  
2  
3  
4  
5  
6 571 influenza. *J Jpn Assoc Infect Dis* 2004;78:846-52.  
7  
8  
9  
10 572 60. Landry ML. Diagnostic tests for influenza infection. *Curr Opin Pediatr*  
11  
12  
13 573 2011;23:91–97.  
14  
15  
16  
17 574 61. Chartrand C, Leeflang MM, Minion J, *et al*. Accuracy of rapid influenza diagnostic  
18  
19  
20 575 tests: a meta-analysis. *Ann Intern Med* 2012;156:500–11.  
21  
22  
23  
24 576 62. Central Intelligence Agency. The world factbook: sex ratio (male/female). 2018.  
25  
26  
27 577 Available at <https://www.cia.gov/library/publications/the-world->  
28  
29  
30 578 [factbook/fields/2018.html](https://www.cia.gov/library/publications/the-world-factbook/fields/2018.html). Accessed 1 December 2018.  
31  
32  
33  
34  
35 579  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6 **580 Figure legends**  
7

8  
9 581

10  
11  
12 582 Figure 1. Histogram of the ages of influenza-infected outpatients in the 2012/13, 2013/14,  
13  
14  
15 583 2014/15, and 2015/16 seasons, according to health insurance administrative data.  
16  
17

18 584

19  
20  
21 585 Figure 2. Histogram of the ages of influenza-infected inpatients in the 2012/13, 2013/14,  
22  
23  
24 586 2014/15, and 2015/16 seasons, according to health insurance administrative data.  
25  
26

27 587

28  
29  
30 588 Figure 3. Number of influenza-infected inpatients with severe complications and  
31  
32  
33 589 proportion of infections and hospitalisation in a health insurance claim database, by age  
34  
35  
36 590 group, between 2012 and 2016.

37  
38  
39 591 Bars represent the number of each severe complication; the line represents the proportion of infections  
40  
41  
42 592 resulting in hospitalisation in each age group. Abbreviation: ARDS, acute respiratory distress syndrome.  
43  
44

45 593

46  
47  
48 594 Figure 4. Number of influenza-infected inpatients with severe complications and  
49  
50  
51 595 proportion of infection and hospitalisation in a health insurance claim database, by age,  
52  
53  
54 596 between 2012 and 2016.  
55  
56  
57  
58  
59  
60



1  
2  
3  
4  
5  
6 597 Bars represent the number of each severe complication; the line represents the proportion of infections

7  
8  
9 598 with hospitalisation. Abbreviation: ARDS, acute respiratory distress syndrome.

10  
11  
12 599

13  
14  
15 600 Figure 5. Number of influenza-infected inpatients and proportion of hospitalisation in

16  
17  
18 601 health insurance claim database between 2012 and 2016.

19  
20  
21 602 Black line represents number of inpatients; red line proportion of infections hospitalised.

22  
23  
24 603

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

Sex, n (%)	Men	Women							
	8885699 (53.4)	7751214 (46.6)							
Patient status, n (%)	Outpatient	Inpatient							
	16488970 (99.0)	164394 (1.0)							
Age, years	0–1	2–5	6–12	13–18	19–44	45–64	65–74		
n (%)	823875 (5.1)	2886462 (17.7)	4193137 (25.7)	1480030 (9.1)	3815970 (23.4)	2872125 (17.6)	2311214 (1.4)		
No. of hospital beds	0–19	20–99	100–199	200–299	300–499	500+			
No. patients (%)	13572391 (83.3)	392179 (2.4)	450850 (2.8)	324418 (2.0)	616989 (3.8)	945892 (5.8)			
Clinical department of diagnosis	Internal medicine	Paediatrics	Otorhinola ryngology	Orthopaedi cs	Dermatolo gy	Surgery	Ophthalmol ogy	Obstetrics &	Psychiatry

								Gynaecol	
								ogy	
	No. patients	1187638	827942	310514	308146	250737	206763	156615	99624
	(%)	(32.4)	(22.6)	(8.5)	(8.4)	(6.8)	(5.6)	(4.3)	(2.7)

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

606  
607  
608

For peer review only

/bmjopen-2018-024687 on 17 January 2019. Downloaded from <http://bmjopen.bmj.com/> on July 7, 2023 by guest. Protected by copyright.

