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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

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Abstract

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

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

Setting: Japanese clinics and hospitals between 2012 and 2016.

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

Primary outcome measures: Incidence of hospitalisation.

Results: We included over 16 million patients diagnosed with a rapid test, 1.0% of whom were hospitalised. Of these, 3361 had acute respiratory failure, 27253 pneumonias, 18 ARDS, 2603 febrile seizures and 159 encephalitis/encephalopathy. The percentage of hospitalisations by age was 2.96% of patients aged 0–1 years; 0.77% aged 2–5; 0.51% aged 6–12; 0.78% aged 13–18; 1.36% aged 19–44; 1.19% aged 45–64; and 2.21% aged 65–74. The incidence of hospitalisations from these five complications

combined was highest in patients aged 0–1 years (94.3 per 10000) compared with 30.7 in those aged 2–5 years and 27.1 in those aged 65–74 years. For pneumonia, incidence was highest for patients aged 0–5 years and 65 years or more. There were statistically significant decreasing trends over the years in the incidence of hospitalisations from pneumonia and febrile seizures.

Conclusions: Japanese administrative data revealed that 1.0% of patients aged under 75 years who tested positive for influenza infection were hospitalised. Male patients had a higher incidence of pulmonary complications and febrile seizures. Children aged 0–5 years and adults aged 65–74 years were at high risk of being admitted to hospital for pneumonia.

Registration: The ethics committee of the School of Medicine, University of Yamanashi approved this study (approval number: H29-1709).

(294 words/300 words)

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.

INTRODUCTION

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

Complications of influenza which cause hospitalisations are a serious public health concern. Reasons for hospital admission include pneumonia, febrile seizure, acute respiratory failure, acute respiratory distress syndrome (ARDS) and encephalitis/encephalopathy.[4 5] We refer to these as 'severe complications'. Hospitalisation rates from influenza infection have been investigated,[4 6] but most studies were conducted in Western countries where testing for influenza is not routine. This means that studies have used either limited sample sizes of positively identified individual hospitalised patients, or extrapolated from influenza surveillance data.[6-8] Hospital-based studies may be underestimating the risk and the number of infections and complications in the community.[9] Previous studies have used estimates of the general population as denominators, rather than assessing the risk of admission amongst the infected population, combing the risk of infection and the risk of complications.

This is problematic because programmes targeting high risk groups, such as vaccination or prophylaxis may reduce the number of infections in high risk groups, biasing estimates of the risk of complications if infected.[9] Also, many studies pre-date the option of administering new neuraminidase inhibitors.[10]

Although it is also seen internationally, influenza encephalitis is a particular concern in Japan owing to a high mortality rate.[11] The prognosis for patients with influenza encephalitis/encephalopathy is very poor; approximately 30% of affected patients die and 20–30% have neurological sequelae.[12] To understand the aetiology and prevalence of this severe outcome, surveillance has been conducted.[13 14] In Japan, influenza-associated encephalopathy is a notifiable disease.[15] Japanese physicians are required to report influenza infection cases with: a) death after coma or hospitalisation with coma for 24 hours or more; and b) a fever of 38°C or higher, central nervous system manifestation or prior influenza infection symptom. This surveillance system has detected 60–100 influenza encephalitis cases annually [16] and 331 cases during the 2009–2010 pandemic;[13] however, underreporting of cases has been acknowledged.[16] Another survey of paediatric departments in 265 hospitals reported 263 influenza-associated encephalopathy cases over 3 years.[14] The authors estimate that there would be 200–300 influenza encephalopathy cases per annum in Japan;[17]

therefore, the incidence of influenza encephalitis/encephalopathy is not accurately known.

To understand the incidence of severe complications in patients with influenza, an analysis of large-scale real-world data is needed, encompassing hospital and community sites. Previous studies using large data sets of routinely collected medical records have had to rely on clinical diagnoses of influenza-like illness or modelling of influenza and other respiratory virus infections using incomplete laboratory data.[7] In Japan, diagnostic testing for influenza is routine, which presents a unique opportunity to combine the benefits of large data sets with positive diagnoses.[18] We therefore sought to estimate the incidence of hospitalisation with one or more of the above five severe complications amongst diagnosed with influenza infection, using Japanese health insurance claim data.

METHODS

Patients and data

We analysed administrative data provided by Japan Medical Data Center Ltd. Tokyo,

Japan.[19] The data comprised the monthly health insurance claim records between January 2012 and December 2016 of approximately three million employees and their families, representing 2.4% of the Japanese population. Within health insurance coverage in Japan, people can consult physicians in any type of hospital and department, and medical doctors in any speciality can diagnose influenza and prescribe anti-influenza medications. The age of patients in the data set ranged from 0 to 74 years because all Japanese people aged 75 or more (except for individuals who are on public assistance) are covered by another health insurance program with lower out-of-pocket expenses.

We extracted the data of outpatients and inpatients who consulted physicians with influenza-like illness and were diagnosed with influenza virus infections. In Japan, a test-and-treat strategy is routine. Even if physicians only slightly suspect influenza infection from clinical features, they use an immunochromatogenic assay point-of-care test [POCT] to diagnose influenza, and then administer antivirals to the patient.[20] Therefore, almost all diagnoses in the data were based upon positive results of a POCT.[10 18]

Outcomes

In our population of patients with a diagnosis of influenza infection, we identified those who were hospitalised with a diagnosis of acute respiratory failure, pneumonia, ARDS, febrile seizure, and encephalitis/encephalopathy, according to International Classification of Diseases (ICD-10) codes. In the data, acute respiratory failure was coded as J960, J988, R060, R068 or R092; pneumonia was coded as J10–J18 or J20–J22, acute respiratory distress syndrome (ARDS) as J80, and febrile seizure as R560. We defined influenza encephalitis/encephalopathy in patients who were diagnosed using ICD-10 codes for influenza infection and encephalitis/encephalopathy (G00–G09 or G41) and had been administered steroid pulse or immunoglobulin therapy.[21]

Statistical analysis

We collected data for the number of consultations and severe complications according to sex, age, outpatient/inpatient status, number of beds in the facility, and clinical speciality. In Japan, clinical facilities with fewer than 20 beds are denoted a "clinic" by law. Clinics are usually run by a single medical doctor and function as a primary care department. Most clinics have no beds but a subset of clinics have 1–19 beds to accommodate inpatients. In contrast, facilities with 20 beds or more are legally termed a "hospital". Hospitals have primary care, specialised outpatient, and general and

specialised inpatient departments. We plotted histograms of the ages of outpatients and inpatients infected with influenza. Additionally, we determined the number of inpatients with the five severe complications and the proportion of hospitalisations, by age group and age. The primary outcomes were incidence of each of the five complications per 10000 influenza infections. We examined this by sex, influenza season and age. Influenza seasons were defined as lasting from September through to the following August. We calculated p values for secular trends of the incidence over influenza seasons. Statistical analyses were performed using SAS statistical software (version 9.4, SAS Institute, Cary, NC, USA). All reported p values were two-sided and we considered $p<0.05$ indicated a significant difference.

Patient and public involvement

The ethics committee of the School of Medicine, University of Yamanashi approved this study (approval number: H29-1709), in accordance with the ethical guidelines and regulations of the Declaration of Helsinki. The data were properly anonymised by the Japan Medical Data Center in the manner permitted by Japanese guideline of Personal Information Protection Commission, Cabinet Office, Government of Japan for the use of data from medical examinations in medical research without individual participants'

consent (Act on the Protection of Personal Information, act no. 57 of 30 May 2003; last version amendment of act no. 65 of 2015).

RESULTS

Characteristics of patients diagnosed with influenza

Table 1 summarises the number of patients infected with influenza in the study population. Among 16636913 infections, 53.4% of the patients were men, and 1.0% were hospitalised. Approximately a quarter (25.7%) of infections were in children aged 6–12 years. Overall 32% of diagnoses were made in the internal medicine department and 23% in paediatrics. Most infections were diagnosed in clinics (n=13572391; 83%). Figures 1 and 2 illustrate the number of outpatients and inpatients with influenza infection, respectively, by age. Influenza was most often diagnosed in outpatients aged 0–12 years, with a second small peak in middle-aged patients. In contrast, inpatient cases were commonest among patients aged less than one year. Table 2 shows the number of complicated cases by department, hospital size and type of hospital management. A total of 3361 patients (0.02%) were admitted to hospital with acute respiratory failure, 27253 (0.16%) with pneumonia, 18 (0.0001%) with ARDS, 2603

(0.02%) with febrile seizures, and 159 (0.001%) with encephalitis/encephalopathy. Most complicated cases were admitted to paediatric departments, with 19012 pneumonia admissions (70% of the total), 1794 with acute respiratory failure (53% of the total), 2461 with febrile seizures (95% of the total), and 63 encephalitis (40% of all cases). The number of inpatients with acute respiratory failure, pneumonia, and febrile seizure tended to increase with the number of hospital beds.

Hospitalisation rates from severe complications

The combined incidence of these five complications was 18.9 per 10000 diagnosed infections. Pneumonia was the commonest complication, with 16.4 per 10000 diagnosed infections, followed by acute respiratory failure (2.0), febrile seizures (1.6), encephalitis/encephalopathy (0.1), and ARDS (0.01). Table 3 shows the incidence of five severe complications by age, sex, and influenza season. Although the incidence of acute respiratory failure, pneumonia, ARDS, and febrile seizures was higher in men, encephalitis/encephalopathy was higher in women. There were decreasing trends over the years in incidence of hospital admissions from pneumonia (p for trend<0.0001), febrile seizure (p for trend<0.0001), and the five severe complications combined (p for trend<0.0001), but not acute respiratory failure (p for trend=0.07),

encephalitis/encephalopathy (p for trend=0.19) or ARDS (p for trend=0.98). In each age group, pneumonia was the commonest complication. The incidence of acute respiratory failure, pneumonia, and febrile seizure was highest in patients aged 0–1 years, ARDS was highest in those 65–74 years, and encephalitis/encephalopathy was highest in patients aged 13–18 years.

Figures 3 and 4 show the number and percentage of inpatients with complications by age group and age over the study period. Young children had most of the severe complications. Across all age groups, pneumonia was by far the most common of the five complications, and the age group with the largest number of cases was children aged 2–5 years. In contrast, the proportion of hospitalisations amongst inpatients was highest in patients aged 0–1 years (2.96%) and second highest in those aged 65–74 years (2.21%).

DISCUSSION

Statement of the principal findings

We described the epidemiology of hospital admissions and five key severe

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

Discussing important differences in results

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

risk factor for pneumonia in children with influenza [24]. Our finding of an increased risk of pneumonia in males may be because asthma is a more common disease in boys than girls.[25] It is also known that male children develop febrile seizures more often than female children.[26] This was also observed in our data for febrile seizures with influenza infection. Worldwide, women may be at higher risk for severe complications of influenza infection.[27] In Japanese surveillance reports from 2007 to 2010, 153 of 263 (58.2%) paediatric patients with encephalopathy were male.[14] In contrast, our data suggest the possibility of a higher risk of encephalitis in women with influenza infection (table 3), although the number of cases is insufficient to draw a strong conclusion.

Our results by age are consistent with those of previous studies, and add to the understanding of the risk of specific complications amongst those with a diagnosis of influenza. Previous studies, being unable to identify a large number of influenza-positive patients, have used small numbers of influenza positive admissions as cases and general population estimates as the denominators. We found that the risk of hospitalisation was highest in infected infants aged 0–1 years (figures 2–4 and table 3). This is consistent with a US study, which found that the highest hospitalisation rate was among infants aged under one year (1.19 per 10,000 population) during the 2009–2010

influenza A(H1N1) pandemic;[6] in addition, we are able to show that the risk of admission is as high as 94.3 per 10000 infections. A study from the UK also reported that children aged 0–11 years had the highest influenza related hospitalisation rates (23.53 per 10,000 population), but based upon only 33 confirmed cases of influenza.[8] A systematic review found large gaps in the evidence base (describing the evidence for risk factors for admissions as "limited to absent").[9] They found contrasting results with children under the age of two years at higher risk of admission to hospital than older children with pandemic H1N1 influenza but the reverse with seasonal influenza.[9] They also found evidence of spectrum bias; studies from hospitals and intensive care units gave lower estimates of risk of death than community-based studies for both the elderly and children compared to young adults. As well as including positively diagnosed patients, our study covers both the community and hospital settings and is of sufficient size to allow estimation for specific causes of admission.

Implications for clinicians and policymakers

During the 2009–2010 pandemic, the World Health Organization [28] and the Centers for Disease Control and Prevention [29] issued guidelines for early neuraminidase inhibitor treatment. There are suggestions that administration of this medication within

48 hours reduces mortality and severe outcomes.[30] A Cochrane review, whilst critical of the quality of trial evidence, found a reduction in secondary infections among children who were prescribed oseltamivir.[31] During the 2000s, four neuraminidase inhibitors became available in Japan: zanamivir in 2000, oseltamivir in 2001, and laninamivir and peramivir in 2010. The decreasing trend with time in the composite incidence of the five severe complications (table 3, $p<0.0001$) might be attributed to the increasingly widespread use of [10] and more options for neuraminidase inhibitors. A recent meta-analysis of randomised controlled trials reported that in patients with pathogen-ascertained influenza, as is practice in Japan, treatment with oseltamivir reduced hospital admissions by 63%.[32]

In our study, the incidence of severe outcomes of acute pneumonia and febrile seizures decreased with time (table 3, both p values <0.0001). This was observed in parallel with increased administration modes of neuraminidase inhibitors. However, there appears to be no trend in the risk of encephalitis/encephalopathy. Because influenza encephalitis appears to be mediated by an acute process during infection,[11] it is important to prevent influenza infection to reduce the incidence of encephalitis. The primary countermeasure to protect individuals from infection is vaccination. In Japan, schoolchildren were vaccinated routinely from 1976 to 1994, when influenza was

removed from the list of routine vaccinations, and vaccination of high risk groups only was then recommended from 2001.[33] Studies of this natural experiment suggest that the former routine vaccination program for schoolchildren indirectly reduced excess mortality among elderly populations;[34 35] however, the effect upon the incidence of encephalitis is unknown. Because current encephalitis treatments are of limited effectiveness, a vaccination program covering a broad population may be the best way to reduce the morbidity associated with influenza encephalitis.

