Research Square

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The Characteristics of Influenza-Like Illness Management in Japan

Shinya Tsuzuki (stsuzuki@hosp.ncgm.go.jp)
National Center for Global Health and Medicine https://orcid.org/0000-0002-8504-1244
Keisuke Yoshihara
Nagasaki Daigaku

Research article

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Abstract

Background: This study aimed to make a quantitative assessment of the management of influenza-like illnesses in Japanese healthcare settings.

Methods: We analysed participants' healthcare-seeking behaviour and physicians' practice in January 2019 using an online survey of 200 households in Japan. Quality of life score, quality-adjusted life years lost, the duration of symptoms, and the duration of absence from work were compared between influenza group and influenza-like illness group with one-to-one propensity score matching. Missing data were imputed using multiple imputation.

Results: In total, 261 of the 600 (43.5%) participants had at least one episode of influenza-like illness during January 2019. Of these, 194 (75.5%) visited healthcare facilities, 167 (86.1%) within 2 days of onset of symptoms. A total of 169 out of 191 (88.5%) received a rapid influenza diagnostic test and 101 were diagnosed with influenza, of whom 92.2% were treated with antivirals. The median quality-adjusted life-years lost was 0.0055 (interquartile range, IQR 0.0040–0.0072) and median absence from work for a single episode of influenza-like illness was 2 days (IQR 1–5 days).

Conclusions: In Japan, most people with influenza-like illnesses visit healthcare facilities soon after symptoms first occur and receive a diagnostic test. Those with influenza are usually treated with antivirals. Absence from work was longer for influenza than other similar illnesses.

Introduction

Seasonal influenza generally occurs in regular annual epidemics and its disease burden is substantial[1–3]. However, it is difficult to evaluate the disease burden precisely because clinical manifestations and severity of influenza infection vary considerably[4]. Most influenza cases are mild and self-limiting, or even asymptomatic[5]. It is therefore difficult to estimate the total number of people with the disease. The concept of influenza-like illness (ILI) adds further complexity, with other respiratory viruses such as rhinovirus and respiratory syncytial virus having similar symptoms to influenza[6–8]. Physicians in most countries do not use virological tests for ILI patients because many of the symptoms are mild and test results will not affect disease management. Most countries therefore use ILI surveillance as an approximate indicator of influenza levels[1, 2], even though this may both undercount actual influenza infections and include some other respiratory infections.

The concept of medically-attended influenza may be helpful in identifying the disease burden of influenza. The burden from seasonal influenza has two aspects. The first is severe disease and deaths, and the second is the economic impact from large number of mild cases which result in absence from work, losses to production, and costs to health and social care services[1]. Deaths will be covered in official statistics but it is difficult to evaluate the economic impact of medically-attended influenza is difficult to be evaluated depends on the national healthcare system, social norms, and physicians' practice[9, 10].

Discussion with infectious disease physicians suggests that Japan has distinct practices for ambulatory care for ILI, but no previous studies have examined the characteristics of ILI management in Japan. We believe that Japanese ILI management has four characteristics that differ significantly from practice in EU/EEA and North American countries:

- High proportion of medically-attended influenza among those with symptomatic ILI;
- Patients make early visits to healthcare facilities;
- Rapid influenza diagnostic test (RIDT) for most cases; and
- Antivirals are provided for most diagnosed cases of influenza.

Previous studies from EU countries and the United States suggest that less than half of ILI patients with influenza-like illnesses visit healthcare facilities, and the proportion of medically-attended influenza is low in these countries[3, 11–15]. However, the situation may be different in Japan. To our knowledge, no previous study has focused on the timing of visits to healthcare facilities by ILI patients. Akaishi and colleagues[16] suggested that the median time between onset of influenza-like symptoms and visiting hospitals in Japan was 26.2 hours. Fowlkes and colleagues, however, reported that 36.0% of medically-attended influenza cases had visited healthcare facilities more than two days after symptom onset[17]. It is difficult to compare these two results directly, but 26.2 hours (about 1 day) from symptom onset seems very early.

The third issue is the popularity of RIDT in Japan. The concept of ILI is not popular in Japan and they prefer a diagnosis of “influenza” to “ILI” or “common cold”. Contrary to the recommendation of the Infectious Disease Society of America[18], Japanese physicians usually use RIDT, rather than a molecular assay such as reverse-transcription polymerase chain reaction (RT-PCR). This may be because the rapid test has extremely high sensitivity and specificity in the early phases of symptoms[16, 19–21] and most patients in Japan visit physicians in these early stages, making the rapid test more appropriate.

