Faculteit Geneeskunde en Gezondheidswetenschappen

Evaluatie van de ziektelast in verband met COVID-19 in Japan van 2020 tot 2021 met een vergelijking met seizoensgriep

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Evaluation of disease burden associated with COVID-19 with comparisons to seasonal influenza in Japan from 2020 to 2021

Thesis submitted for the degree of Doctor of Medical Sciences at the University of Antwerp to be defended by Shinya TSUZUKI

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Contents

1. List of abbreviations

AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
ATE	Average treatment effect
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CEA	Cost-effectiveness analysis
CFR	Case fatality rate
COVID-19	Coronavirus disease 2019
COVIREGI-JP	the COVID-19 Registry of Japan
DALYs	Disability-adjusted life-years
DCC	Disease Control and Prevention Center
DSA	Deterministic sensitivity analysis
ECDC	European Centers for Disease Control and Prevention
EQ-VAS	EuroQol's Visual Analogue Scale
EU/EEA	European Union/European Economic Area
GBD	The Global Burden of Disease
GDP	Gross Domestic Product
HEOR	Health economics and outcomes research
HIV	Human immunodeficiency virus

HRQoL	Health-related Quality of Life
IHME	the Institute for Health Metrics and Evaluation
ICER	Incremental cost-effectiveness ratio
IRR	Incidence rate ratio
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
JPY	Japanese Yen
ILI	Influenza like illness
IPW	Inverse-probability weighted
IQR	Interquartile range
MAI	Medically attended influenza
MCMC	Markov Chain Monte Carlo
MMR	Measles, Mumps and Rubella
NA	Not available
NCGM	National Center for Global Health and Medicine
NICE	the National Institute for Health and Care Excellence
NIID	National Institute of Infectious Diseases
NPIs	Non-pharmaceutical interventions
PrEP	Pre-exposure prophylaxis
PROs	Patient-reported outcome measures
PS	Propensity score

PSA	Probabilistic sensitivity analysis
QALYs	Quality-adjusted life years
QoL	Quality of Life
RIDT	Rapid influenza diagnostic test
RSV	Respiratory syncytial virus
RT-PCR	Reverse-transcription polymerase chain reaction
SARS-CoV-2	Severe acute respiratory coronavirus 2
SD	Standard deviation
SE	Standard error
SEIR	Susceptible-Exposed-Infectious-Recovered
SMD	Standardized mean difference
SMDM	Society for Medical Decision Making
UK	United Kingdom
US	United States
USD	United States Dollar
VIF	Variance inflation factor
VOC	Variant of concern
WHO	World Health Organization
WTP	Willingness to pay
YLD	Years Lived with Disability
YLL	Years of Life Lost

2. Introduction

2.1 What is disease burden?

Disease burden is an evaluation of health problems measured by financial cost, mortality, morbidity, or other indicators. It is one of the approaches measuring health status and quantifies not only the number of deaths but also the impact of premature death and disability on a population. It combines these factors into a single unit of the overall "burden of disease" on the population [1].

When discussing disease burden, it is necessary to mention the Global Burden of Disease (GBD) study led by the Institute for Health Metrics and Evaluation (IHME) [2]. IHME states that it "endeavors to measure disability and death from a multitude of causes worldwide" through this study.

The most critical characteristic of the GBD approach is that it is a quantitative evaluation. Prior to the widespread acceptance of the GBD concept, disease evaluation was primarily descriptive and qualitative. However, from an economic perspective, our resources are finite, while our desires are infinite [3]. In other words, although we may desire to address all the diseases in the world, in reality, we have limited resources available. Therefore, a "quantitative" evaluation is beneficial in determining how to allocate our limited resources to each disease, even though the experience of the disease is qualitative and individual for those who are suffering from it.

In this context, Health-related Quality of Life (HRQoL) is one of the most important indicators used to assess the burden of each disease quantitatively [4,5]. Quality of Life (QoL) is defined by the World Health Organization (WHO) as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" [6]. While QoL has a wide range of contexts, including the fields of international development, healthcare, politics, and employment, HRQoL is an evaluation of QoL and its relationship with health [7]. HRQoL covers the subjective perceptions of the positive and negative aspects of patients' symptoms, including physical, emotional, social, and cognitive functions, and, importantly, the disease symptoms and side effects of treatment [8].

Needless to say, the concept of HRQoL includes non-negligible limitations [9–12]. Since HRQoL is a patient-reported outcome measure (PROM), its assessment is inevitably subjective. For instance, the status of blindness can impair our HRQoL. However, its impact varies from person to person. Additionally, the assessment may differ even in the same person as time goes by. Considering the example of blindness, a person who became blind this month tends to report a much lower value of HRQoL, whereas a person who became blind 20 years ago may report a higher value of it.