Strengths and weaknesses in relation to other studies

A main strength of this study is that the included patients were diagnosed with influenza by testing. The majority of influenza-like illness is usually caused by infections other than influenza.[37] Diagnoses were based on rapid antigen detection with immunochromatogenic assay. Because POCTs for influenza are less invasive and require less time than laboratory tests, they are an essential tool for physicians to evaluate influenza in outpatient and inpatient clinical practice in Japan.[18] Although low sensitivity (59–93%) [38] is a weak point for POCTs, the specificity is 98–100%.[20 39] This means that nearly all individuals with influenza-like illness who have POCT-positive results (the participants in this study) were infected with influenza.

This makes routinely collected Japanese data unique. Therefore, we did not greatly overestimate the number of infected patients and thus did not underestimate the risk of complications and hospitalisations.

There are limitations inherent to the data set used in this study. The administrative data from employees and their families used here do not permit analysis of patients aged 75 years or more. Also, owing to employment patterns in Japan, the number of male patients was slightly higher than female patients (table 1). The sex ratio varies across generations in Japan, with more males in younger populations and women predominating in older populations.[36] However, the incidence of hospitalisation amongst infected patients in both sexes and the studied age groups should not be biased by this imbalance. Second, we were unable to estimate influenza-related mortality in this data set, but the data are sufficient to allow examination of serious complications that are major public health concerns. Although we were unable to define encephalitis/encephalopathy cases virologically, we added the requirement of receiving specific therapy to the definition of encephalitis/encephalopathy cases.[21] This more stringent definition reduces the likelihood that we have overestimated this outcome. Further analysis of influenza-related mortality in Japan is needed, and this should encompass older adults. The effect of neuraminidase inhibitors should be examined

using observational data, as clinical trials are likely to be underpowered for rare but important complications such as encephalopathy.

Conclusions

Using Japanese administrative data, 1.0% of patients who tested positive for influenza infection were hospitalised. Male patients had a higher incidence of pulmonary complications and febrile seizures. Children aged 0–5 years and adults aged 65–74 years were at high risk of being admitted to hospital for pneumonia, with the highest absolute numbers of hospitalised patients among young children. Further efforts are needed, such as active prescription of neuraminidase inhibitors and vaccination programs, to prevent hospitalisations from severe complications in these age groups.

(2894 words)

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Authors' contributions All of the authors agreed with the manuscript's results and conclusion and approved the final version of the manuscript. HY conceived the study. HY, MM, JL, RK, TY and ZY contributed to the design of the study and interpretation of the data analyses. HY analysed the data. HY, JL, MM and RK wrote the first draft of the manuscript. JL, RK, MM, ZY and HY contributed to revision of the manuscript. ZY and HY were responsible for data integrity. HY obtained funding.

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Competing interests. None.

Patient consent Not required.

Ethics approval The ethics committee of the School of Medicine, University of Yamanashi approved this study (approval number: H29-1709).

Data sharing statement The original administrative data are available through a formal request to the Japan Medical Data Center Ltd., subject to frees.

References

1. Ghebrehewet S, MacPherson P, Ho A. Influenza. BMJ 2016;355:i6258. doi: 10.1136/bmj.i6258.

2. Kaiser L, Wat C, Mills T, *et al*. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalisations. Arch Intern Med 2003;163:1667-72.

3. Iuliano AD, Roguski KM, Chang HH, *et al*. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. Lancet 2017. doi.org/10.1016/S0140-6736(17)33293-2.

4. Thompson WW, Shay DK, Weintraub E, *et al*. Influenza-associated hospitalizations in the United States. JAMA 2004;292:1333-40.

5. Newland JG, Laurich VM, Rosenquist AW, *et al*. Neurologic complications in children hospitalized with influenza: characteristics, incidence, and risk factors. J Pediatr 2006;150:306-10. doi: 10.1016/j.jpeds.2006.11.054.

6. Louie JK, Acosta M, Winter K, *et al*. Factors associated with death or hospitalization due to pandemic 2009 influenza A (H1N1) infection in California. JAMA 2009;302:1896-902.

7. Pitman R, Melegaro A, Gelb D, *et al*. Assessing the burden of influenza and other

respiratory infections in England and Wales. J Infect 2007;54:530-38.

8. Nicholson KG, McNally T, Silverman M, *et al*. Rates of hospitalisation for influenza, respiratory syncytial virus and human metapneumovirus among infants and young children. Vaccine 2006;24:102-08.

9. Mertz D, Kim TH, Johnstone J, *et al*. Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis. BMJ 2013;347:f5061.

10. Sugaya N. Widespread use of neuraminidase inhibitors in Japan. J Infect Chemother 2011;17:595.

11. Amin R, Ford-Jones E, Richardson SE, *et al*. Acute childhood encephalitis and encephalopathy associated with influenza: a prospective 11-year review. Pediatr Infect Dis J 2008;27:390-95.

12. Wang GF, Li W, Li K. Acute encephalopathy and encephalitis caused by influenza virus infection. Curr Opin Neurol 2010;23:305-11. doi: 10.1097/WCO.0b013e328338f6c9.

13. Gu Y, Shimada T, Yasui Y, *et al*. National surveillance of influenza-associated encephalopathy in Japan over six years, before and during the 2009–2010 influenza pandemic. Plos One 2013;8:e54786.

14. Hoshino A, Saitoh M, Oka A, *et al*. Epidemiology of acute encephalopathy in Japan,

with emphasis on the association of viruses and syndromes. Brain Dev 2012;34:337-43.

15. Okumura A, Nakagawa S, Kawashima H, *et al*. Deaths associated with pandemic (H1N1) 2009 among children, Japan, 2009–2010. Emerg Infect Dis 2011;17:1993.

16. National Institute of Infectious Diseases and Mnistry of Health, Labout and Welfare. Infectious agents surveillance report 36. 2015. Available at https://www0.niid.go.jp/niid/idsc/iasr/36/429j.pdf. Japanese. Accessed 12 June 2018.

17. Mizuguchi M. Influenza encephalopathy and related neuropsychiatric syndromes. Influenza Other Resp 2013;7:67-71.

18. Sugaya N, Shinjoh M, Mitamura K, *et al*. Very low pandemic influenza A (H1N1) 2009 mortality associated with early neuraminidase inhibitor treatment in Japan: analysis of 1000 hospitalized children. J Infect 2011;63:288-94.

19. Tanaka S, Seto K, Kawakami K. Pharmacoepidemiology in Japan: medical databases and research achievements. J Pharm Health Care Sci 2015;1:16.

20. Suzuki M, Yoshimine H, Harada Y, *et al*. Estimating the influenza vaccine effectiveness against medically attended influenza in clinical settings: a hospital-based case-control study with a rapid diagnostic test in Japan. Plos One

2013;8:e52103.

21. Study Group of Influenza Encephalitis, Ministry of Health Labour and Welfare. Guideline of treatmant for influenza encephalitis. Revised edition. Japanese. Available at http://www.tokyo-med.ac.jp/pediat/data/info0925-01.pdf. Japanese. Accessed 12 June 2018.

22. Kumar S, Havens PL, Chusid MJ, *et al*. Clinical and epidemiologic characteristics of children hospitalized with 2009 pandemic H1N1 influenza A infection. Pediatr Infect Dis J 2010;29:591-94. doi: 10.1097/INF.0b013e3181d73e32.

23. O'Riordan S, Barton M, Yau Y, *et al*. Risk factors and outcomes among children admitted to hospital with pandemic H1N1 influenza. Can Med Assoc J 2010;182:39-44. doi: 10.1503/cmaj.091724.

24. Lee JJ, Bankhead C, Smith M, *et al*. Risk factors for influenza-related complications in children during the 2009/10 pandemic: a UK primary care cohort study using linked routinely collected data. Epidemiol Infect 2018:1-7. doi: 10.1017/S0950268818000353.

25. Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. BMJ 1996;312:1195-99. doi: 10.1136/bmj.312.7040.1195.

26. Tsuboi T. Epidemiology of febrile and afebrile convulsions in children in Japan. Neurology 1984;34:175-75. doi: 10.1212/wnl.34.2.175.

27. Klein SL, Hodgson A, Robinson DP. Mechanisms of sex disparities in influenza pathogenesis. J Leukocyte Biol 2012;92:67-73.

28. World Health Organization. Rapid advice guidelines for pharmacological management of pandemic influenza (H1N1) 2009 and other influenza viruses. 2010. Available at http://www.who.int/csr/resources/publications/swineflu/h1n1_guidelines_pharmaceutical_mngt.pdf. Accessed 12 June 2018.

29. Centers for Disease Control and Prevention. Updated interim recommendations for the use of antiviral medications in the treatment and prevention of influenza for the 2009–2010 season. Available at https://www.cdc.gov/h1n1flu/recommendations.htm. Accessed 12 June 2018.

30. Muthuri SG, Myles PR, Venkatesan S, *et al*. Impact of neuraminidase inhibitor treatment on outcomes of public health importance during the 2009–2010 influenza A (H1N1) pandemic: a systematic review and meta-analysis in hospitalized patients. J Infect Dis 2012;207:553-63.

31. Jefferson T, Jones MA, Doshi P, *et al*. Neuraminidase inhibitors for preventing and

treating influenza in healthy adults and children. Cochrane Database Syst Rev 2012;1 Art:CD008965.

32. Dobson J, Whitley RJ, Pocock S, *et al*. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. Lancet 2015;385:1729-37.

33. Hirota Y, Kaji M. History of influenza vaccination programs in Japan. Vaccine 2008;26:6451-54. doi.org/10.1016/j.vaccine.2008.06.042.

34. Reichert TA, Sugaya N, Fedson DS, *et al*. The Japanese experience with vaccinating schoolchildren against influenza. N Engl J Med 2001;344:889-96.

35. Charu V, Viboud C, Simonsen L, *et al*. Influenza-related mortality trends in Japanese and American seniors: evidence for the indirect mortality benefits of vaccinating schoolchildren. Plos One 2011;6:e26282.

36. Central Intelligence Agency. The world factbook: sex ratio (male/female). 2018. Available at https://www.cia.gov/library/publications/the-world-factbook/fields/2018.html. Accessed 12 June 2018.

37. Hayward AC, Fragaszy EB, Bermingham A, *et al*. Comparative community burden and severity of seasonal and pandemic influenza: results of the Flu Watch Cohort Study. Lancet Resp Med 2014;2:445-54.

453 38. Paules C, Subbarao K. Influenza. Lancet 2017;390:697-708. doi:
454 10.1016/S0140-6736(17)30129-0.
455 39. Poehling KA, Zhu Y, Tang Y-W, *et al*. Accuracy and impact of a point-of-care rapid
456 influenza test in young children with respiratory illnesses. Arch Pediatr Adolescent
457 Med 2006;160:713-18.

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Figure legends

Figure 1. 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.

Figure 2. 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.

Figure 3. 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.

Figure 4. Number of influenza-infected inpatients with severe complications and proportion of hospitalisation, by age, between 2012 and 2016.
Abbreviation: ARDS, acute respiratory distress syndrome.

Table 1. Population Characteristics: Number (%) of 16636913 Japanese patients infected with influenza between 2012–2016, in health 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	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)	231120 (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	Otorhinolaryngology	Orthopaedics	Dermatology	Surgery	Ophthalmology	Obstetrics &	Psychiatry

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

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

Category	Acute respiratory failure	Pneumonia	ARDS	Febrile seizure	Encephalitis/ encephalopathy
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

Abbreviation: ARDS, acute respiratory distress syndrome.

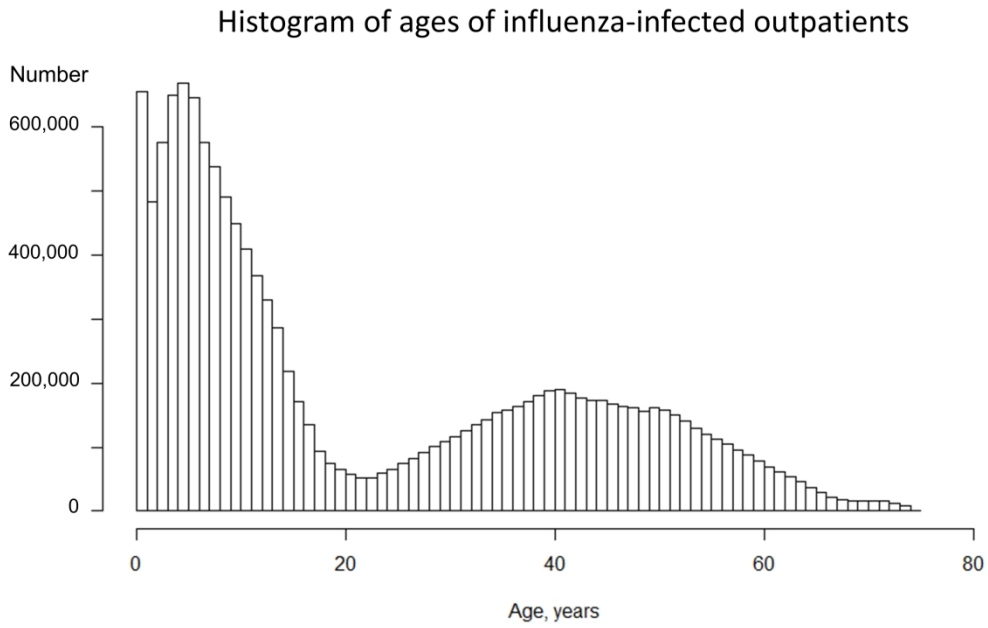
Table 3. Incidence of hospitalisation with severe complications per 10000 confirmed influenza infections.

No. of inpatients per 10,000 influenza infections	All five complications	Acute respiratory failure	Pneumonia	ARDS	Febrile seizure	Encephalitis /encephalopathy
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

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

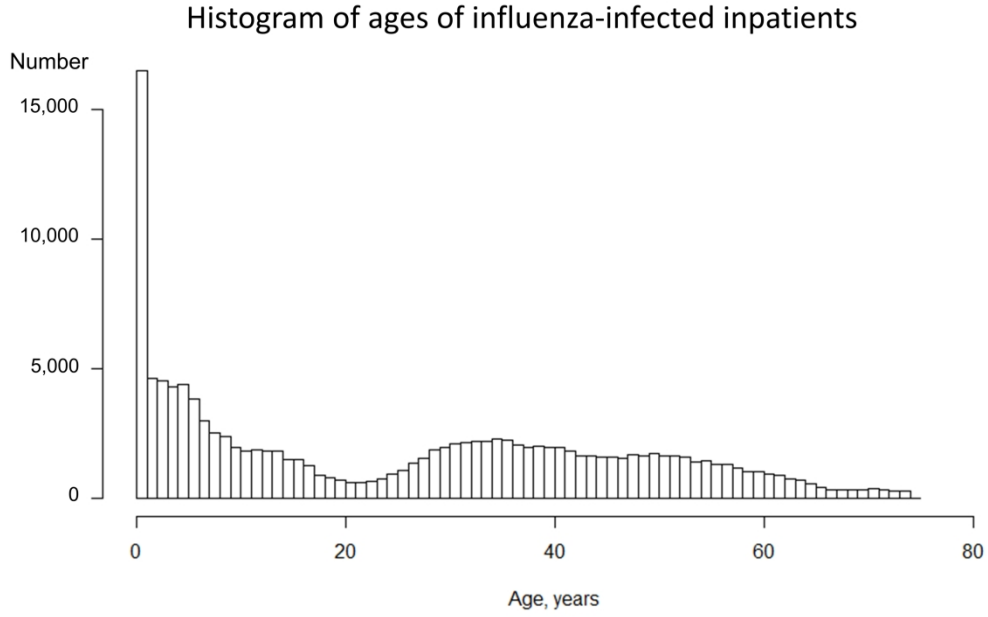
Abbreviation: ARDS, acute respiratory distress syndrome.