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 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.

Table 3. Incidence of hospitalisation with severe complications per 100000 confirmed influenza infections.

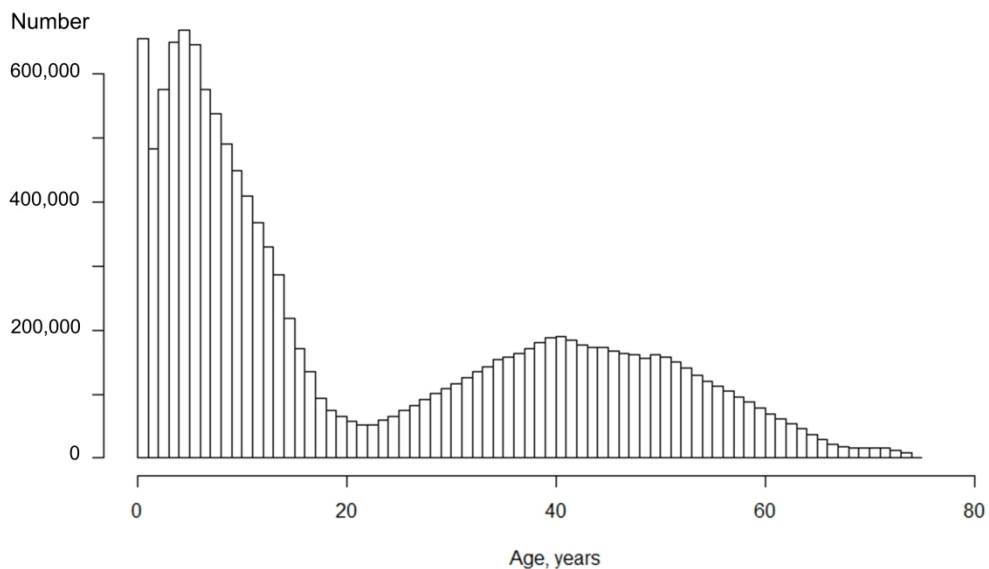
No. of inpatients per 100,000 influenza infections	Hospitalisation	Any of five complications	Acute respiratory failure	Pneumonia	ARDS	Febrile seizure	Encephalitis/encephalopathy
Sex*	p<0.0001	p<0.0001	p<0.0001	p<0.0001	p=0.08	p<0.0001	p=0.08
Male (n=8885794)	970	191	22.2	171	0.15	17.8	0.8
Female (n=7751279)	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.