Furthermore, there are other limitations in HRQoL that we should consider when we use it. The most important and easily conceivable criticism against HRQoL is that it is a single numerical metric between 0 and 1. If we imagine that we have two different health difficulties (e.g., blindness and deafness), we will soon notice that it may be very difficult to compare these two conditions and conclude which one is more serious for us because these two difficulties have different significance in each context. Deafness will impair almost all the pleasure of listening music, and blindness may be critical for enjoying reading. Therefore, we cannot make unconditionally compare these two difficulties in view of quantitative evaluation.

Quality-adjusted life years (QALYs) lost and Disability-adjusted life years (DALYs) is important indicators to assess HRQoL. Both QALYs lost and DALYs not only includes the potential years of life lost due to premature death, but also includes equivalent years of “healthy” life lost by virtue of being in states of poor health or disability.

The concept of the QALY was developed in the 1960s; it represents the products of years lived and the associated utility values, ranging from 0 (dead) to 1 (perfect health). Utility estimates represent the perspective of an individual’s values or preferences, based on the central tenet of welfarist economics that individuals are the best judges of their own welfare, and improved societal welfare is based on the sum of these individual utilities. In addition, QALYs also integrate so-called “extra-welfarist” elements to utility assessment, such as the contribution of particular states of health, functioning, and patient preferences to utility estimation [13,14].

As mentioned above, utility was evaluated from the perspective of an individual's values or preferences, at least with regard to QALYs. Therefore, HRQoL is usually assessed using questionnaires. Several questionnaires have been developed and validated, such as EQ-5D questionnaire, Short-Form Health survey, and others. Both EQ-5D and SF were widely used as standardised questionnaires. The former can provide a profile of patient health on the day of questionnaire completion [15], while the latter has a recall period [16,17].

EQ-5D consists of two pages, the EQ-5D-descriptive system and the EQ-5D visual analogue scale (EQ-VAS). The first part, EQ-5D descriptive system, comprises five dimensions: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. The number of levels in these dimensions differ in the EQ-5D-3L (three levels) and the EQ-5D-5L (five levels). The EQ-5D-Y has the same five dimensions, but they are worded more appropriately for young people. The second part, EQ-VAS, is a vertical 20 cm scale that is calibrated from “the worst health you can imagine” (scored 0) at its base to “the best health you can imagine” (scored 100) at its apex. Respondents are asked to ‘mark an X on the scale to indicate how your health is TODAY’ and to write the number in an adjoining box [15].

SF also comprises a family of questionnaires classified by the number of questions; SF-36 and SF-12. The SF-36 consists of eight scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. A shorter version is the SF-12, which contains 12 items rather than 36. If having only adequate physical and mental health summary scores is of interest, then the SF12 may be the instrument of choice [18].

In this thesis, I used 15D questionnaire in addition to these two questionnaires. The 15D questionnaire is another generic, comprehensive (15-dimensional), self-administered instrument for measuring HRQoL among adults (aged 16 and older). It combines the advantages of a profile and a preference-based, single index measure [19].

In contrast, the DALY was developed in the 1990s by the GBD initiative to assess burden of disease at a population level, to understand leading causes of health loss worldwide, and to compare population health across geographic settings [20]. DALYs reflect the sum of years of life lost due to premature mortality and years lived with disability. The disability weights used for DALYs are inverse to that of utility weights, with "0" referring to no disability and "1" representing the dead state. DALYs also do not explicitly integrate extra-welfarist concepts; for example, disability weights are defined not based on surveys of individuals but based on expert opinion, as in the view of its developers a single set of weights anchored to specific diseases better facilitated cross-cultural comparisons than did some form of self-assessment [21]. Previously age-stratified weighting and discounting were used to calculate DALYs, WHO had abandoned the ideas of age weighting and time discounting from 2010 [22–27].

Both QALYs and DALYs are indicators that represent disparities between the reality and the counterfactual state of well-being. Therefore, it is impossible to know whether the estimated values are correct or not. Furthermore, the value of counterfactual well-being varies between individuals, which increases its uncertainty. In short, “health” has low affinity for quantitative evaluation.

We should take notice of both the benefits and limitations of the concept of “disease burden” mentioned above. The term “disease burden” indicates a quantitative evaluation of “health” and sometimes includes broader concepts such as welfare. This is necessary and useful for health policy decision making, despite the inevitable limitations it presents.

2.2 The significance of disease burden in infectious diseases

The concept of disease burden is suitable for the evaluation of chronic diseases and sequelae than can persist for years. the quantitative evaluation of the burden of infectious diseases is equally important as that of chronic diseases. Healthcare policy makers must always decide how to allocate finite resources to all the diseases in our society, and a quantitative evaluation of each disease’s burden, which enables us to compare the weight of the burden between diseases, is necessary.