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



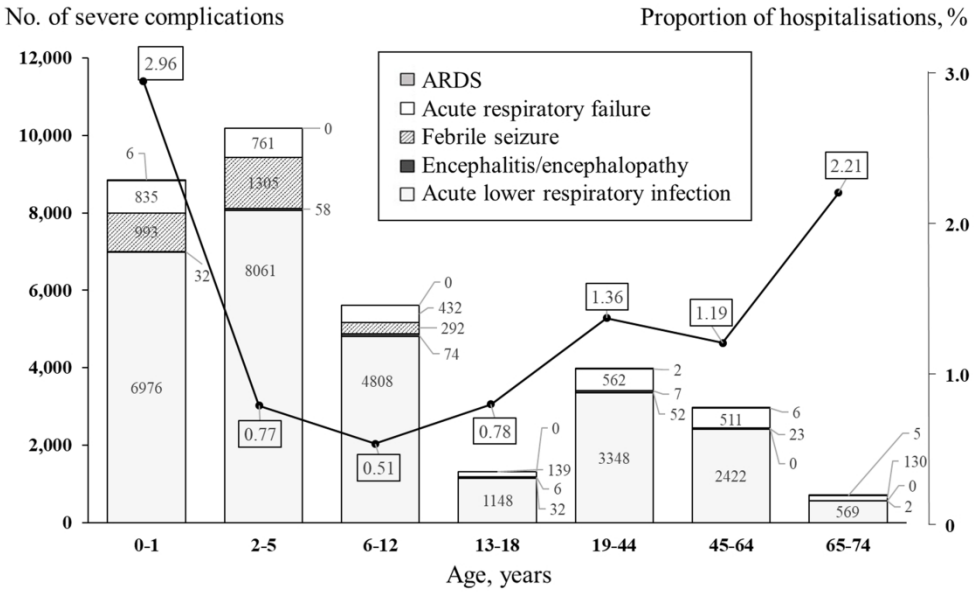
Histogram of the ages of influenza-infected outpatients in the 2012/13, 2013/14, 2014/15, and 2015/16 seasons, according to health insurance administrative data.

284x189mm (300 x 300 DPI)



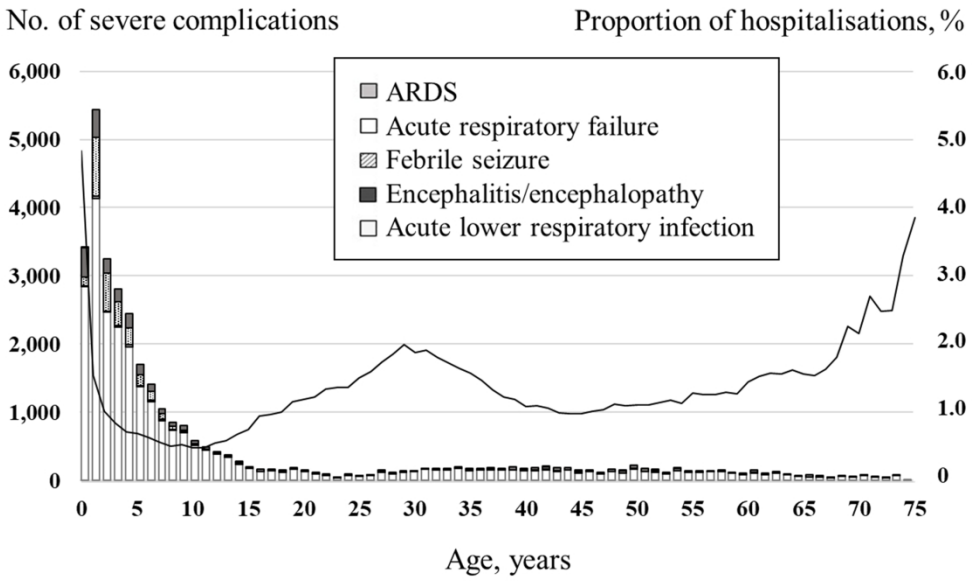
Histogram of the ages of influenza-infected inpatients in the 2012/13, 2013/14, 2014/15, and 2015/16 seasons, according to health insurance administrative data.

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
Introduction			
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
Methods			
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
Results			

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
Discussion			
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
Other information			
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.

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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

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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

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Abstract

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

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

Setting: Japanese clinics and hospitals between 2012 and 2016.

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

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

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

hospitalisations by age was 2.96% of patients aged 0–1 years; 0.77% aged 2–5; 0.51% aged 6–12; 0.78% aged 13–18; 1.36% aged 19–44; 1.19% aged 45–64; and 2.21% aged 65–74. The incidence of hospitalisations from these five complications combined was highest in influenza-positive patients aged 0–1 years (943 per 100000) compared with 307 in those aged 2–5 years and 271 in those aged 65–74 years. For pneumonia, incidence was highest for influenza-positive patients aged 0–5 years and 65 years or more. There were statistically significant decreasing trends over the years in the incidence of all-cause hospitalisations, pneumonia and febrile seizures.

Conclusions: Japanese administrative data revealed that 1.0% of influenza-positive patients aged under 75 years were hospitalised. Male patients had a higher incidence of pulmonary complications and febrile seizures. Children aged 0–5 years and adults aged 65–74 years were at high risk of being admitted to hospital for pneumonia.

Registration: The ethics committee of the School of Medicine, University of Yamanashi approved this study (approval number: H29-1709).

(292 words/300 words)

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.

INTRODUCTION

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

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

denominators, rather than assessing the risk of admission amongst the infected population, combing the risk of infection and the risk of complications. This is problematic because programmes targeting high risk groups, such as vaccination or prophylaxis may reduce the number of infections in high risk groups, biasing estimates of the risk of complications if infected.[12] Also, many studies pre-date the option of administering new neuraminidase inhibitors.[13]

Although it is also seen internationally,[14-18] influenza encephalitis is a particular concern amongst Japanese physicians owing to a high incidence and mortality rate in Japan.[7 19-23] The prognosis for patients with influenza encephalitis/encephalopathy is very poor; approximately 30% of affected patients die and 20–30% have neurological sequelae.[24] To understand the aetiology and prevalence of this severe outcome, surveillance has been conducted.[25 26] In Japan, influenza-associated encephalopathy is a notifiable disease.[27] Japanese physicians are required to report influenza infection cases with: a) death after coma or hospitalisation with coma for 24 hours or more; and b) a fever of 38°C or higher, central nervous system manifestation or prior influenza infection symptoms. This surveillance system has detected 60–100

influenza encephalitis cases annually [28] and 331 cases during the 2009–2010 pandemic;[26] however, underreporting of cases has been acknowledged.[28] Another survey of paediatric departments in 265 hospitals reported 263 influenza-associated encephalopathy cases over 3 years.[25] The authors estimate that there are 200–300 influenza encephalopathy cases per annum in Japan;[29] therefore, the incidence of influenza encephalitis/encephalopathy is not accurately known.

To understand the incidence of severe complications in patients with influenza, an analysis of large-scale real-world data is needed, encompassing hospital and community sites. Previous studies using large data sets of routinely collected medical records have had to rely on clinical diagnoses of influenza-like illness or modelling of influenza and other respiratory virus infections using incomplete laboratory data.[11] In Japan, diagnostic testing for influenza is routine, which presents a unique opportunity to combine the benefits of large data sets with positive diagnoses.[6] We therefore sought to estimate the incidence of hospitalisation with the above five severe complications per influenza infection, using Japanese health insurance claim data.

METHODS

Patients and data

We analysed administrative data provided by Japan Medical Data Center Ltd. (renamed to JMDC) Tokyo, Japan.[30] The data source was the monthly health insurance claim records between January 2012 and December 2016 of approximately three million employees and their dependents, representing 2.4% of the Japanese population. Within health insurance coverage in Japan, people can consult physicians in any type of hospital and department, and medical doctors in any speciality can diagnose influenza and prescribe anti-influenza medications. The age of patients in the data set ranged from 0 to 74 years because all Japanese people aged 75 or more (except for individuals who are on public assistance) are covered by another health insurance program with lower out-of-pocket expenses.

From the database, we extracted the data of individuals who consulted physicians with influenza-like illness episodes. We then included only patients with a diagnosis of influenza virus infection. In Japan, the use of immunochromatogenic assay point-of-care tests [POCT] in clinical practice has been covered by public health insurance from 1999.[23] As recommended in Japanese guidelines,[31] a test-and-treat strategy is

routine.[23 32] Even if physicians only slightly suspect influenza infection, they use a POCT to diagnose influenza, and administer antivirals to the positive patients.[31 33 34] Testing would be indicated in fever, sore throat, malaise, non-productive cough or a history of family's infection, for example.[23 35] During the 2009–2010 pandemic influenza A(H1N1) season, physicians performed this test in majority of cases (>90%) and we believe this was likely to be the case during the period of this study because in Japan paediatric patients with an influenza-like illness are required to obtain a medical certificate showing they do not have influenza before return to school.[36]

Outcomes

Hospitalisation was recorded in the health insurance claims of inpatients. In patients with a diagnosis of influenza infection, we identified those who were hospitalised with a diagnosis of acute respiratory failure, pneumonia, ARDS, febrile seizure, and encephalitis/encephalopathy, according to International Classification of Diseases (ICD-10) codes in their records. The primary outcomes were the incidence of each of the five severe complications per 100000 influenza infections. Acute respiratory failure was coded as J960, J988, R060, R068 or R092; pneumonia was coded as J10–J18 or J20–J22, acute respiratory

distress syndrome (ARDS) as J80, and febrile seizures as R560. We defined influenza encephalitis/encephalopathy as patients who were diagnosed using ICD-10 codes for influenza infection and encephalitis/encephalopathy (G00–G09 or G41) and had been administered steroid pulse or immunoglobulin therapy.[37]

Statistical analysis

We examined the number of diagnosed influenza infections and severe complications by sex, age, outpatient/inpatient status, number of beds in the facility, and clinical speciality. In Japan, clinical facilities with fewer than 20 beds are denoted a "clinic" by law. Clinics are usually run by a single medical doctor and function as a primary care department. Most clinics have no beds but a very small subset of clinics have 1–19 beds to accommodate inpatients. In contrast, facilities with 20 beds or more are legally termed a "hospital". Hospitals have primary care, specialised outpatient, and general and specialised inpatient departments. In this study, hospitalised influenza-positive patients were inpatients in both "clinic" and "hospital" settings. We plotted histograms of the ages of outpatients and inpatients infected with influenza. We determined the incidence of inpatients with the five severe complications by dividing the number of complications by the number of infections. We stratified this by

sex, influenza season and age. We also examined the numbers of the influenza-infected patients and the proportions of inpatients over calendar time at the request of a reviewer. Influenza seasons were defined as lasting from September through to the following August. We calculated p values for secular trends of incidence over influenza seasons. Statistical analyses were performed using SAS statistical software (version 9.4, SAS Institute, Cary, NC, USA). All reported p values were two-sided and we considered $p<0.05$ indicated a significant difference.

Patient and public involvement

The ethics committee of the School of Medicine, University of Yamanashi approved this study (approval number: H29-1709), in accordance with the ethical guidelines and regulations of the Declaration of Helsinki. The data were properly anonymised by the JMDC in the manner permitted by Japanese guideline of Personal Information Protection Commission, Cabinet Office, Government of Japan for the use of data from medical examinations in medical research without individual participants' consent (Act on the Protection of Personal Information, act no. 57 of 30 May 2003; last version amendment of act no. 65 of 2015).

Patients were not actively involved in developing the research question and protocol including outcome measures. The participants will be provided the final study results by clinical research information services and homepage of the University of Yamanashi.

RESULTS

Characteristics of patients diagnosed with influenza

Table 1 summarises the number of patients with diagnoses of influenza infection in the study population. Among 16636913 infections, 53.4% of the patients were men, and 1.0% were hospitalised. Approximately a quarter (25.7%) of infections were in children aged 6–12 years. Overall 32% of diagnoses were made in the internal medicine department and 23% in paediatrics. Most infections were diagnosed in clinics (n=13572391; 83%). Figures 1 and 2 illustrate the number of outpatients and inpatients with influenza infection, respectively, by age. Influenza was most often diagnosed in outpatients aged 0–12 years, with a second small peak in middle-aged patients. In contrast, inpatient cases were commonest among patients

aged less than one year. Table 2 shows the number of complicated cases by department, hospital size and type of hospital management. A total of 3361 patients (0.02%) were admitted to hospital with acute respiratory failure, 27253 (0.16%) with pneumonia, 18 (0.0001%) with ARDS, 2603 (0.02%) with febrile seizures, and 159 (0.001%) with encephalitis/encephalopathy. Most complicated cases were admitted to paediatric departments, with 19012 pneumonia admissions (70% of the total), 1794 with acute respiratory failure (53% of the total), 2461 with febrile seizures (95% of the total), and 63 encephalitis (40% of all cases). The number of inpatients with acute respiratory failure, pneumonia, and febrile seizure tended to increase with the number of hospital beds.