Finally, both patients and physicians in Japan prefer antiviral treatment. In the United States in 2009–2010, only 36% of patients clinically diagnosed with influenza were treated with antivirals[11] and only 20.4% of medically-attended influenza cases were prescribed antivirals between 2009 and 2016[17]. In Japan, most patients request antivirals when they have a diagnosis of influenza and physicians do not hesitate to prescribe them although there is no publicly available data on the benefits.

The ILI management in Japan therefore has several distinct characteristics but quantitative data and available evidence are scarce. This study’s primary objective was to identify the characteristics of management of these diseases in Japan, looking at both patients’ healthcare-seeking behaviour and physicians’ clinical practice. We also evaluated the disease burden of both influenza cases diagnosed using RIDT and similar illnesses caused by other respiratory viruses.

Methods

Setting

We conducted an online survey of 600 people in 200 households. The participants were voluntarily and randomly recruited from registrants of NEO MARKETING INC, a Japanese marketing research company. The basic characteristics of registrants are shown in Table S1 in Appendix. The survey period was during February 2019 and participants were asked to answer about episodes of ILI which they or their family members had experienced during January 2019. Only one person per household could respond and that person answered question about the whole household. Responders had to be at least 18 years old. Informed consent was given before starting the survey. There was no monetary incentive to complete the questionnaire. The survey included questions about demographic data such as gender, age, number of family members, household income, education, past medical history, and smoking habits of family members. Where a respondent or family member had ILI symptoms during January 2019, the respondent answered questions about the duration of symptoms, healthcare-seeking behaviour (healthcare facility visit, days between symptom onset and healthcare facility visit, and vaccination status), and their physicians' practice (RIDT use, prescription of antivirals, and class of antivirals prescribed).

Statistical Analysis

Besides descriptive analysis of online survey data, we estimated disease burden of influenza diagnosed by RIDT (influenza group) and similar symptoms caused by other respiratory viruses (ILI group), by quality of life (QOL), quality-adjusted life-years (QALYs) lost, and duration of absence from work. We also compared these indicators between the two groups.

SF–12v2 Standard, Japanese questionnaire (SF–12v2® Health Survey © 1994, 2002, 2009 Quality Metric Incorporated, Medical Outcomes Trust and Shunichi Fukuhara. All rights reserved)[22] was included in the questionnaire to estimate the QOL at the onset of symptoms and QALYs lost by each episode of illness. In principle, responders answered SF–12v2 questionnaire for their own health status. They also answered about their children's health status because the survey excluded respondents under 18 years old. QOL values were calculated using the method of Brazier and colleagues[23]. QALYs lost to each ILI episode was calculated as:

[Due to technical limitations, the formula could not be displayed here. Please see the supplementary files section to access the formula.]

The duration of absence was defined as the number of days in which patients or their caregivers had to take leave from work.

We compared the difference in QOL values, QALYs lost, duration of symptoms, and duration of absence between the two groups using multiple imputation[24] to handle missing data. The imputation procedure uses all the known covariates thought to be associated with the missingness mechanism to help predict the values of missing items. A scales logit transformation was chosen to give normally distributed and

plausible values. The results across 10 imputed datasets were combined using Rubin's rules. For comparison, we also performed the analysis on the subset of complete cases.

We used linear regression analyses with one-to-one propensity score matching (one-to-one nearest neighbour pair matching, calliper = 0.2)[25] calculated by multivariate logistic regression model predicting the likelihood of diagnosis of influenza as opposed to other ILIs. Two-sided *p*-values of < 0.05 were considered to show statistical significance. As a sensitivity analysis, we used inverse-probability weighted propensity score matching (IPW-PS) analysis instead of one-to-one matching. All statistical analyses used R, version 3.6.1[26].

Results

Population Characteristics and Participants' Behaviour

In total, 261 of 600 (43.5%) participants had at least one episode of ILI influenza-like illness during January 2019. Of these, 194 (75.5%) visited healthcare facilities, 167 (86.1%) of those within 2 days of symptom onset. A total of 88.5% of these patients were tested using RIDT and 101 were diagnosed as having influenza, of whom 92.2% were given antivirals. The details of the descriptive analysis are shown in Table 1. Figure 1 shows a histogram of days from symptom onset at healthcare facility visit.