In addition, infectious diseases sometimes include a chronic phase of disease burden. For instance, bacterial meningitis may cause irreversible sequalae such as paralysis of the limbs, deafness, and other impairments [28–31]. Human immunodeficiency virus (HIV) infection usually exhibits a chronic clinical course that lasts for years before presenting acquired immunodeficiency syndrome (AIDS), but people living with HIV are forced to undergo lifelong antiretroviral therapy (ART), which can be inconvenient [32–36]. Notably, the GBD study reported that meningitis caused 21.87 million DALYs globally, including 1.48 million YLDs [37]. According to Kyu et al. [38], HIV/AIDS globally imposed 874.1 age-standardized DALYs per 100,000 population in 2017, accounting for about one tenth of all infectious diseases' burden and about 2.7% of all disease burden. Cost-effectiveness analysis of countermeasures for HIV/AIDS (e.g., ART, PrEP, etc.) will be necessary. For instance, a previous study reported that highly accessible PrEP in sub-Saharan Africa may be beneficial under highly HIV-prevalent circumstances [39]. Such evaluations will be useful and necessary for health policy decision making, and quantitative evaluation by the concept of disease burden makes them feasible.

2.3 Influenza

Influenza-like illnesses (ILIs) are also a source of substantial disease burden similar to other infectious diseases although almost all of their burden is derived from their acute phase [38]. Especially, seasonal influenza has attracted interests of infectious disease epidemiologists and public health specialists because it has been a source of non-negligible disease burden to our society [40].

Although it is impossible to determine when influenza first infected humans or when the first influenza pandemic occurred, many historians agree that the year 1510 A.D., over 500 years ago, marked the first recognition of pandemic influenza [41]. By the end of the 16th century, influenza was likely beginning to be understood as a specific, recognizable disease with epidemic and endemic forms [42]. The first flu pandemic to occur with vital statistics being recorded was a minor influenza pandemic occurred from 1847 to 1851, and influenza mortality was clearly recorded for the first time [43]. The 1918 influenza pandemic, also known as “the Spanish flu”, was the most devastating influenza pandemic and one of the deadliest ones in history, occurring from 1918 to 1920. By the end of 1920, it is estimated that about a third to half of all people in the world had been infected, resulting in tens of millions of deaths [44,45]. This fact demonstrated that influenza can be a major cause of disease burden on our society and led to further research progress in this area.

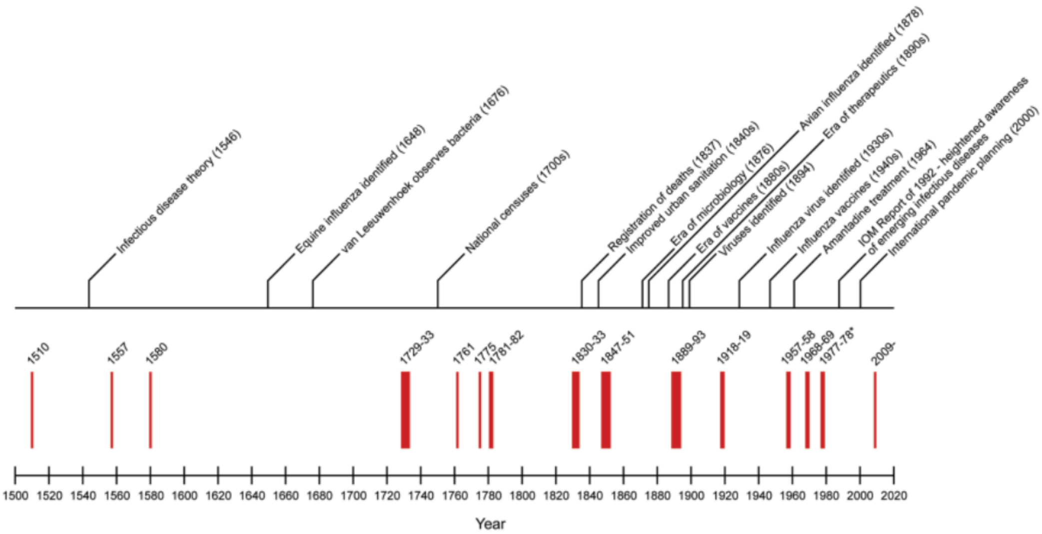


Figure 2-1. Five centuries of documented influenza pandemics with a timeline of selected significant events related to understanding and controlling influenza, 1510–2010 (Reproduced from [41]**).**

Nevertheless, we have repeatedly experienced influenza pandemic such as the 1957-1958 pandemic (so called "Asian flu"), the 2009 H1N1 pandemic (so called "swine flu"), and so forth after this desperate pandemic. Despite continuing progress in many areas including enhanced human and animal surveillance, large-scale viral genomic screening, access to effective vaccines and antivirals, pandemics probably will continue to occur. [41,44,46].

If we accept that influenza pandemics will continue to occur sporadically, it becomes more important for us to assess the disease burden caused by influenza for preparedness for the next pandemic. That is exactly the reason we have to evaluate it in an appropriate way.