Hospitalisation rates from severe complications

The combined incidence of the five complications was 189 per 100000 diagnosed infections. Pneumonia was the commonest complication, with 164 per 100000 diagnosed infections, followed by acute respiratory failure (20.2), febrile seizures (15.7), encephalitis/encephalopathy (0.9), and ARDS (0.10). Table 3 shows the incidence of five severe complications by age, sex, and influenza season. Although the incidence of acute respiratory failure, pneumonia, ARDS, and febrile seizures was higher in men,

encephalitis/encephalopathy was higher in women. There were decreasing trends over the years in incidence of hospital admissions from pneumonia (p for trend<0.0001), febrile seizure (p for trend<0.0001), and the five severe complications combined (p for trend<0.0001), but not acute respiratory failure (p for trend=0.07), encephalitis/encephalopathy (p for trend=0.19) or ARDS (p for trend=0.98). In each age group, pneumonia was the commonest complication. The incidence of acute respiratory failure, pneumonia, and febrile seizure was highest in patients aged 0–1 years, ARDS was highest in those 65–74 years, and encephalitis/encephalopathy was highest in patients aged 13–18 years.

Figures 3 and 4 show the number and percentage of inpatients with complications by age group and age over the study period. Young children had most of the severe complications. Across all age groups, pneumonia was by far the most common of the five complications, and the age group with the largest number of cases was children aged 2–5 years. In contrast, the proportion of infections hospitalised was highest in patients aged 0–1 years (2.96%) and second highest in those aged 65–74 years (2.21%).

Figure 5 shows the numbers of influenza-infected patients and the proportion who

were inpatients by calendar month between 2012 and 2016. Every year the number of infections increased from winter to spring while the proportion admitted peaked in summer. The number of infections was similar between 2014 and 2016. The proportion hospitalised gradually decreased between 2012 and 2016.

DISCUSSION

Principal findings

We described the epidemiology of hospital admissions and five key severe complications in large cross-sectional data of influenza-positive patient visits. Influenza diagnoses were commonest in young children and middle-aged patients (table 1 and figures 1–2). The incidence and absolute number of hospital admissions with complications of influenza was highest in young children (figure 2 and table 3). The most common complication was pneumonia (table 1). The incidence and absolute number of admissions for pulmonary complications were highest in children (figures 3–4 and table 3). Patients aged 65–74 years were also at high risk for admission from complications, but the absolute number of both

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

Comparison with previous research

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

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

Our results by age are consistent with those of previous studies, and add to understanding the risk of specific complications amongst those with a diagnosis of influenza. Previous studies, being unable to identify a large number of influenza-positive patients, have used small numbers of influenza positive admissions as cases and general population estimates as the denominators. This combines the risk of infection and the risk of complications. We found that the risk of hospitalisation was highest in infected infants aged 0–1 years (figures 2–4 and table 3). This is consistent with a US study, which found that the highest hospitalisation rate was among infants aged under one year (11.9 per 100000 population) during the 2009–2010 influenza A(H1N1) pandemic;[9] in addition, we are able to show that the risk of admission is as high as 943 per 100000 infections. A study from the

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

A systematic review found large gaps in the evidence base (describing the evidence for risk factors for admissions as "limited to absent").[12] They found contrasting results with children under the age of two years at higher risk of admission to hospital than older children with pandemic H1N1 influenza but the reverse with seasonal influenza.[12] They also found evidence of spectrum bias; studies from hospitals and intensive care units gave lower estimates of risk of death than community-based studies for both the elderly and children compared to young adults. As well as including positively diagnosed patients, our study covers both the community and hospital settings and is of sufficient size to allow estimation for specific causes of admission. In addition, because vaccination reduces the hospitalisation rate,[43-45] vaccination programmes in other countries that target high risk groups may bias hospitalisation rate estimates for these patients. In Japan all individuals have had to pay a fee to receive influenza vaccine irrespective of their risk profile since 1994, when free vaccination for primary and secondary school students was stopped.[46] This means that high-risk groups in Japan are less resistant to severe disease than in other countries,

reducing this bias in our hospitalisation rates.

Implications for clinicians and policymakers

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

This decreasing trend was not altered in the 2014/15 season when influenza A(H3N2) spread internationally including in Japan.[51] A recent meta-analysis of randomised controlled trials reported that in patients with pathogen-ascertained influenza, as is practice in Japan, treatment with oseltamivir reduced hospital admissions by 63%.[52]

In our study, the incidence of hospitalisations, acute pneumonia and febrile seizures decreased with time (table 3, all p values <0.0001). This was observed in parallel with increased administration of neuraminidase inhibitors. However, there appears to be no trend in the risk of encephalitis/encephalopathy. Because influenza encephalitis appears to be mediated by an acute process during infection,[14] it is important to prevent influenza infection to reduce the incidence of encephalitis. The primary countermeasure to protect individuals from infection is vaccination. National vaccine policies may have impacted upon variation in the hospitalisation incidence between countries. In Japan, schoolchildren were vaccinated routinely from 1976 to 1993, when influenza was removed from the list of free routine vaccinations, and vaccination of high risk groups was only recommended from 2001, albeit for a fee which has limited uptake.[53] Studies of this natural experiment suggest that the former routine vaccination program for schoolchildren indirectly reduced excess

mortality among the elderly.[46 54] The previous results suggest indirect effect of the vaccines upon reducing severe complication risk amongst children; however, the effect upon the incidence of encephalitis is unknown. Because current encephalitis treatments are of limited effectiveness, a vaccination program covering a broad population may be the best way to reduce the morbidity associated with influenza encephalitis.

Strengths and weaknesses

A main strength of this study is that the included patients were diagnosed with influenza by testing. The majority of influenza-like illness is usually caused by infections other than influenza.[55] Diagnoses were based on rapid antigen detection with immunochromatogenic assay. Because POCTs for influenza are less invasive and require less time than laboratory tests, they are an essential tool for physicians to evaluate influenza in outpatient and inpatient clinical practice in Japan.[6] Although low sensitivity (59–93%) [56] is a weak point for POCTs, the specificity is 98–100%.[34 57] This means that nearly all individuals with influenza-like illness who have POCT-positive results (the participants in this study) were infected with influenza. This makes routinely collected Japanese data unique. Additionally, all Japanese people who are hospitalised with severe complications of influenza infection

should be present in universal health insurance data. Therefore, we did not greatly overestimate the number of infected patients or underestimate severe complications, and thus did not underestimate the risk of complications and hospitalisations.

There are limitations inherent to the data set used in this study. Firstly, POCTs for influenza are known to have variable sensitivity. In the 2010s, 20 or more POCT kits were available in Japan.[58] Sensitivity would have been influenced by the following factors: (1) time from the onset of illness;[59 60] (2) patient age;[60 61] (3) influenza type A/B/C;[61] (4) operator technique;[60] (5) number of times patients were tested. (1) Reportedly, the sensitivity is lower 0–24 hours from symptom onset and higher in days 2–4.[59 60] Parents tend to bring children to paediatricians at an earlier stage of the infection while infected employed adults tend to consult physicians in mid- or later stages. This would bias sensitivity toward comparatively low in children compared to adults. (2) In contrast children are known to have higher viral load and longer shedding and consequently POCTs have higher sensitivity in children.[60 61] (3) POCT sensitivity is higher in influenza A than in B.[61] In Japan, influenza type A spreads early in winter, type B late in winter, and type C in all seasons. Therefore, the sensitivity might have been relatively low between Jan 2012–Aug 2012 and

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

Second, the administrative data from employees and their families used here do not permit analysis of patients aged 75 years or more. Also, due to employment patterns in Japan, the number of male patients was slightly higher than female patients (table 1). The sex ratio

varies across generations in Japan, with more males in younger populations and women predominating in older populations.[62] However, the incidence of hospitalisation amongst infected patients in both sexes and the studied age groups should not be biased by this imbalance. Third, we were unable to estimate influenza-related mortality in this data set, but the data are sufficient to allow examination of serious complications that are major public health concerns. Although we were unable to define encephalitis/encephalopathy cases virologically, we added the requirement of receiving specific therapy to the definition of encephalitis/encephalopathy cases.[37] This more stringent definition reduces the likelihood that we have overestimated this outcome. Further analyses of influenza-related mortality in Japan are needed, and this should encompass older adults. The effect of neuraminidase inhibitors should be examined using observational data, as clinical trials are likely to be underpowered for rare but important complications such as encephalopathy.

Conclusions

Using Japanese administrative data, 1.0% of patients who tested positive for influenza infection were hospitalised. Male patients had a higher incidence of pulmonary complications and febrile seizures. Children aged 0–5 years and adults aged 65–74 years

were at high risk of being admitted to hospital for pneumonia, with the highest absolute numbers of hospitalised patients among young children. Further efforts are needed, such as active prescription of neuraminidase inhibitors and vaccination programs, to prevent hospitalisations from severe complications in these age groups.

(3854 words)

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Authors' contributions All of the authors agreed with the manuscript's results and conclusion and approved the final version of the manuscript. HY conceived the study. HY, MM, JL, RK, TY and ZY contributed to the design of the study and interpretation of the data analyses. HY analysed the data. HY, JL, MM and RK wrote the first draft of the manuscript. JL, RK, MM, ZY and HY contributed to revision of the manuscript. ZY and HY were responsible for data integrity. HY obtained funding.

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Competing interests. None.

Patient consent Not required.

Ethics approval The ethics committee of the School of Medicine, University of Yamanashi approved this study (approval number: H29-1709).

Data sharing statement The original administrative data are available through a formal request to the JMDC, subject to fees.

References

1. Ghebrehewet S, MacPherson P, Ho A. Influenza. *BMJ* 2016;355:i6258.

2. Kaiser L, Wat C, Mills T, *et al.* Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalisations. *Arch Intern Med* 2003;163:1667–72.

3. Iuliano AD, Roguski KM, Chang HH, *et al.* Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *Lancet* 2017;391:1285–1300.

4. Thompson WW, Shay DK, Weintraub E, *et al*. Influenza-associated hospitalizations in the United States. *JAMA* 2004;292:1333–40.

5. Newland JG, Laurich VM, Rosenquist AW, *et al*. Neurologic complications in children hospitalized with influenza: characteristics, incidence, and risk factors. *J Pediatr* 2006;150:306–10.

6. Sugaya N, Shinjoh M, Mitamura K, *et al.* Very low pandemic influenza A (H1N1) 2009 mortality associated with early neuraminidase inhibitor treatment in Japan: analysis of 1000 hospitalized children. *J Infect* 2011;63:288–94

7. Influenza Working Group of the Japan Pediatric Society. Secondary treatment guideline of 2013/2014 influenza infection. 2014. Japanese.

https://www.jpeds.or.jp/uploads/files/2013_2014_influenza_all.pdf. Accessed 23 October 2018.

8. Cromer D, van Hoek AJ, Jit M, *et al.* The burden of influenza in England by age and clinical risk group: a statistical analysis to inform vaccine policy. *J Infect* 2014;68:363–71.

9. Louie JK, Acosta M, Winter K, *et al.* Factors associated with death or hospitalization due to pandemic 2009 influenza A (H1N1) infection in California. *JAMA* 2009;302:1896–902.

10. Nicholson KG, McNally T, Silverman M, *et al.* Rates of hospitalisation for influenza, respiratory syncytial virus and human metapneumovirus among infants and young children. *Vaccine* 2006;24:102–08.

11. Pitman R, Melegaro A, Gelb D, *et al.* Assessing the burden of influenza and other respiratory infections in England and Wales. *J Infect* 2007;54:530–38.

12. Mertz D, Kim TH, Johnstone J, *et al.* Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis. *BMJ* 2013;347:f5061.

13. Sugaya N. Widespread use of neuraminidase inhibitors in Japan. *J Infect Chemother* 2011;17:595.

14. Amin R, Ford-Jones E, Richardson SE, *et al.* Acute childhood encephalitis and

encephalopathy associated with influenza: a prospective 11-year review. *Pediatr Infect Dis J* 2008;27:390–95.

15. Ekstrand JJ, Herbener A, Rawlings J*, et al.* Heightened neurologic complications in children with pandemic H1N1 influenza. *Ann Neurol* 2010;68:762–66.

16. Evans A, Agadi S, Siegel J*, et al.* Neurologic complications associated with novel influenza A (H1N1) virus infection in children-Dallas, Texas, May 2009. *MMWR-Morb. Mortal. Wkly. Rep* 2009;58:773–78.

17. Rellosa N, Bloch KC, Shane AL*, et al.* Neurologic manifestations of pediatric novel H1N1 influenza infection. *Pediatr Infect Dis J* 2011;30:165–67.

18. Baltagi SA, Shoykhet M, Felmet K*, et al.* Neurological sequelae of 2009 influenza A (H1N1) in children: a case series observed during a pandemic. *Pediatr Crit Care Med* 2010;11:179–84.

19. Kasai T, Togashi T, Morishima T. Encephalopathy associated with influenza epidemics. *Lancet* 2000;355:1558–59.

20. Morishima T, Togashi T, Yokota S*, et al.* Encephalitis and encephalopathy associated with an influenza epidemic in Japan. *Clin Infect Dis* 2002;35:512–17.

21. Sugaya N. Influenza-associated encephalopathy in Japan. *Semin Pediatr Infect Dis*

2002;13:79–84.

22. Akihisa O, Satoshi N, Hisashi K*, et al.* Deaths associated with pandemic (H1N1) 2009 among children, Japan, 2009–2010. *Emerg Infect Dis J* 2011;17:1993–2000.

23. Zaraket H, Saito R. Japanese surveillance systems and treatment for influenza. *Curr Treat Options Infect Dis* 2016;8:311–28

24. Wang GF, Li W, Li K. Acute encephalopathy and encephalitis caused by influenza virus infection. *Curr Opin Neurol* 2010;23:305–11

25. Hoshino A, Saitoh M, Oka A*, et al.* Epidemiology of acute encephalopathy in Japan, with emphasis on the association of viruses and syndromes. *Brain Dev* 2012;34:337–43.

26. Gu Y, Shimada T, Yasui Y*, et al.* National surveillance of influenza-associated encephalopathy in Japan over six years, before and during the 2009–2010 influenza pandemic. *Plos One* 2013;8:e54786.

27. Okumura A, Nakagawa S, Kawashima H*, et al.* Deaths associated with pandemic (H1N1) 2009 among children, Japan, 2009–2010. *Emerg Infect Dis* 2011;17:1993–2000.

28. National Institute of Infectious Diseases and Mnistry of Health, Labout and Welfare. Infectious agents surveillance report 36. 2015. Japanese. Available at https://www0.niid.go.jp/niid/idsc/iasr/36/429j.pdf. Accessed 23 October 2018.

29. Mizuguchi M. Influenza encephalopathy and related neuropsychiatric syndromes. *Influenza Other Resp* 2013;7:67–71.

30. Tanaka S, Seto K, Kawakami K. Pharmacoepidemiology in Japan: medical databases and research achievements. *J Pharm Health Care Sci* 2015;1:16.