### Histogram of ages of influenza-infected outpatients

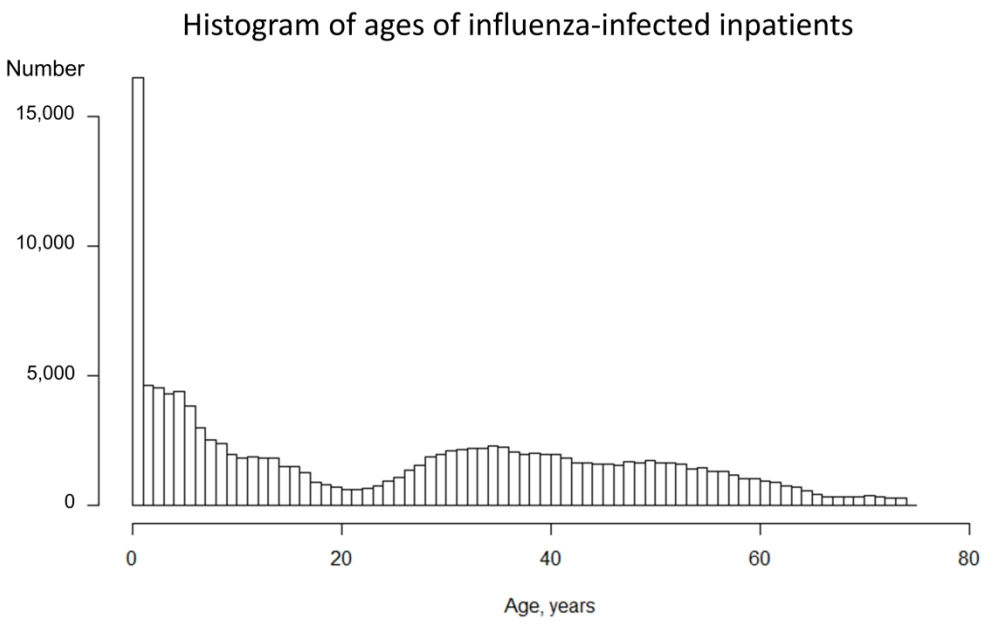


Histogram of the ages of influenza-infected outpatients in the 2012/13, 2013/14, 2014/15, and 2015/16 seasons, according to health insurance administrative data.

284x189mm (300 x 300 DPI)

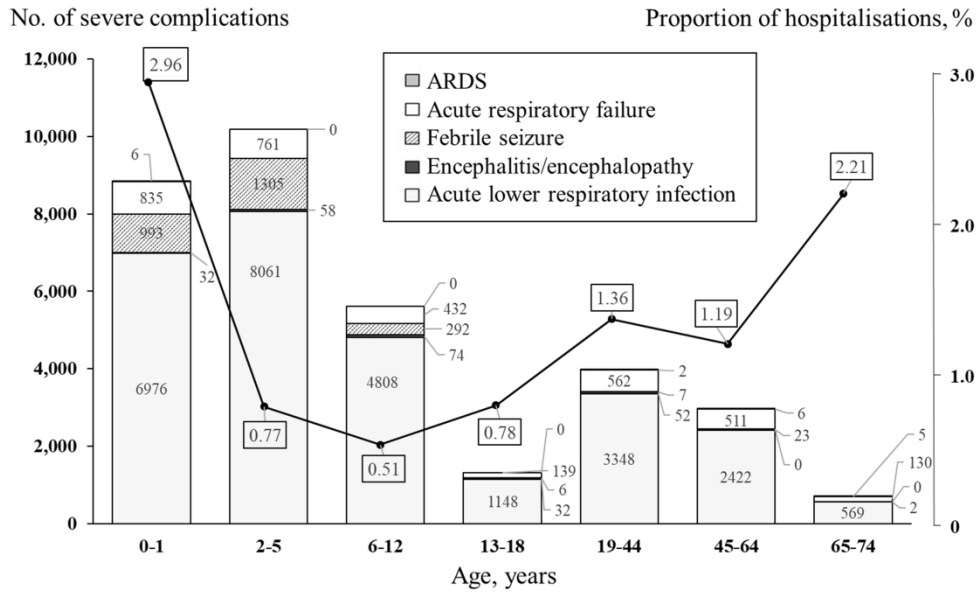


1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



Histogram of the ages of influenza-infected inpatients in the 2012/13, 2013/14, 2014/15, and 2015/16 seasons, according to health insurance administrative data.

277x181mm (300 x 300 DPI)



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.

267x167mm (300 x 300 DPI)