2.4 Emergence of COVID-19

In early December 2019, the first cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia were identified in Wuhan, the capital city of Hubei province [47,48]. This emerging infectious disease was later named as COVID-19 soon became one of the most important health threats in the world [49].

Despite COVID-19 being classified as a type of respiratory viral infection, i.e., a kind of ILIs, it presents unique features that make it particularly challenging to deal with. First of all, its severity and fatality risk are higher than most ILIs [50,51]. Additionally, COVID-19 has a longer incubation period compared to other ILIs, such as influenza [52,53], and a larger proportion of asymptomatic cases [54–56]. As viral shedding can occur even in asymptomatic cases [57,58], it is challenging to isolate a sufficient number of people to prevent the spread of the disease.

At the early phase of the pandemic, effective treatment drugs and vaccines were not available. Therefore, many countries implemented strict non-pharmaceutical interventions (NPIs) such as “lockdowns” [59–62]. The Japanese government also declared a “state of emergency”, which recommended that the general population to avoid non-essential travel, although it had no legal binding force [63].

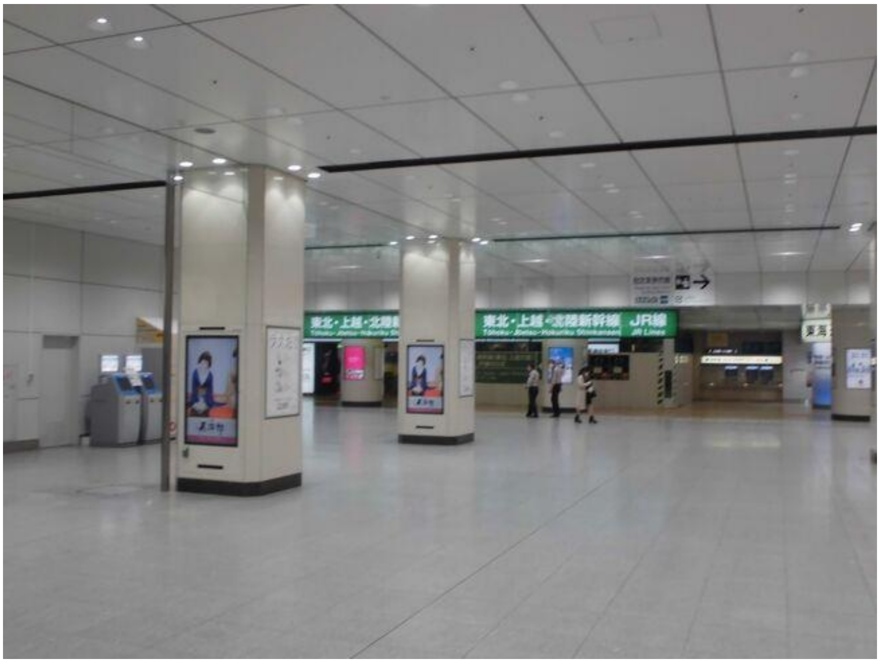


Figure 2-2. Tokyo station under declaration of the state of emergency (reprint from https://4travel.jp/travelogue/11731069)

Needless to say, such restriction on social mobility gave an economic burden on our society. Nevertheless, we could not surpass the epidemic of COVID-19 completely and its disease burden seems significant compared with other major causes [64–66].

At present, COVID-19 seems to become a kind of epidemic like seasonal influenza, or, at least it is difficult for us now to imagine COVID-19 will disappear from our society thoroughly. Then therefore we need to assess the burden brought by COVID-19 appropriately because we will have to live our daily live with COVID-19. Adequate evaluation of its disease burden will provide us to what extent we should prioritise and emphasize the countermeasures against COVID-19.

2.5 Motivation and aim

Although a number of non-pharmaceutical and pharmaceutical countermeasures against COVID-19 have been implemented in Japan to date, there is currently a lack of quantitative evaluation of the disease burden caused by this emerging infectious disease.

In fact, the Japanese government has carried out these interventions at considerable economic cost. However, before COVID-19, we have to some extent accepted the disease burden caused by ILIs such as seasonal influenza albeit unconsciously. We should quantify the disease burden caused by COVID-19 and compare it with other ILIs, and then we can evaluate whether or not the countermeasures we have taken or will take to mitigate the burden of COVID-19 have been or will be appropriate.

The aim of this thesis is to evaluate the disease burden caused by COVID-19 in Japan during the first two years of the pandemic (from the beginning of 2020 to the end of 2021) and compare it with that caused by seasonal influenza before the COVID-19 pandemic era. Through the process of assessing the disease burden due to seasonal influenza, we aim to evaluate the impact of societal factors specific to the Japanese society and the optimal vaccination policy for seasonal influenza that can best reduce its burden. In addition, we intend to quantify the change in social contact behaviour in this pandemic era for our future work.