31. Uehara S, Sunakawa K, Eguchi H, *et al.* Japanese guidelines for the management of respiratory infectious diseases in children 2007 with focus on pneumonia. *Pediatr Int* 2011;53:264–76.

32. Ito M, Watanabe M, Nakagawa N, *et al.* Rapid detection and typing of influenza A and B by loop-mediated isothermal amplification: comparison with immunochromatography and virus isolation. *J Virol Methods* 2006;135:272–75.

33. Sugaya N, Mitamura K, Yamazaki M, *et al.* Lower clinical effectiveness of oseltamivir against influenza B contrasted with influenza a infection in children. *Clin Infect Dis* 2007;44:197–202.

34. Suzuki M, Yoshimine H, Harada Y, *et al.* Estimating the influenza vaccine effectiveness against medically attended influenza in clinical settings: a hospital-based case-control study with a rapid diagnostic test in Japan. *Plos One* 2013;8:e52103.

35. Watanabe M, Nakagawa N, Ito M, *et al.* Sensitivity of rapid immunoassay for influenza

A and B in the early phase of the disease. *Pediatr Int* 2009;51:211–15.

36. Komiya N, Gu Y, Kamiya H*, et al.* Clinical features of cases of influenza A (H1N1) v in Osaka prefecture, Japan, May 2009. *Eurosurveillance* 2009;14:19272.

37. Study Group of Influenza Encephalitis. Ministry of Health, Labour and Welfare. Guideline of treatmant for influenza encephalitis. revised edition. 2011. Japanese. https://www.mhlw.go.jp/kinkyu/kenkou/influenza/hourei/2009/09/dl/info0925-01.pdf. Accessed 23 October 2018.

38. Kumar S, Havens PL, Chusid MJ*, et al.* Clinical and epidemiologic characteristics of children hospitalized with 2009 pandemic H1N1 influenza A infection. *Pediatr Infect Dis J* 2010;29:591–94.

39. O'Riordan S, Barton M, Yau Y, *et al*. Risk factors and outcomes among children admitted to hospital with pandemic H1N1 influenza. *Can Med Assoc J* 2010;182:39–44.

40. Lee JJ, Bankhead C, Smith M, *et al*. Risk factors for influenza-related complications in children during the 2009/10 pandemic: a UK primary care cohort study using linked routinely collected data. *Epidemiol Infect* 2018:1–7.

41. Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. *BMJ*

1996;312:1195–99.

42. Tsuboi T. Epidemiology of febrile and afebrile convulsions in children in Japan. *Neurology* 1984;34:175–75.

43. Talbot HK, Zhu Y, Chen Q, *et al.* Effectiveness of influenza vaccine for preventing laboratory-confirmed influenza hospitalizations in adults, 2011–2012 influenza season. *Clin Infect Dis* 2013;56:1774–77.

44. Yokomichi H, Kurihara S, Yokoyama T, *et al.* The pandemic influenza A (H1N1) 2009 vaccine does not increase the mortality rate of idiopathic interstitial pneumonia: a matched case-control study. *Plos One* 2014;9:e88927.

45. Yokomichi H, Kurihara S, Yokoyama T, *et al.* Safety of the influenza A (H1N1)2009 vaccine in chronic obstructive pulmonary disease: a matched case-control study. *J Vaccines Vaccination* 2012;3:1000148.

46. Reichert TA, Sugaya N, Fedson DS, *et al.* The Japanese experience with vaccinating schoolchildren against influenza. *N Engl J Med* 2001;344:889–96.

47. World Health Organization. Rapid advice guidelines for pharmacological management of pandemic influenza (H1N1) 2009 and other influenza viruses. 2010. Available at http://www.who.int/csr/resources/publications/swineflu/h1n1_guidelines_pharmaceutical_

mngt.pdf. Accessed 23 October 2018.

48. Centers for Disease Control and Prevention. Updated interim recommendations for the use of antiviral medications in the treatment and prevention of influenza for the 2009–2010 season. Available at https://www.cdc.gov/h1n1flu/recommendations.htm. Accessed 23 October 2018.

49. Muthuri SG, Myles PR, Venkatesan S, *et al*. Impact of neuraminidase inhibitor treatment on outcomes of public health importance during the 2009–2010 influenza A (H1N1) pandemic: a systematic review and meta-analysis in hospitalized patients. *J Infect Dis* 2012;207:553–63.

50. Jefferson T, Jones MA, Doshi P, *et al*. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev* 2012;1 Art:CD008965.

51. Pebody R, Warburton F, Andrews N*, et al.* Effectiveness of seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2014/15 end of season results. *Eurosurveillance* 2015;20:30013.

52. Dobson J, Whitley RJ, Pocock S*, et al.* Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. *Lancet* 2015;385:1729–37.

53. Hirota Y, Kaji M. History of influenza vaccination programs in Japan. *Vaccine* 2008;26:6451–54.

54. Charu V, Viboud C, Simonsen L*, et al.* Influenza-related mortality trends in Japanese and American seniors: evidence for the indirect mortality benefits of vaccinating schoolchildren. *Plos One* 2011;6:e26282.

55. Hayward AC, Fragaszy EB, Bermingham A*, et al.* Comparative community burden and severity of seasonal and pandemic influenza: results of the Flu Watch cohort study. *Lancet Resp Med* 2014;2:445–54.

56. Paules C, Subbarao K. Influenza. *Lancet* 2017;390:697–708.

57. Poehling KA, Zhu Y, Tang Y-W, *et al*. Accuracy and impact of a point-of-care rapid influenza test in young children with respiratory illnesses. *Arch Pediatr Adolescent Med* 2006;160:713–18.

58. Sakai-Tagawa Y, Ozawa M, Tamura D*, et al.* Sensitivity of influenza rapid diagnostic tests to H5N1 and 2009 pandemic H1N1 viruses. *J Clin Microbiol* 2010;48:2872–77.

59. Hata A, Asada J, Mizumoto H*, et al.* Appropriate use of rapid diagnostic testing for influenza. *J Jpn Assoc Infect Dis* 2004;78:846-52.

60. Landry ML. Diagnostic tests for influenza infection. *Curr Opin Pediatr* 2011;23:91–97.

61. Chartrand C, Leeflang MM, Minion J, *et al.* Accuracy of rapid influenza diagnostic tests: a meta-analysis. *Ann Intern Med* 2012;156:500–11.

62. Central Intelligence Agency. The world factbook: sex ratio (male/female). 2018. Available at https://www.cia.gov/library/publications/the-world-factbook/fields/2018.html. Accessed 23 October 2018.

Figure legends

Figure 1. 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.

Figure 2. 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.

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

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

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

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

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

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

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 8885699 (53.4)	Women 7751214 (46.6)							
Patient status, n (%)	Outpatient 16488970 (99.0)	Inpatient 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)	231122 (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	Otorhinolaryngology	Orthopaedics	Dermatology	Surgery	Ophthalmology	Obstetrics & Gynaecology	Psychiatry

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

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

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

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

Abbreviation: ARDS, acute respiratory distress syndrome.

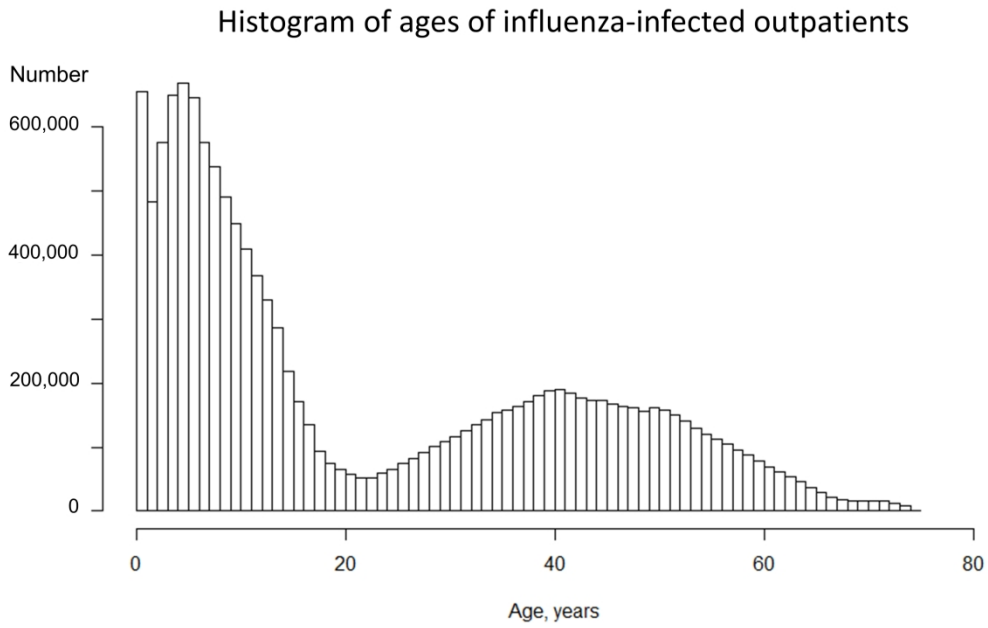
Table 3. Incidence of hospitalisation with severe complications per 100000 confirmed influenza infections.

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

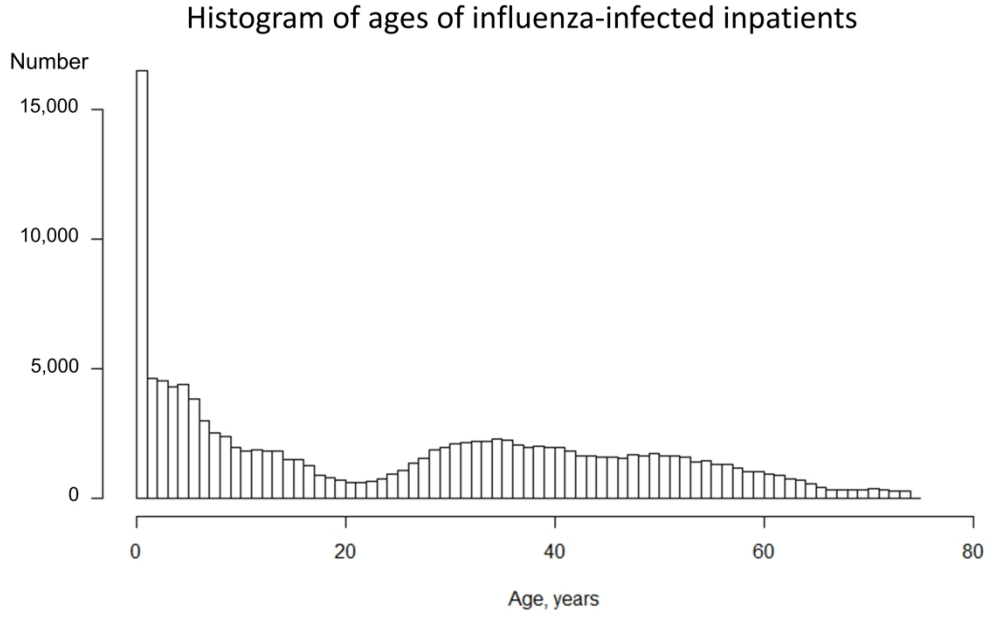
Abbreviation: ARDS, acute respiratory distress syndrome.

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



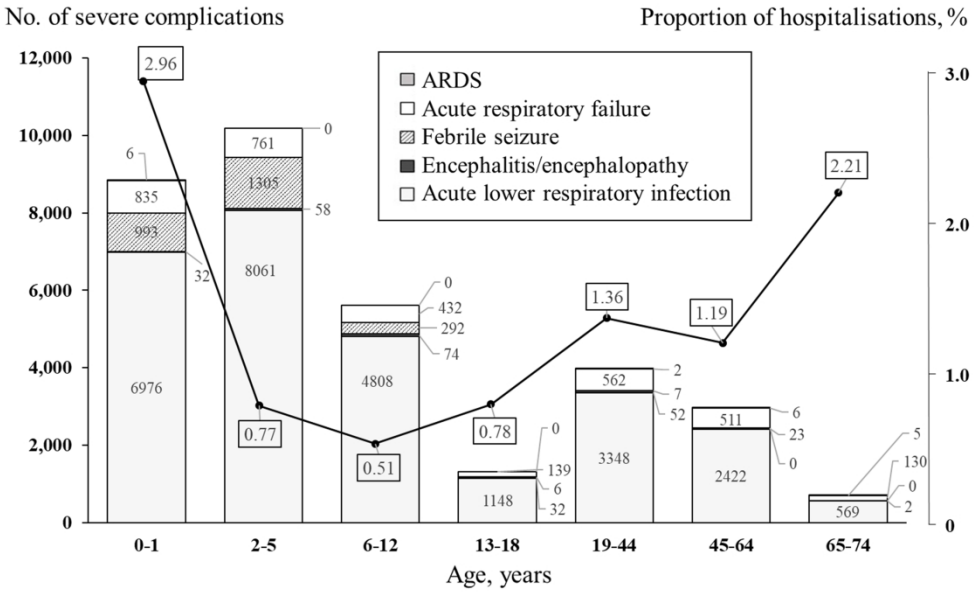
Histogram of the ages of influenza-infected outpatients in the 2012/13, 2013/14, 2014/15, and 2015/16 seasons, according to health insurance administrative data.