(Figure 1)

Figure 1. Days from symptom onset at healthcare facility visit

Table 1. Demographic and behavioural characteristics of the participants

Variable	Number (Percentage) or median (IQR)	
Number of household members	4 (3-4)	
Male	295/600 (49.2%)	
Age (year)	42 (21-57)	
High-risk group*	46/201 (22.9%)	
Smoker	81 (13.5%)	
Healthcare facility visit	194/261 (75.5%)	
Duration of symptoms (days)	2 (1-3)	
Day of healthcare facility visit (days from symptom onset)	1 (0-2)	
Patients examined by RIDT	169/191 (88.5%)	
Influenza diagnosed by RIDT	101/200 (50.5%)	
Treated by antivirals among influenza cases diagnosed by RIDT	59/101 (92.2%)	
Class of antivirals prescribed	Oseltamivir	22 (37.3%)
	Baloxavir	20 (33.9%)
	Laninamivir	9 (15.3%)
	Zanamivir	4 (6.8%)
	Unknown	4 (6.8%)
Vaccinated for seasonal influenza	87 (34.5%)	
Income level of household	< 50,000 USD**/year	64 (32.0%)
	50,000 USD/year < < 100,000 USD/year	86 (43.0%)
	> 100,000 USD/year	28 (14.0%)
Education level of householder	Primary	1 (0.5%)
	Secondary	83 (46.5%)
	Tertiary	95 (47.5%)
	Advanced	11 (5.5%)

IQR: Interquartile range, RIDT: Rapid influenza diagnostic test, USD: US dollars

*Participants who have past medical history associated with high-risk of severe influenza

**1 USD = 100 Japanese yen

Disease Burden

The median value of QOL and QALYs lost during the period of ILI were 0.67 (interquartile range [IQR] 0.60-0.79) and 0.0055 (IQR 0.0040–0.0072). The median duration of symptoms and absence were 2 days (IQR 1-3 days) and 2 days (IQR 1-5 days).

Difference between Influenza and Other ILIs

The median QOL score during symptomatic period of influenza group and ILI group was 0.66 (IQR 0.58-0.79) and 0.66 (IQR 0.59-0.79). The median QALYs lost per episode was 0.0044 (IQR 0.0034-0.0066) in the influenza group and ILI group were 0.0044 (IQR, 0.0034-0.0066) and 0.0036 (IQR 0.0018-0.0054), respectively. The basic characteristics of influenza group and ILI group are shown in Table 2.

Table 2. Characteristics and disease burden of the influenza group and the ILI group

Variable	Influenza group (N=72)	ILI group (N=73)
Number of household members	4 (2-4)	3 (2-4)
Male	34 (47.9%)	46 (63.8%)
Age	42 (17-53)	42 (22-55)
High-risk group	15 (20.8%)	22 (30.1%)
Smoker	10 (13.9%)	19 (26.0%)
Day of healthcare facility visit	1 (1-2)	1 (1-2)
(days from symptom onset)		
Patients examined by RIDT	71 (97.2%)	57 (80.3%)
Treated by antivirals	38 (90.5%)	1 (4.3%)
Vaccinated for seasonal influenza	28 (38.9%)	22 (31.9%)
Income level		
< 50,000 USD*/year	20 (30.3%)	22 (33.8%)
50,000 USD/year <	34 (51.5%)	34 (52.3%)
< 100,000 USD/year		
> 100,000 USD/year	12 (18.2%)	9 (13.8%)
Education level of householder		
Primary	0	0
Secondary	33 (45.8%)	32 (43.8%)
Tertiary	37 (51.4%)	34 (46.6%)
Advanced	2 (2.8%)	7 (9.6%)
Duration of symptoms (days)	2 (2-3)	2 (1-3)
QOL during symptomatic period	0.66 (0.58-0.79)	0.66 (0.59-0.79)
QALYs lost per episode	0.0044 (0.0034-0.0066)	0.0036 (0.0018-0.0054)
Duration of absenteeism (days)	5 (4-6)	2 (1-3)

Values are shown as absolute number (percentage) or median (interquartile range).

RIDT: Rapid influenza diagnostic test, QOL: quality of life, QALYs: quality-adjusted life-years, USD: US dollars

*1 USD = 100 Japanese Yen

We imputed the missing values in the dataset before comparing the two groups. The number of missing items is shown in Table S2 in the Appendix. After one-to-one propensity score matching for the influenza group versus the ILI group with imputed data, differences in QOL score, QALYs lost, and duration of symptoms were not statistically significant. However, those with influenza were off work about two days longer than the other group. The comparison is shown in Table 3.