2.6 Outline of the thesis

This thesis is composed of three main parts: i) estimation of disease burden due to seasonal influenza in Japan, ii) estimation of disease burden due to COVID-19 in Japan, in 2020-2021, and iii) general discussion.

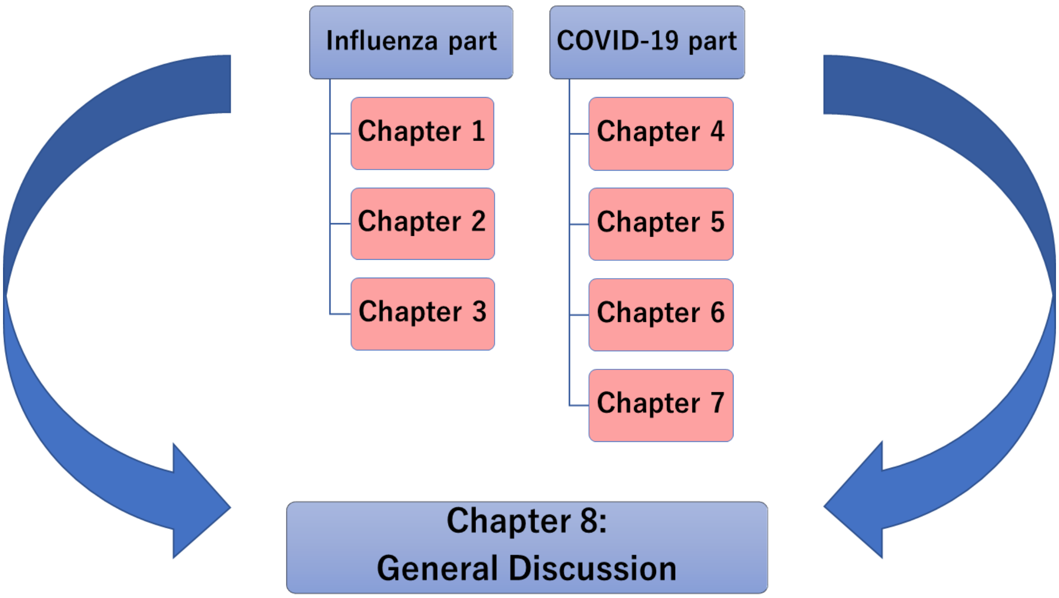


Figure 2-2. Overview of the thesis structure

Chapter 1: The characteristics of influenza-like illness management in Japan

The clinical management of influenza-like illness (including seasonal influenza) in Japan appears to be specific, especially compared with that of other developed countries before the emergence of COVID-19. The main features described were a high proportion of medically attended influenza and high prescription rate of antivirals, which may place an additional disease burden on our society.

Chapter 2: Disease burden caused by societal aspects of seasonal influenza management in Japan

In addition to the factors described in Chapter 1, there was another distinctive practice in the management of seasonal influenza in Japan. Before the COVID-19 pandemic, Japanese schoolchildren who had influenza often had to provide their school with a certificate to prove that they had recovered from the illness. This practice meant that both the children and their caregivers (in most cases, their mothers) had to visit the doctor twice if the children got influenza. This is another opportunity for productivity loss and can of course be an additional burden.

Chapter 3: Total disease burden caused by seasonal influenza in Japan and its optimal vaccination policy

We tried to assess the optimal vaccination policy of seasonal influenza in Japan, with these factors mentioned above taken into consideration. We developed a Susceptible-Exposed-Infectious-Recovered (SEIR) model to capture the transmission dynamics of seasonal influenza and conducted a cost-effectiveness analysis using the incremental cost-effectiveness ratio (ICER) as an indicator. As a result, we were able to estimate the total disease burden caused by seasonal influenza.

Chapter 4: Indirect burden of COVID-19 on our society

COVID-19 was also one of ILIs, however, it is an emerging infectious disease. In this chapter, we estimated the QALYs lost due to each episode of COVID-19 infection, including the effect of the isolation policy imposed by the Japanese government. This elucidated the difference of disease burden between COVID-19 and seasonal influenza at the individual level.

Chapter 5: Disease burden caused by post COVID-19 condition

One of the significant differences between COVID-19 and other ILIs is post COVID-19 condition (long-COVID). Similar to other ILIs, COVID-19 is an acute and mild disease for young adults, however, if they have a post COVID-19 condition, their disease burden caused by COVID-19 will increase significantly. We have attempted to estimate the disease burden of post COVID-19 condition at the individual level.

Chapter 6: Behavioural change in social contact after emergence of COVID-19

NPIs against COVID-19 could mitigate the disease burden in terms of health utility, whereas such interventions should substantially change our behaviour. We conducted an online questionnaire survey to update the social contact behaviour in Japan after emergence of COVID-19. Additionally, we compared the frequency of social contact during and after the Tokyo Olympic Games 2020 (which were actually postponed to 2021).