284x189mm (300 x 300 DPI)



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)

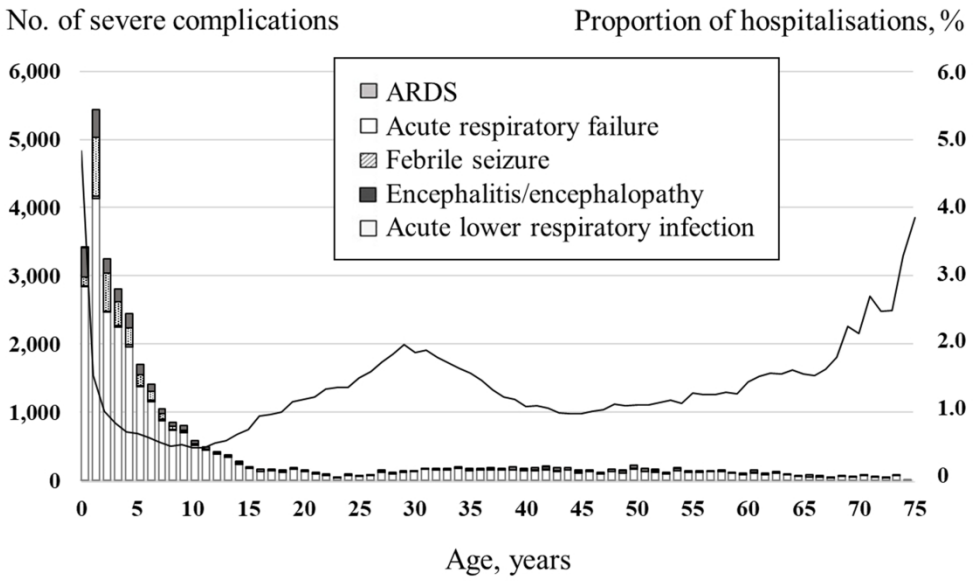


Figure 4. Number of influenza-infected inpatients with severe complications and proportion of infection and hospitalisation in a health insurance claim database, by age, between 2012 and 2016. Bars represent the number of each severe complication; the line represents the proportion of infections with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

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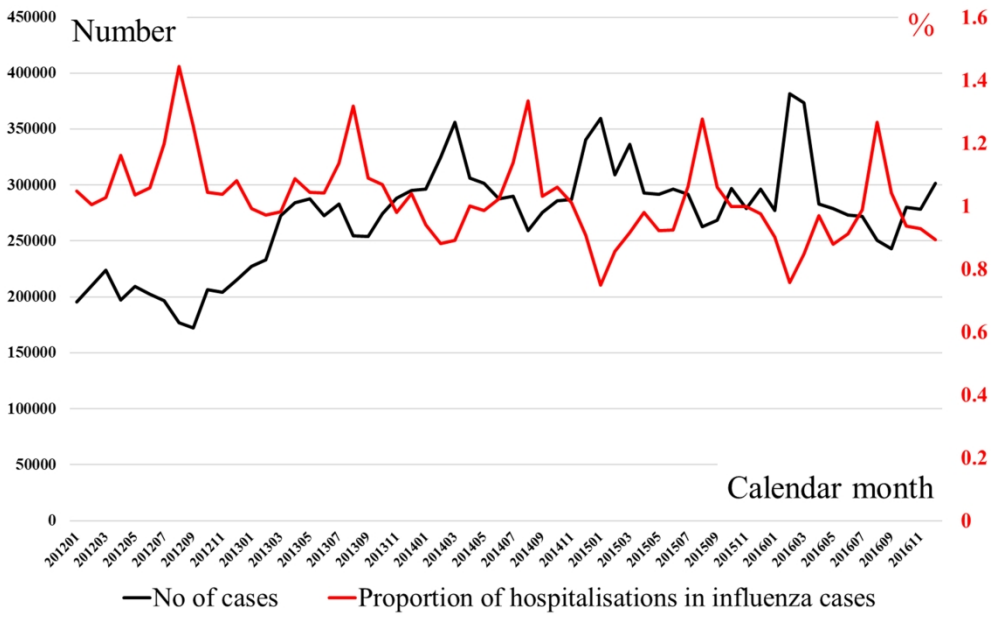

Number of influenza-infected inpatients and proportion of hospitalisation in health insurance claim database between 2012 and 2016. Black line represents number of inpatients; red line proportion of infections hospitalised.

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 #
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
Introduction			
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
Methods			
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
Results			
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
Discussion			
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
Other information			
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.

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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

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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

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Abstract

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

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

Setting: Japanese clinics and hospitals between 2012 and 2016.

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

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

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

65–74. The incidence of hospitalisations from these five complications combined was highest in influenza-positive patients aged 0–1 years (943 per 100000) compared with 307 in those aged 2–5 years and 271 in those aged 65–74 years. For pneumonia, incidence was highest for influenza-positive patients aged 0–5 years and 65 years or more. There were statistically significant decreasing trends over the years in the incidence of all-cause hospitalisations, pneumonia and febrile seizures.

Conclusions: Japanese administrative data revealed that 1.0% of influenza-positive patients aged under 75 years were hospitalised. Male patients had a higher incidence of pulmonary complications and febrile seizures. Children aged 0–5 years and adults aged 65–74 years were at high risk of being admitted to hospital for pneumonia.

Registration: The ethics committee of the School of Medicine, University of Yamanashi approved this study (approval number: H29-1709).

(292 words/300 words)

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.

INTRODUCTION

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

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

the infected population, combing the risk of infection and the risk of complications. This is problematic because programmes targeting high risk groups, such as vaccination or prophylaxis may reduce the number of infections in high risk groups, biasing estimates of the risk of complications if infected.[12] Also, many studies pre-date the option of administering new neuraminidase inhibitors.[13]

Although it is also seen internationally,[14-18] influenza encephalitis is a particular concern amongst Japanese physicians owing to a high incidence and mortality rate in Japan.[7 19-23] The prognosis for patients with influenza encephalitis/encephalopathy is very poor; approximately 30% of affected patients die and 20–30% have neurological sequelae.[24] To understand the aetiology and prevalence of this severe outcome, surveillance has been conducted.[25 26] In Japan, influenza-associated encephalopathy is a notifiable disease.[27] Japanese physicians are required to report influenza infection cases with: a) death after coma or hospitalisation with coma for 24 hours or more; and b) a fever of 38°C or higher, central nervous system manifestation or prior influenza infection symptoms. This surveillance system has detected 60–100 influenza encephalitis cases annually [28] and 331 cases during the 2009–2010 pandemic;[26] however, underreporting of cases has been acknowledged.[28] Another survey of paediatric departments in 265 hospitals reported

263 influenza-associated encephalopathy cases over 3 years.[25] The authors estimate that there are 200–300 influenza encephalopathy cases per annum in Japan;[29] therefore, the incidence of influenza encephalitis/encephalopathy is not accurately known.

To understand the incidence of severe complications in patients with influenza, an analysis of large-scale real-world data is needed, encompassing hospital and community sites. Previous studies using large data sets of routinely collected medical records have had to rely on clinical diagnoses of influenza-like illness or modelling of influenza and other respiratory virus infections using incomplete laboratory data.[11] In Japan, diagnostic testing for influenza is routine, which presents a unique opportunity to combine the benefits of large data sets with positive diagnoses.[6] We therefore sought to estimate the incidence of hospitalisation with the above five severe complications per influenza infection, using Japanese health insurance claim data.

METHODS

Patients and data

We analysed administrative data provided by Japan Medical Data Center Ltd. (renamed to JMDC) Tokyo, Japan.[30] The data source was the monthly health insurance claim records between January 2012 and December 2016 of approximately three million employees and their dependents, representing 2.4% of the Japanese population. Within health insurance coverage in Japan, people can consult physicians in any type of hospital and department, and medical doctors in any speciality can diagnose influenza and prescribe anti-influenza medications. The age of patients in the data set ranged from 0 to 74 years because all Japanese people aged 75 or more (except for individuals who are on public assistance) are covered by another health insurance program with lower out-of-pocket expenses.

From the database, we extracted the data of individuals who consulted physicians with influenza-like illness episodes. We then included only patients with a diagnosis of influenza virus infection. In Japan, the use of immunochromatogenic assay point-of-care tests [POCT] in clinical practice has been covered by public health insurance from 1999.[23] As recommended in Japanese guidelines,[31] a test-and-treat strategy is routine.[23 32] Even if physicians only slightly suspect influenza infection, they use a POCT to diagnose influenza, and administer antivirals to the positive patients.[31 33 34] Testing would be indicated in fever, sore throat, malaise, non-

productive cough or a history of family's infection, for example.[23 35] During the 2009–2010 pandemic influenza A(H1N1) season, physicians performed this test in majority of cases (>90%) and we believe this was likely to be the case during the period of this study because in Japan paediatric patients with an influenza-like illness are required to obtain a medical certificate showing they do not have influenza before return to school.[36]

Outcomes

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

and had been administered steroid pulse or immunoglobulin therapy.[37]

Statistical analysis

We examined the number of diagnosed influenza infections and severe complications by sex, age, outpatient/inpatient status, number of beds in the facility, and clinical speciality. In Japan, clinical facilities with fewer than 20 beds are denoted a "clinic" by law. Clinics are usually run by a single medical doctor and function as a primary care department. Most clinics have no beds but a very small subset of clinics have 1–19 beds to accommodate inpatients. In contrast, facilities with 20 beds or more are legally termed a "hospital". Hospitals have primary care, specialised outpatient, and general and specialised inpatient departments. In this study, hospitalised influenza-positive patients were inpatients in both "clinic" and "hospital" settings. We plotted histograms of the ages of outpatients and inpatients infected with influenza. We determined the incidence of inpatients with the five severe complications by dividing the number of complications by the number of infections. We stratified this by sex, influenza season and age. We also examined the numbers of the influenza-infected patients and the proportions of inpatients over calendar time at the request of a reviewer. Influenza seasons were defined as lasting from September through to the following August. We calculated p values for secular

trends of incidence over influenza seasons. Statistical analyses were performed using SAS statistical software (version 9.4, SAS Institute, Cary, NC, USA). All reported p values were two-sided and we considered $p<0.05$ indicated a significant difference.

Ethical approval

The ethics committee of the School of Medicine, University of Yamanashi approved this study (approval number: H29-1709), in accordance with the ethical guidelines and regulations of the Declaration of Helsinki. The data were properly anonymised by the JMDC in the manner permitted by Japanese guideline of Personal Information Protection Commission, Cabinet Office, Government of Japan for the use of data from medical examinations in medical research without individual participants' consent (Act on the Protection of Personal Information, act no. 57 of 30 May 2003; last version amendment of act no. 65 of 2015).

Patient and public involvement

Patients were not actively involved in developing the research question and protocol including outcome measures. The participants will be provided the final study results by clinical research information services and homepage of the University of Yamanashi.

RESULTS

Characteristics of patients diagnosed with influenza

Table 1 summarises the number of patients with diagnoses of influenza infection in the study population. Among 16636913 infections, 53.4% of the patients were men, and 1.0% were hospitalised. Approximately a quarter (25.7%) of infections were in children aged 6–12 years. Overall 32% of diagnoses were made in the internal medicine department and 23% in paediatrics. Most infections were diagnosed in clinics (n=13572391; 83%). Figures 1 and 2 illustrate the number of outpatients and inpatients with influenza infection, respectively, by age. Influenza was most often diagnosed in outpatients aged 0–12 years, with a second small peak in middle-aged patients. In contrast, inpatient cases were commonest among patients aged less than one year. Table 2 shows the number of complicated cases by department, hospital size and type of hospital management. A total of 3361 patients (0.02%) were admitted to hospital with acute respiratory failure, 27253 (0.16%) with pneumonia, 18 (0.0001%) with ARDS, 2603 (0.02%) with febrile seizures, and 159 (0.001%) with encephalitis/encephalopathy. Most complicated cases were admitted to paediatric departments, with 19012 pneumonia admissions (70% of the total),

1794 with acute respiratory failure (53% of the total), 2461 with febrile seizures (95% of the total), and 63 encephalitis (40% of all cases). The number of inpatients with acute respiratory failure, pneumonia, and febrile seizure tended to increase with the number of hospital beds.

Hospitalisation rates from severe complications

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

failure, pneumonia, and febrile seizure was highest in patients aged 0–1 years, ARDS was highest in those 65–74 years, and encephalitis/encephalopathy was highest in patients aged 13–18 years.

Figures 3 and 4 show the number and percentage of inpatients with complications by age group and age over the study period. Young children had most of the severe complications. Across all age groups, pneumonia was by far the most common of the five complications, and the age group with the largest number of cases was children aged 2–5 years. In contrast, the proportion of infections hospitalised was highest in patients aged 0–1 years (2.96%) and second highest in those aged 65–74 years (2.21%).

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

DISCUSSION

Principal findings

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

Comparison with previous research

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

respiratory failure, pneumonia, and febrile seizures (table 3). This is consistent with previous studies reporting that during the 2009–2010 pandemic influenza A(H1N1) season, the incidence of hospitalisation in male children was greater than in female children in the US (56%),[38] Canada (60%),[39] and Japan (64.3%).[6] Asthma is a risk factor for pneumonia in children with influenza.[40] Our finding of an increased risk of pneumonia in males may be because asthma is a more common disease in boys than girls.[41] It is also known that boys get febrile seizures more often than girls.[42] This was also observed in our data for febrile seizures with influenza infection. In contrast, our data suggest the possibility of a higher risk of encephalitis/encephalopathy in women with influenza infection (table 3). However, in Japanese surveillance reports from 2007 to 2010, 153 of 263 (58.2%) paediatric patients with encephalopathy were male.[25] Because the means of data collection in previous studies were different, we are unable to conclude in which sex complications are more common. Further study with another large data set is needed to investigate risk factors, including sex, for hospitalisation and incidence of encephalitis/encephalopathy in Asian people.