Table 3. Differences in outcomes between the two group after propensity score matching

Outcome	Estimate	SE	*p*-value
QOL score			
Intercept	0.698	0.0174	< 0.001
Influenza group	-0.0231	0.0228	0.314
QALYs lost			
Intercept	0.00413	0.000503	< 0.001
Influenza group	0.000650	0.000620	0.297
Duration of symptoms			
Intercept	2.189	0.250	< 0.001
Influenza group	0.456	0.346	0.192
Duration of absenteeism			
Intercept	2.099	0.277	< 0.001
Influenza group	2.010	0.392	< 0.001

ILI: influenza like illness, QOL: quality of life, QALYs: quality-adjusted life-years,

SE: standard error

Sensitivity Analysis

For sensitivity analyses, we used one-to-one propensity score matching for the influenza group versus the other group for responses with complete data only. We also used IPW-PS analysis with the imputed dataset.

Only 58 of the 200 cases contained complete data. After one-to-one propensity score matching, we had 13 pairs of cases, providing 26 complete cases for analysis. Linear regression analysis showed that duration of absence was significantly different between the two groups, but there were no significant differences between QOL score, QALYs lost, and duration of symptoms. The details are shown in Table S3 in the Appendix.

IPW-PS analysis with the imputed dataset showed that QOL scores were similar between the two groups, but duration of symptoms and absence were longer for those with influenza. As a result, QALYs lost was also greater for those with influenza. These results are shown in Table S4 in the Appendix.

Discussion

The result of this study suggests that most ILI patients in Japan visited healthcare facilities soon after the onset of symptoms and most physicians used RIDT to assess them. Most people with a diagnosis of influenza were given antivirals. These preferences were observed in our study and are also consistent with the expectations of experts. However, they are quite different from ILI management in other countries[3, 17]. Direct medical costs from medically-attended influenza can be considered one of the main parts of the influenza disease burden[27, 28], so the high proportion of medically-attended influenza in Japan contributes to a heavier disease burden than in EU/EEA countries and the United States.

Our analysis showed that QOL score during the symptomatic period did not differ between those with influenza and ILIs. However, this should be interpreted carefully because most people with influenza received antivirals, which might also reduce the severity of ILI[29]. If antiviral treatment had not been provided, the QOL score of people with influenza might have been worse than people with other ILIs. The effect of antiviral treatment also modifies the duration of symptoms[30], so without antivirals, the duration of influenza symptoms might be longer than ILIs. The IPS-PS analysis, however, showed different results in the sensitivity analysis. Previous studies reported differently about difference of QOL score and duration of symptoms between influenza and ILI[31, 32], so further work would be helpful in this specific area.

The duration of absence varied between the two groups in spite of the similar duration of symptoms. This may be because the Japanese School Health and Safety Act[33] provides that school-age children with influenza have to remain at home for five days after symptom onset, but does not define the duration of absence for other ILIs. Adults with school-age children therefore often have to take nursing leave even after the children's recovery from symptoms. This regulation might increase the societal burden of influenza[34]. Asymptomatic influenza patients have weaker infectivity than those with symptoms[4], so it is possible that a five-day absence is longer than necessary.

One strength of this study is that the methodology enabled us to maximize the amount of information from the original data. Our data included only 200 households, which might be a limitation. However, the multiple imputation process allowed us to include all respondents' answers in our analysis and propensity score matching ensured the robustness of our comparison. Another strength is that our results identified the distinct characteristics of Japanese ILI management in ambulatory care settings. To our knowledge, this is the first study to focus quantitatively on the proportion of medically-attended influenza, antiviral treatment, and days between symptom onset and healthcare facility visit. These findings will help to estimate the national disease burden of ILI and could provide a baseline for future studies.

The study had several limitations. First, the SF–12v2 questionnaire is not the standard tool for calculating QOL scores in Japan. Some researchers have tried to estimate QOL scores using SF–12v2 in Japan, drawing on Brazier and colleagues[23], but this method has not yet been officially accredited. Second, we could not stratify the influenza group into "treated" and "untreated" because almost all of them were given antivirals. Comparison between those with influenza and other ILIs might be a good proxy, but ideally comparison among those with the same diagnosis would be better. Third, our data were based on an online survey. Unlike conventional questionnaire surveys, online surveys require participants to have basic internet literacy. The data may therefore not be fully representative.

In conclusion, this study showed that ILI management in Japan has distinct characteristics. ILI patients tend to visit healthcare facilities soon after onset of symptoms, and physicians use RIDT to detect influenza, and then prescribe antivirals in most cases. These behaviours and practices might influence the disease burden of ILI in Japan, and further work to evaluate the situation more fully would be helpful.

Declarations

Acknowledgment

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Availability of data and materials

All data used in the manuscript are derived from the results of questionnaire survey conducted by a private company. The raw data are available upon reasonable request to the corresponding author.