Chapter 7: Total disease burden caused by COVID-19 in Japan from the beginning of 2020 to the end of 2021

We estimated the total disease burden experienced during the first two years of the COVID-19 pandemic, taking into account the main findings of the previous chapters in the form of QALYs lost. Compared with the results of previous studies in other countries, Japan has experienced a relatively lower disease burden due to COVID-19 during 2020-2021.

Chapter 8: General discussion

We discussed what our estimate of the disease burden due to COVID-19 in Japan meant to us based on our other main findings, especially considering its difference from seasonal influenza. We also mentioned future works related to our findings that would contribute to more appropriate health-policy decision making in implementing countermeasures against ILIs, such as seasonal influenza, COVID-19, and so forth.

3. Chapter 1: The characteristics of influenza-like illness management in Japan

This chapter is based on published work: "Tsuzuki S and Yoshihara K (2020). The characteristics of influenza-like illness management in Japan. BMC Public Health 2020 Vol. 20 Issue 1", doi:10.1186/s12889-020-08603-x [67].

Summary

This study aimed to make a quantitative assessment of the management of influenza-like illnesses (ILIs) in Japanese healthcare settings. 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 the influenza ILI group and the non-influenza ILI group with one-to-one propensity score matching. Missing data were imputed using multiple imputation. 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 95.0% were treated with antivirals. The median quality-adjusted life-years (QALYs) 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). Albeit QALYs lost per episode was not different between two groups, the influenza ILI group showed longer duration of absence from work (5 days, IQR 4–6 days) than the non-influenza ILI group (2 days, IQR 1–3days). 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.

3.1 Background

Seasonal influenza generally occurs in regular annual epidemics and its disease burden is substantial [68–70]. However, it is difficult to evaluate the disease burden precisely because clinical manifestations and severity of influenza infection vary considerably [57]. Most influenza cases are mild and self-limiting, or even asymptomatic [71]. 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 [72–74]. 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 [68,69], 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 [68]. 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 [75,76].

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:

(1) High proportion of medically-attended influenza among those with symptomatic ILI;

(2) Patients make early visits to healthcare facilities;

(3) Rapid influenza diagnostic test (RIDT) for most cases; and

(4) 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 [70,77–81]. 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 [82] 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 [83]. 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 [84], 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 [82,85–87] 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 US in 2009–2010, only 36% of patients clinically diagnosed with influenza were treated with antivirals [77] and only 20.4% of medically-attended influenza cases were prescribed antivirals between 2009 and 2016 [83]. 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.

3.2 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 S3-1 in Supplementary information 1. The original version of the questionnaire created by the authors is also available as Supplementary information 2. 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. We defined ILI as symptoms measured fever of ≥ 38 C° and cough, in accordance with the definition by World Health Organization [88]. 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 for seasonal influenza), and their physicians' practice (RIDT use, prescription of antivirals, and class of antivirals prescribed).

Statistical Analysis

As described in "Setting", we obtained data of 600 persons from 200 responders' answer. We used these 600 persons' data to conduct descriptive analysis about their basic characteristics and healthcare seeking behaviour. Besides descriptive analysis of online survey data, we estimated disease burden of influenza with 200 responders' data by quality of life (QOL), quality-adjusted life-years (QALYs) lost, and duration of absence from work. Of those 200 responders, who were diagnosed as influenza when they have ILI symptoms by their physicians were classified as "influenza ILI group" and who were diagnosed as ILI caused by respiratory viruses other than influenza viruses (e.g., rhinovirus, respiratory syncytial virus, and so forth) were classified as "non-influenza ILI group". We also compared these indicators between the two groups. Those who did not visit any healthcare facility while they have ILI symptoms were excluded from this comparison.

SF-12v2 Standard, Japanese questionnaire (SF-12v2® Health Survey © 1994, 2002, 2009 Quality Metric Incorporated, Medical Outcomes Trust and Shunichi Fukuhara. All rights reserved) [17] 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 [16]. QALYs lost to each ILI episode was calculated as:

$$QALYs\ lost = (1 - \mathrm{QOL}) \times \frac{duration\ of\ symptoms}{365}$$

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 [89] 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) [90] calculated by multivariable logistic regression model predicting the likelihood of diagnosis of influenza as opposed to other ILIs. We included age, sex, risk factor for severe illness, smoking, vaccination history for seasonal influenza, household income, education level, antibiotic prescription, and QOL value in the model to calculate propensity score. 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 [91].

3.3 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 95.0% were given antivirals. The details of the descriptive analysis are shown in Table 3-1.