Our results by age are consistent with those of previous studies, and add to understanding the risk of specific complications amongst those with a diagnosis of influenza. Previous studies, being unable to identify a large number of influenza-positive

patients, have used small numbers of influenza positive admissions as cases and general population estimates as the denominators. This combines the risk of infection and the risk of complications. We found that the risk of hospitalisation was highest in infected infants aged 0–1 years (figures 2–4 and table 3). This is consistent with a US study, which found that the highest hospitalisation rate was among infants aged under one year (11.9 per 100000 population) during the 2009–2010 influenza A(H1N1) pandemic;[9] in addition, we are able to show that the risk of admission is as high as 943 per 100000 infections. A study from the UK also reported that children aged 6 months to 4 years had the high influenza related hospitalisation rates between 2001 and 2007 (3360 per 100000 population).[8]

A systematic review found large gaps in the evidence base (describing the evidence for risk factors for admissions as "limited to absent").[12] They found contrasting results with children under the age of two years at higher risk of admission to hospital than older children with pandemic H1N1 influenza but the reverse with seasonal influenza.[12] They also found evidence of spectrum bias; studies from hospitals and intensive care units gave lower estimates of risk of death than community-based studies for both the elderly and children compared to young adults. As well as including positively diagnosed patients, our study covers both the community and hospital settings

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

Implications for clinicians and policymakers

During the 2009–2010 pandemic, the World Health Organization [47] and the Centers for Disease Control and Prevention [48] issued guidelines for early neuraminidase inhibitor treatment. There are suggestions that administration of this medication within 48 hours reduces mortality and severe outcomes.[49] A Cochrane review, whilst critical of the quality of trial evidence, found a reduction in secondary infections among children who were prescribed oseltamivir.[50] During the 2000s, four neuraminidase inhibitors became available in Japan: zanamivir in 2000, oseltamivir in 2001, and laninamivir and peramivir in 2010.[23] The Japanese Association for Infectious Diseases also recommended post-

exposure prophylaxis of zanamivir and oseltamivir in hospitals and geriatric facilities in 2012. Reportedly, seven to eight million patients per annum were prescribed with neuraminidase inhibitors from 2011 to 2015; more than half of all patients infected with influenza received these medicines.[23] The decreasing trend with time in the hospitalisation and the composite incidence of the five severe complications (table 3, $p<0.0001$) might be attributed to the increasingly widespread use of [13 33] and more options for neuraminidase inhibitors.[6 23] This decreasing trend was not altered in the 2014/15 season when influenza A(H3N2) spread internationally including in Japan.[51] A recent meta-analysis of randomised controlled trials reported that in patients with pathogen-ascertained influenza, as is practice in Japan, treatment with oseltamivir reduced hospital admissions by 63%.[52]

In our study, the incidence of hospitalisations, acute pneumonia and febrile seizures decreased with time (table 3, all p values <0.0001). This was observed in parallel with increased administration of neuraminidase inhibitors. However, there appears to be no trend in the risk of encephalitis/encephalopathy. Because influenza encephalitis appears to be mediated by an acute process during infection,[14] it is important to prevent influenza infection to reduce the incidence of encephalitis. The primary countermeasure to protect individuals from infection is vaccination. National vaccine policies may have

impacted upon variation in the hospitalisation incidence between countries. In Japan, schoolchildren were vaccinated routinely from 1976 to 1993, when influenza was removed from the list of free routine vaccinations, and vaccination of high risk groups was only recommended from 2001, albeit for a fee which has limited uptake.[53] Studies of this natural experiment suggest that the former routine vaccination program for schoolchildren indirectly reduced excess mortality among the elderly.[46 54] The previous results suggest indirect effect of the vaccines upon reducing severe complication risk amongst children; however, the effect upon the incidence of encephalitis is unknown. Because current encephalitis treatments are of limited effectiveness, a vaccination program covering a broad population may be the best way to reduce the morbidity associated with influenza encephalitis.

Strengths and weaknesses

A main strength of this study is that the included patients were diagnosed with influenza by testing. The majority of influenza-like illness is usually caused by infections other than influenza.[55] Diagnoses were based on rapid antigen detection with immunochromatogenic assay. Because POCTs for influenza are less invasive and require less time than laboratory tests, they are an essential tool for physicians to evaluate

influenza in outpatient and inpatient clinical practice in Japan.[6] Although low sensitivity (59–93%) [56] is a weak point for POCTs, the specificity is 98–100%.[34 57] This means that nearly all individuals with influenza-like illness who have POCT-positive results (the participants in this study) were infected with influenza. This makes routinely collected Japanese data unique. Additionally, all Japanese people who are hospitalised with severe complications of influenza infection should be present in universal health insurance data. Therefore, we did not greatly overestimate the number of infected patients or underestimate severe complications, and thus did not underestimate the risk of complications and hospitalisations.

There are limitations inherent to the data set used in this study. Firstly, POCTs for influenza are known to have variable sensitivity. In the 2010s, 20 or more POCT kits were available in Japan.[58] Sensitivity would have been influenced by the following factors. (1) Time from the onset of illness. Reportedly, the sensitivity is lower 0–24 hours from symptom onset and higher in days 2–4.[59 60] Parents tend to bring children to paediatricians at an earlier stage of the infection while infected employed adults tend to consult physicians in mid- or later stages. This would bias sensitivity toward comparatively low in children compared to adults. (2) Patient age. In contrast children are known to have higher viral load and longer shedding and consequently POCTs have

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

Second, the administrative data from employees and their families used here do not permit analysis of patients aged 75 years or more. Also, due to employment patterns in Japan, the number of male patients was slightly higher than female patients (table 1). The sex ratio varies across generations in Japan, with more males in younger populations and women predominating in older populations.[62] However, the incidence of hospitalisation amongst infected patients in both sexes and the studied age groups should not be biased by this imbalance. Third, we were unable to estimate influenza-related mortality in this data set, but the data are sufficient to allow examination of serious complications that are major public health concerns. Although we were unable to define encephalitis/encephalopathy cases virologically, we added the requirement of receiving specific therapy to the definition of encephalitis/encephalopathy cases.[37] This more stringent definition reduces the likelihood that we have overestimated this outcome. Further analyses of influenza-related mortality in Japan are needed, and this should encompass older adults. The effect of neuraminidase inhibitors should be examined using observational data, as clinical trials are likely to be underpowered for rare but important complications such as encephalopathy.

Conclusions

Using Japanese administrative data, 1.0% of patients who tested positive for influenza infection were hospitalised. Male patients had a higher incidence of pulmonary complications and febrile seizures. Children aged 0–5 years and adults aged 65–74 years were at high risk of being admitted to hospital for pneumonia, with the highest absolute numbers of hospitalised patients among young children. Further efforts are needed, such as active prescription of neuraminidase inhibitors and vaccination programs, to prevent hospitalisations from severe complications in these age groups.

(3849 words)

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Authors' contributions All of the authors agreed with the manuscript's results and conclusion and approved the final version of the manuscript. HY conceived the study. HY, MM, JL, RK, TY and ZY contributed to the design of the study and interpretation of the data analyses. HY analysed the data. HY, JL, MM and RK wrote the first draft of

the manuscript. JL, RK, MM, ZY and HY contributed to revision of the manuscript. ZY and HY were responsible for data integrity. HY obtained funding.

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Competing interests. None.

Patient consent Not required.

Ethics approval The ethics committee of the School of Medicine, University of Yamanashi approved this study (approval number: H29-1709).

Data sharing statement The original administrative data are available through a formal request to the Japan Medical Data Center Ltd., subject to fees.

References

1. Ghebrehewet S, MacPherson P, Ho A. Influenza. *BMJ* 2016;355:i6258.

2. Kaiser L, Wat C, Mills T, *et al.* Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalisations. *Arch Intern Med* 2003;163:1667–72.

3. Iuliano AD, Roguski KM, Chang HH, *et al.* Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *Lancet* 2017;391:1285–1300.

4. Thompson WW, Shay DK, Weintraub E, *et al*. Influenza-associated hospitalizations in the United States. *JAMA* 2004;292:1333–40.

5. Newland JG, Laurich VM, Rosenquist AW, *et al*. Neurologic complications in children hospitalized with influenza: characteristics, incidence, and risk factors. *J Pediatr* 2006;150:306–10.

6. Sugaya N, Shinjoh M, Mitamura K, *et al.* Very low pandemic influenza A (H1N1) 2009 mortality associated with early neuraminidase inhibitor treatment in Japan: analysis of 1000 hospitalized children. *J Infect* 2011;63:288–94.

7. Influenza Working Group of the Japan Pediatric Society. Secondary treatment guideline of 2013/2014 influenza infection. 2014. Japanese. https://www.jpeds.or.jp/uploads/files/2013_2014_influenza_all.pdf. Accessed 1 December 2018.

8. Cromer D, van Hoek AJ, Jit M, *et al.* The burden of influenza in England by age and clinical risk group: a statistical analysis to inform vaccine policy. *J Infect* 2014;68:363–71.

9. Louie JK, Acosta M, Winter K, *et al.* Factors associated with death or hospitalization due to pandemic 2009 influenza A (H1N1) infection in California. *JAMA* 2009;302:1896–902.

10. Nicholson KG, McNally T, Silverman M, *et al.* Rates of hospitalisation for influenza, respiratory syncytial virus and human metapneumovirus among infants and young children. *Vaccine* 2006;24:102–08.

11. Pitman R, Melegaro A, Gelb D, *et al.* Assessing the burden of influenza and other respiratory infections in England and Wales. *J Infect* 2007;54:530–38.

12. Mertz D, Kim TH, Johnstone J, *et al.* Populations at risk for severe or complicated

influenza illness: systematic review and meta-analysis. *BMJ* 2013;347:f5061.

13. Sugaya N. Widespread use of neuraminidase inhibitors in Japan. *J Infect Chemother* 2011;17:595.

14. Amin R, Ford-Jones E, Richardson SE*, et al.* Acute childhood encephalitis and encephalopathy associated with influenza: a prospective 11-year review. *Pediatr Infect Dis J* 2008;27:390–95.

15. Ekstrand JJ, Herbener A, Rawlings J*, et al.* Heightened neurologic complications in children with pandemic H1N1 influenza. *Ann Neurol* 2010;68:762–66.

16. Evans A, Agadi S, Siegel J*, et al.* Neurologic complications associated with novel influenza A (H1N1) virus infection in children-Dallas, Texas, May 2009. *MMWR-Morb. Mortal. Wkly. Rep* 2009;58:773–78.

17. Rellosa N, Bloch KC, Shane AL*, et al.* Neurologic manifestations of pediatric novel H1N1 influenza infection. *Pediatr Infect Dis J* 2011;30:165–67.

18. Baltagi SA, Shoykhet M, Felmet K*, et al.* Neurological sequelae of 2009 influenza A (H1N1) in children: a case series observed during a pandemic. *Pediatr Crit Care Med* 2010;11:179–84.

19. Kasai T, Togashi T, Morishima T. Encephalopathy associated with influenza epidemics. *Lancet* 2000;355:1558–59.

20. Morishima T, Togashi T, Yokota S*, et al.* Encephalitis and encephalopathy associated with an influenza epidemic in Japan. *Clin Infect Dis* 2002;35:512–17.

21. Sugaya N. Influenza-associated encephalopathy in Japan. *Semin Pediatr Infect Dis* 2002;13:79–84.

22. Akihisa O, Satoshi N, Hisashi K*, et al.* Deaths associated with pandemic (H1N1) 2009 among children, Japan, 2009–2010. *Emerg Infect Dis J* 2011;17:1993–2000.

23. Zaraket H, Saito R. Japanese surveillance systems and treatment for influenza. *Curr Treat Options Infect Dis* 2016;8:311–28.

24. Wang GF, Li W, Li K. Acute encephalopathy and encephalitis caused by influenza virus infection. *Curr Opin Neurol* 2010;23:305–11.

25. Hoshino A, Saitoh M, Oka A*, et al.* Epidemiology of acute encephalopathy in Japan, with emphasis on the association of viruses and syndromes. *Brain Dev* 2012;34:337–43.

475 26. Gu Y, Shimada T, Yasui Y*, et al.* National surveillance of influenza-associated
476 encephalopathy in Japan over six years, before and during the 2009–2010 influenza
477 pandemic. *Plos One* 2013;8:e54786.

478 27. Okumura A, Nakagawa S, Kawashima H*, et al.* Deaths associated with pandemic
479 (H1N1) 2009 among children, Japan, 2009–2010. *Emerg Infect Dis* 2011;17:1993–
480 2000.

481 28. National Institute of Infectious Diseases and Mnistry of Health, Labout and Welfare.
482 Infectious agents surveillance report 36. 2015. Japanese. Available at
483 https://www0.niid.go.jp/niid/idsc/iasr/36/429j.pdf. Accessed 1 December 2018.

484 29. Mizuguchi M. Influenza encephalopathy and related neuropsychiatric syndromes.
485 *Influenza Other Resp* 2013;7:67–71.

486 30. Tanaka S, Seto K, Kawakami K. Pharmacoepidemiology in Japan: medical
487 databases and research achievements. *J Pharm Health Care Sci* 2015;1:16.

488 31. Uehara S, Sunakawa K, Eguchi H*, et al.* Japanese guidelines for the management of
489 respiratory infectious diseases in children 2007 with focus on pneumonia. *Pediatr Int*
490 2011;53:264–76.

32. Ito M, Watanabe M, Nakagawa N, *et al.* Rapid detection and typing of influenza A and B by loop-mediated isothermal amplification: comparison with immunochromatography and virus isolation. *J Virol Methods* 2006;135:272–75.

33. Sugaya N, Mitamura K, Yamazaki M, *et al.* Lower clinical effectiveness of oseltamivir against influenza B contrasted with influenza a infection in children. *Clin Infect Dis* 2007;44:197–202.

34. Suzuki M, Yoshimine H, Harada Y, *et al.* Estimating the influenza vaccine effectiveness against medically attended influenza in clinical settings: a hospital-based case-control study with a rapid diagnostic test in Japan. *Plos One* 2013;8:e52103.

35. Watanabe M, Nakagawa N, Ito M, *et al.* Sensitivity of rapid immunoassay for influenza A and B in the early phase of the disease. *Pediatr Int* 2009;51:211–15.

36. Komiya N, Gu Y, Kamiya H, *et al.* Clinical features of cases of influenza A (H1N1) v in Osaka prefecture, Japan, May 2009. *Eurosurveillance* 2009;14:19272.

37. Study Group of Influenza Encephalitis. Ministry of Health, Labour and Welfare. Guideline of treatmant for influenza encephalitis. revised edition. 2011. Japanese.

https://www.mhlw.go.jp/kinkyu/kenkou/influenza/hourei/2009/09/dl/info0925-01.pdf. Accessed 1 December 2018.

38. Kumar S, Havens PL, Chusid MJ, *et al.* Clinical and epidemiologic characteristics of children hospitalized with 2009 pandemic H1N1 influenza A infection. *Pediatr Infect Dis J* 2010;29:591–94.

39. O'Riordan S, Barton M, Yau Y, *et al*. Risk factors and outcomes among children admitted to hospital with pandemic H1N1 influenza. *Can Med Assoc J* 2010;182:39–44.

40. Lee JJ, Bankhead C, Smith M, *et al*. Risk factors for influenza-related complications in children during the 2009/10 pandemic: a UK primary care cohort study using linked routinely collected data. *Epidemiol Infect* 2018:1–7.

41. Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. *BMJ* 1996;312:1195–99.

42. Tsuboi T. Epidemiology of febrile and afebrile convulsions in children in Japan. *Neurology* 1984;34:175–75.

43. Talbot HK, Zhu Y, Chen Q, *et al.* Effectiveness of influenza vaccine for preventing laboratory-confirmed influenza hospitalizations in adults, 2011–2012 influenza season. *Clin Infect Dis* 2013;56:1774–77.

44. Yokomichi H, Kurihara S, Yokoyama T, *et al.* The pandemic influenza A (H1N1) 2009 vaccine does not increase the mortality rate of idiopathic interstitial pneumonia: a matched case-control study. *Plos One* 2014;9:e88927.

45. Yokomichi H, Kurihara S, Yokoyama T, *et al.* Safety of the influenza A (H1N1)2009 vaccine in chronic obstructive pulmonary disease: a matched case-control study. *J Vaccines Vaccination* 2012;3:1000148.