Author contributions

ST conceived the study. ST and KY designed the questionnaire and obtained ethical approval. ST conducted the statistical analyses and drafted the first version of the manuscript. KY critically reviewed the manuscript and both authors approved the final version of the manuscript.

Ethical approval and consent to participate

This study was approved by the institutional ethical review board of the Institute of Tropical Medicine, Nagasaki University (Japan) and conducted in accordance with the approved guideline. Informed consent was obtained by each participant before starting the survey through an electronic form.

Consent for publication

Not applicable.

Competing interests

All the authors declare that they have no potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Figures

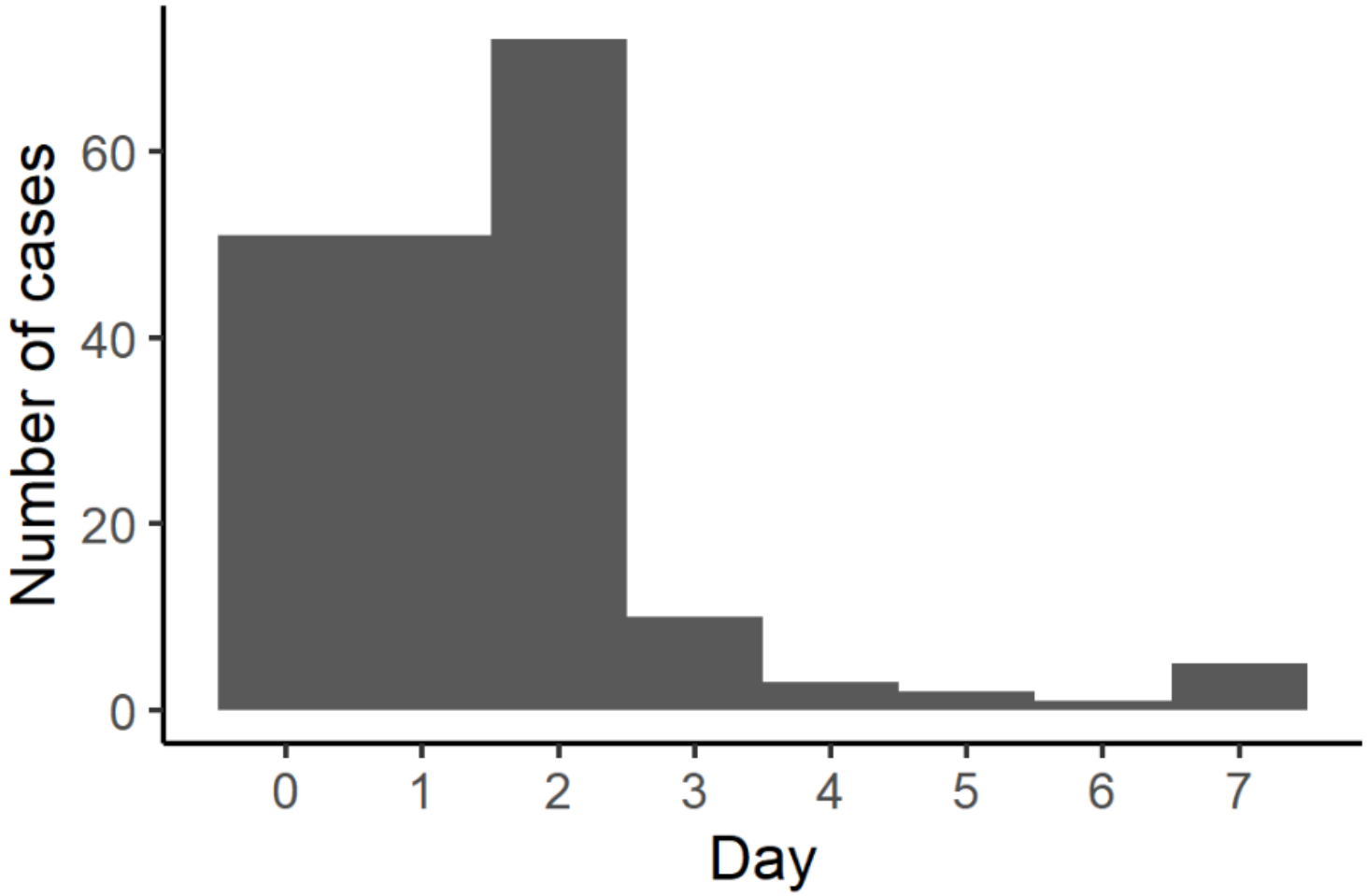

Figure 1

Days from symptom onset at healthcare facility visit

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Methodsformula.docx
- TsuzukiILIAppendix.docx