Table 3-1. 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	81/600 (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%)	
Patients diagnosed as influenza at healthcare facility	101/194 (52.1%)	
Influenza diagnosed by RIDT	97/101 (96.0%)	
Treated by antivirals among influenza cases diagnosed by RIDT	96/101 (95.0%)	
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 (JPY)

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 the influenza ILI group and the non-influenza 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 ILI group and the non-influenza ILI group were 0.0044 (IQR, 0.0034-0.0066) and 0.0036 (IQR 0.0018-0.0054), respectively. The basic characteristics of the influenza ILI group and the non-influenza ILI group are shown in Table 3-2. Figure 3-1, Figure 3-2, and Figure 3-3 show the difference between two groups in duration of symptoms, QALYs lost per episode, and duration of absenteeism, respectively.

Table 3-2. Characteristics and disease burden of the influenza ILI group and the non-influenza ILI group

Variable	Influenza ILI group (N=72)	Non-influenza 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 (days from symptom onset)	**1 (1-2)**	**1 (1-2)**
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 < < 100,000 USD/year	**34 (51.5%)**	**34 (52.3%)**
> 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**	**0.0036**

	(0.0034-0.0066)	**(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 (JPY)

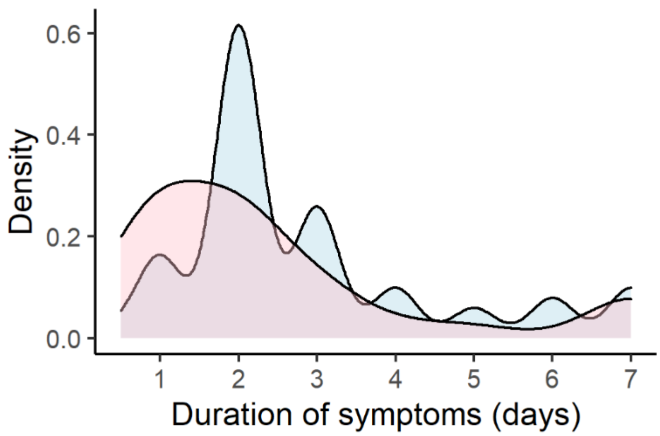


Fig 3-1. Probability density curve of duration of symptoms in the influenza ILI group and the non-influenza ILI group

ILI; influenza like illness.

Blue area represents the influenza ILI group and Red area represents the non-influenza ILI group.

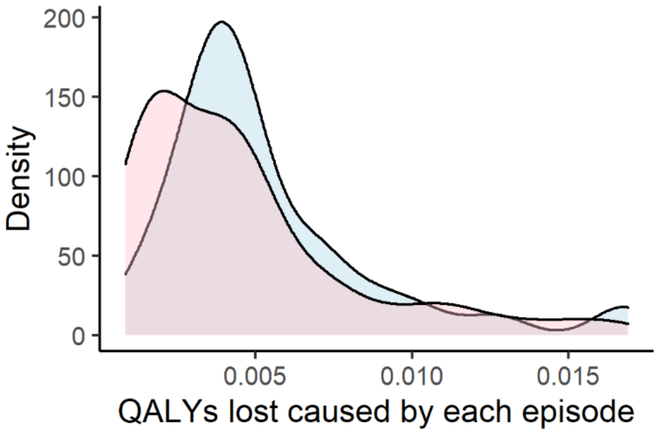


Fig 3-2. Probability density curve of QALYs lost in the influenza ILI group and the non-influenza ILI group

ILI; influenza like illness, QALYs; quality-adjusted life years.

Blue area represents the influenza ILI group and Red area represents the non-influenza ILI group.

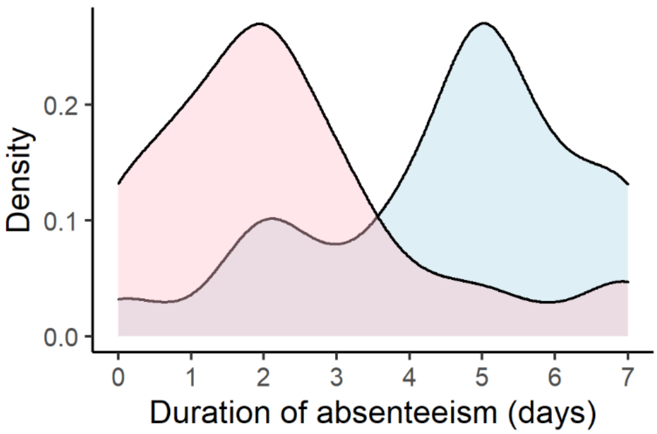


Fig 3-3. Probability density curve of duration of absenteeism in the influenza ILI group and the non-influenza ILI group

ILI; influenza like illness.

Blue area represents the influenza ILI group and Red area represents the non-influenza ILI group.

In addition, we compared outcomes (QOL score, QALYs lost, duration of symptoms and duration of absenteeism) of vaccinated group and unvaccinated group in order to examine the influence of vaccination for seasonal influenza on the course of illness. We found no significant difference between two groups and details of the results are shown in Table 3-3.