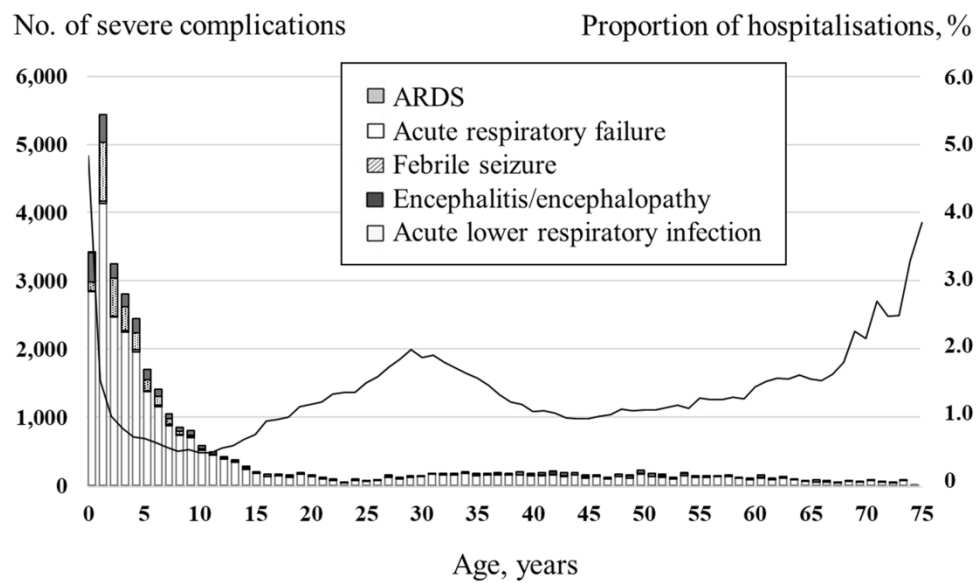
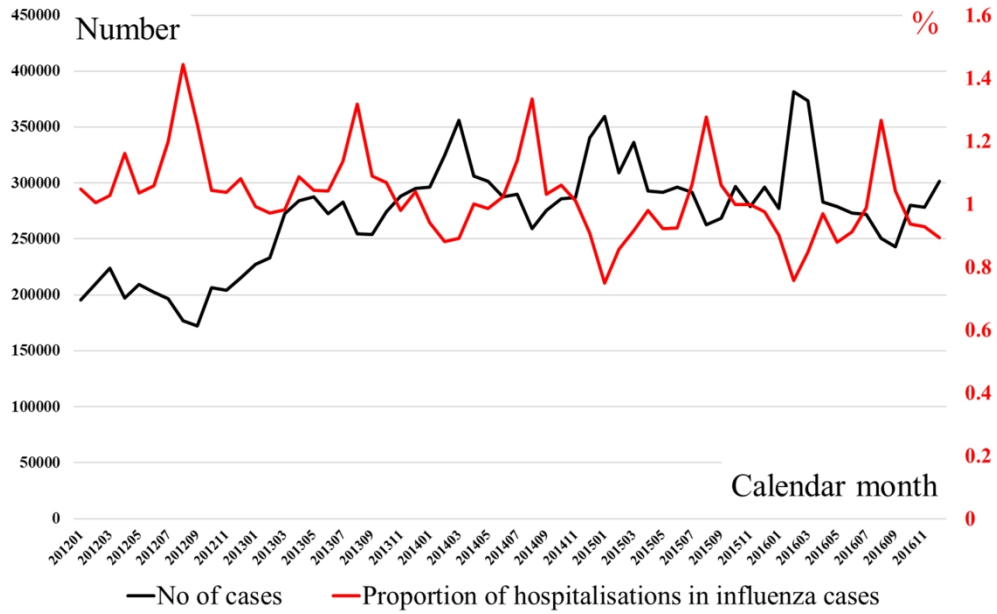


Figure 4. Number of influenza-infected inpatients with severe complications and proportion of infection and hospitalisation in a health insurance claim database, by age, between 2012 and 2016. Bars represent the number of each severe complication; the line represents the proportion of infections with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

258x156mm (300 x 300 DPI)



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.

539x340mm (300 x 300 DPI)

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies***

Section/Topic	Item #	Recommendation	Reported on page #
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3–4
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6–8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	9–10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10–11
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9–10
Bias	9	Describe any efforts to address potential sources of bias	9–11
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10–11
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	11–12
		(b) Describe any methods used to examine subgroups and interactions	10–11
		(c) Explain how missing data were addressed	9
		(d) If applicable, describe analytical methods taking account of sampling strategy	9
		(e) Describe any sensitivity analyses	Figures 3 and 4
<b>Results</b>			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13–14
		(b) Give reasons for non-participation at each stage	Not Applicable
		(c) Consider use of a flow diagram	Not Applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Not Applicable
Outcome data	15*	Report numbers of outcome events or summary measures	Table 2
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3 and figures 3–4
		(b) Report category boundaries when continuous variables were categorized	Table 3 and figures 3–4
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not Applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 3 and figures 3–4
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	22–24
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16–24
Generalisability	21	Discuss the generalisability (external validity) of the study results	24
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	26

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).