46. Reichert TA, Sugaya N, Fedson DS, *et al.* The Japanese experience with vaccinating schoolchildren against influenza. *N Engl J Med* 2001;344:889–96.

47. World Health Organization. Rapid advice guidelines for pharmacological management of pandemic influenza (H1N1) 2009 and other influenza viruses. 2010. Available at http://www.who.int/csr/resources/publications/swineflu/h1n1_guidelines_pharmaceutical_mngt.pdf. Accessed 1 December 2018.

48. Centers for Disease Control and Prevention. Updated interim recommendations for the use of antiviral medications in the treatment and prevention of influenza for the 2009–2010 season. Available at https://www.cdc.gov/h1n1flu/recommendations.htm. Accessed 1 December 2018.

49. Muthuri SG, Myles PR, Venkatesan S, *et al*. Impact of neuraminidase inhibitor treatment on outcomes of public health importance during the 2009–2010 influenza A (H1N1) pandemic: a systematic review and meta-analysis in hospitalized patients. *J Infect Dis* 2012;207:553–63.

50. Jefferson T, Jones MA, Doshi P, *et al*. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev* 2012;1 Art:CD008965.

51. Pebody R, Warburton F, Andrews N, *et al.* Effectiveness of seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2014/15 end of season results. *Eurosurveillance* 2015;20:30013.

52. Dobson J, Whitley RJ, Pocock S, *et al.* Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. *Lancet* 2015;385:1729–37.

555 53. Hirota Y, Kaji M. History of influenza vaccination programs in Japan. *Vaccine*
556 2008;26:6451–54.

557 54. Charu V, Viboud C, Simonsen L*, et al.* Influenza-related mortality trends in
558 Japanese and American seniors: evidence for the indirect mortality benefits of
559 vaccinating schoolchildren. *Plos One* 2011;6:e26282.

560 55. Hayward AC, Fragaszy EB, Bermingham A*, et al.* Comparative community burden
561 and severity of seasonal and pandemic influenza: results of the Flu Watch cohort
562 study. *Lancet Resp Med* 2014;2:445–54.

563 56. Paules C, Subbarao K. Influenza. *Lancet* 2017;390:697–708.

564 57. Poehling KA, Zhu Y, Tang Y-W, *et al*. Accuracy and impact of a point-of-care rapid
565 influenza test in young children with respiratory illnesses. *Arch Pediatr Adolescent*
566 *Med* 2006;160:713–18.

567 58. Sakai-Tagawa Y, Ozawa M, Tamura D*, et al.* Sensitivity of influenza rapid
568 diagnostic tests to H5N1 and 2009 pandemic H1N1 viruses. *J Clin Microbiol*
569 2010;48:2872–77.

570 59. Hata A, Asada J, Mizumoto H*, et al.* Appropriate use of rapid diagnostic testing for

influenza. *J Jpn Assoc Infect Dis* 2004;78:846-52.

60. Landry ML. Diagnostic tests for influenza infection. *Curr Opin Pediatr* 2011;23:91–97.

61. Chartrand C, Leeflang MM, Minion J*, et al.* Accuracy of rapid influenza diagnostic tests: a meta-analysis. *Ann Intern Med* 2012;156:500–11.

62. Central Intelligence Agency. The world factbook: sex ratio (male/female). 2018. Available at https://www.cia.gov/library/publications/the-world-factbook/fields/2018.html. Accessed 1 December 2018.

Figure legends

Figure 1. 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.

Figure 2. 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.

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

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

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

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

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

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

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

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	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)	231125 (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	Otorhinolaryngology	Orthopaedics	Dermatology	Surgery	Ophthalmology	Obstetrics &	Psychiatry

No. patients (%)	1187638 (32.4)	827942 (22.6)	310514 (8.5)	308146 (8.4)	250737 (6.8)	206763 (5.6)	165913 (4.5)	Gynaecology 156615 (4.3)	99624 (2.7)

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

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

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

Abbreviation: ARDS, acute respiratory distress syndrome.

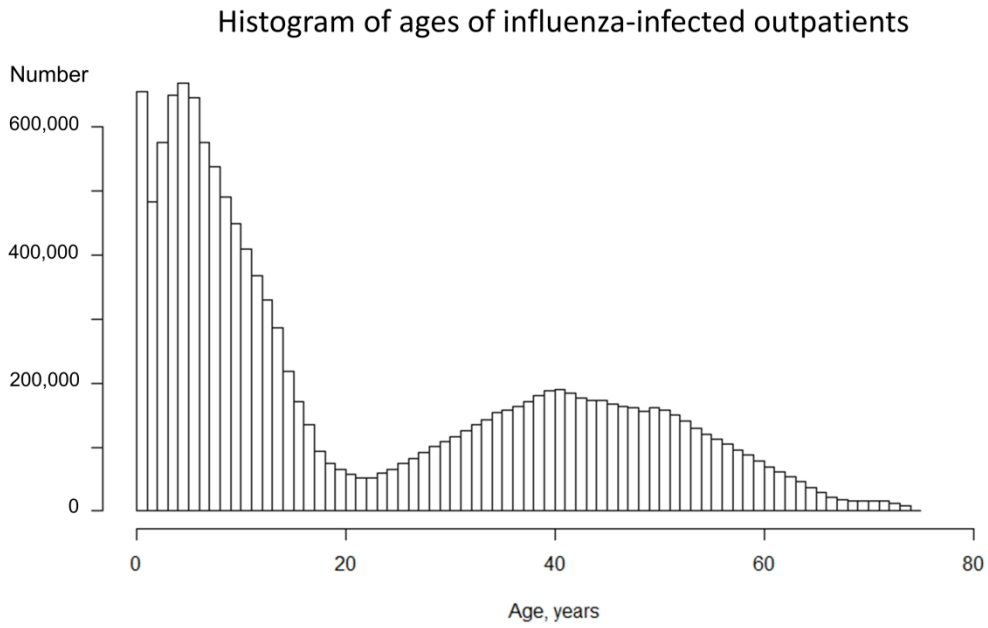
Table 3. Incidence of hospitalisation with severe complications per 100000 confirmed influenza infections.

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

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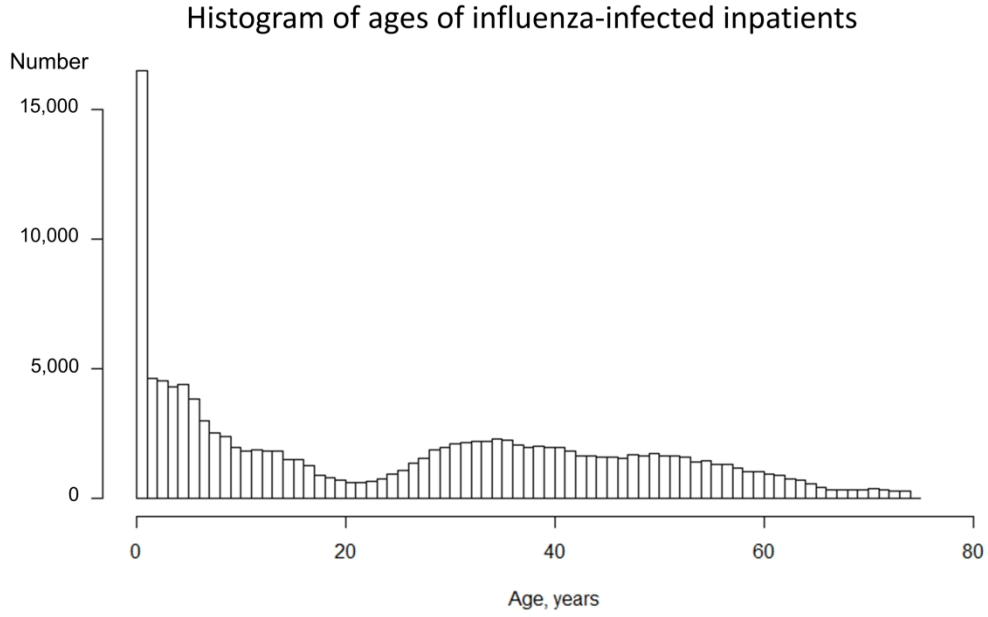

Histogram of the ages of influenza-infected inpatients in the 2012/13, 2013/14, 2014/15, and 2015/16 seasons, according to health insurance administrative data.

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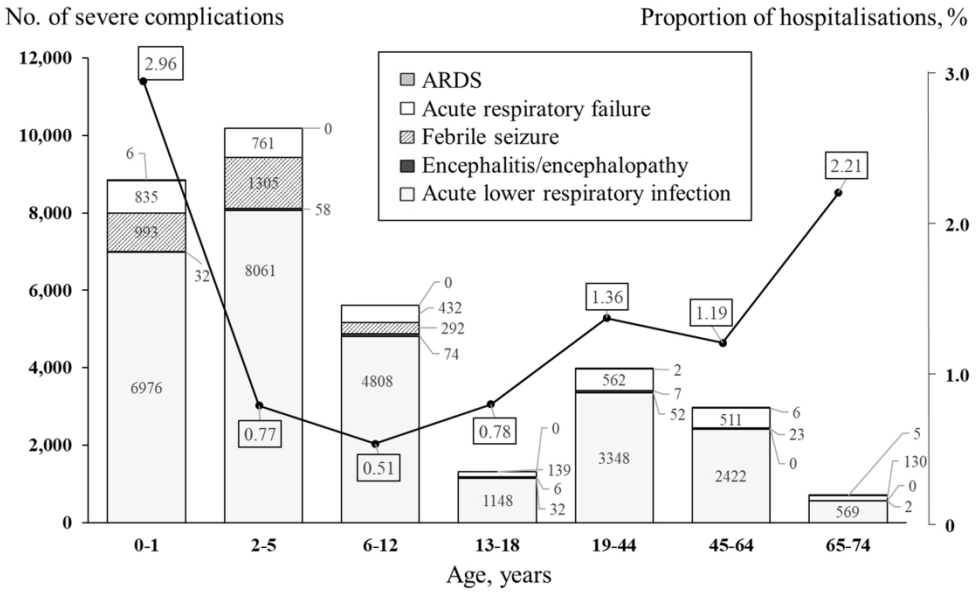

Number of influenza-infected inpatients with severe complications and proportion of infections and hospitalisation in a health insurance claim database, by age group, between 2012 and 2016. Bars represent the number of each severe complication; the line represents the proportion of infections resulting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

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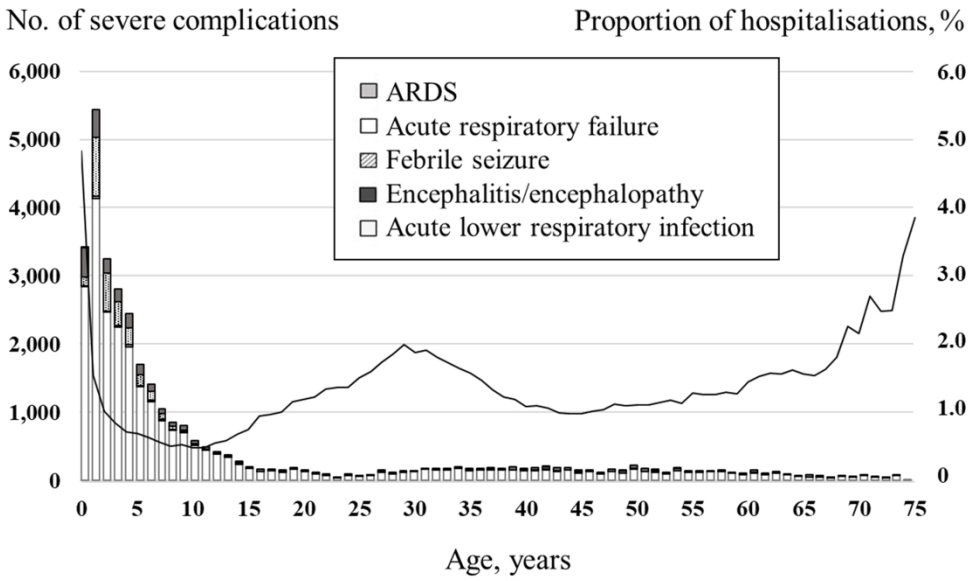
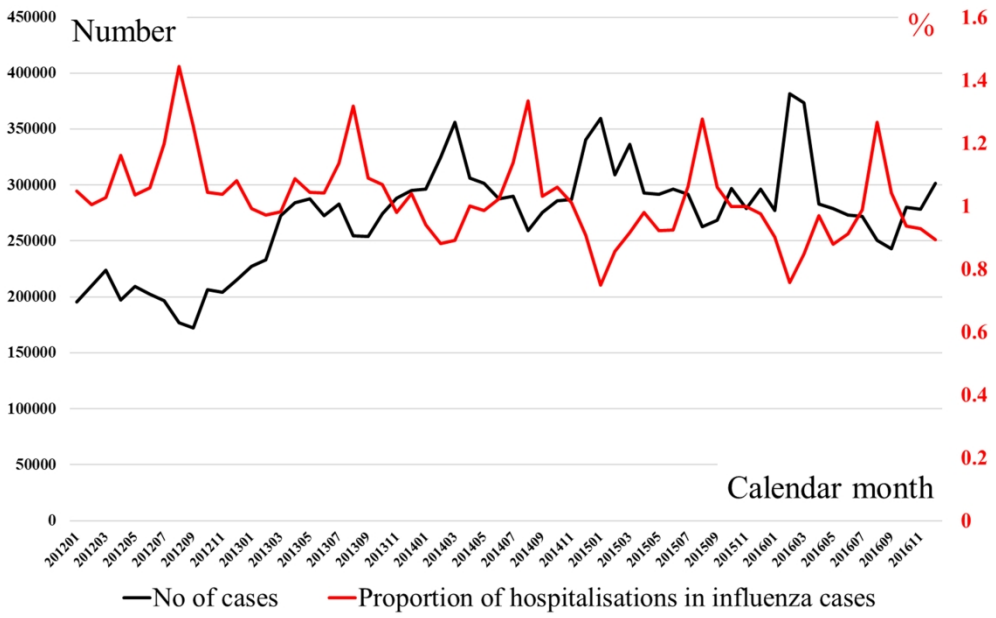


Figure 4. Number of influenza-infected inpatients with severe complications and proportion of infection and hospitalisation in a health insurance claim database, by age, between 2012 and 2016. Bars represent the number of each severe complication; the line represents the proportion of infections with 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 #
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
Introduction			
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
Methods			
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
Results			

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
Discussion			
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
Other information			
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.