Table 3-3. Differences in outcomes between vaccinated group and unvaccinated group

Outcome	Vaccinated**	Unvaccinated**	*p*-value
QOL score*			
Influenza ILI group	**0.657 (0.585-0.765)**	**0.660 (0.586-0.795)**	**0.668**
Non-influenza ILI group	**0.677 (0.632-0.723)**	**0.660 (0.580-0.817)**	**0.694**
QALYs lost*			
Influenza ILI group	**0.00427 (0.00360-0.00529)**	**0.00456 (0.00329-0.00684)**	**0.791**
Non-influenza ILI group	**0.00362 (0.00232-0.00456)**	**0.00379 (0.00169-0.00506)**	**0.824**

Duration of symptoms*			
Influenza ILI group	**2.0 (2.0-3.0)**	**2.0 (2.0-3.5)**	**0.834**
Non-influenza ILI group	**2.0 (1.0-3.0)**	**2.0 (1.0-3.0)**	**0.832**
Duration of absenteeism*			
Influenza ILI group	**5.0 (2.5-5.5)**	**5.0 (4.0-6.0)**	**0.513**
Non-influenza ILI group	**2.0 (1.0-3.0)**	**2.0 (1.0-3.0)**	**0.944**

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

*These outcomes were compared by Mann-Whitney *U* test.

** Values are shown as median (interquartile range).

We imputed the missing values in the dataset before comparing the two groups. The number of missing items is shown in Table S3-2 in the Supplementary information 1. After one-to-one propensity score matching for the influenza ILI group versus the non-influenza 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 3-4.

Table 3-4. 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 ILI group	**-0.0231**	**0.0228**	**0.314**
QALYs lost			
Intercept	**0.00413**	**0.000503**	**< 0.001**
Influenza ILI group	**0.000650**	**0.000620**	**0.297**
Duration of symptoms			
Intercept	**2.189**	**0.250**	**< 0.001**
Influenza ILI group	**0.456**	**0.346**	**0.192**
Duration of absenteeism			
Intercept	**2.099**	**0.277**	**< 0.001**
Influenza ILI 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 S3-3 in Supplementary information 1.

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 S3-4 in Supplementary information 1.

3.4 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 [70,83]. Direct medical costs from medically-attended influenza can be considered one of the main parts of the influenza disease burden [92,93], so the high proportion of medically-attended influenza in Japan contributes to a heavier disease burden than in EU/EEA countries and the US.

Our analysis showed that QOL score during the symptomatic period did not differ between those with influenza ILI and non-influenza ILIs. However, this should be interpreted carefully because most people with influenza received antivirals, which might also reduce the severity of ILI [94]. If antiviral treatment had not been provided, the QOL score of people with influenza ILI might have been worse than people with other non-influenza ILIs. The effect of antiviral treatment also modifies the duration of symptoms [95], so without antivirals, the duration of influenza ILI symptoms might be longer than non-influenza ILIs. The IPW-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 ILI and non-influenza ILIs [96,97], 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 [98] 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 non-influenza 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 [99]. Asymptomatic influenza patients have weaker infectivity than those with symptoms [57], 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 [16], but this method has not yet been officially accredited. Additionally, we assumed the baseline value of all participants' QOL as 1.0, although in practice this may be lower.

Second, we could not stratify the influenza ILI group into "treated" and "untreated" because almost all of them were given antivirals. Comparison between those with influenza ILI and other non-influenza 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. Additionally, we have no data about their response rate to the questionnaire. It is possible that the response rate was low so that only people deeply interested in ILI answered the questionnaire then the data we obtained were biased. For example, the proportion of vaccinated participants in the influenza ILI group was higher than that of in the non-influenza ILI group. It seems paradoxical because vaccinated people usually show lower risk of influenza infection. This can be explained by higher interest in their health status and their healthcare seeking behaviour in the vaccinated group because diagnosis of influenza is made by physicians. Considering this, participants of our survey might have higher interest in their health status than Japanese general population do, especially in the influenza ILI group.

Fourth, the comparison about duration of symptoms showed different results between one-to-one propensity score matching and IPW-PS analysis. In the present study, both methods have their own merits and challenges. In one-to-one matching, we have to discard some cases due to mismatch although we can avoid extreme weighting for each case. Our data do not have a large number of participants then we would like to keep all cases, if possible. Conversely, if we use IPW-PS, we can use all cases in our analysis, however, some cases might be extremely weighted. We adopted one-to-one matching as the main method in accordance with the principle of propensity score method [90] in spite of its limitation. Then therefore we believe that IPW-PS is an appropriate option for sensitivity analysis. The results were partially inconsistent between these two methods, then we are not sure whether duration of symptoms is different between influenza and ILI or not. Last, our survey results are based on participants' self-reported answers. It is possible that some participants do not understand what their physicians told them then therefore some of their answers might be inaccurate.

3.5 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.

4. Chapter 2: Disease burden caused by social aspects of seasonal influenza management in Japan

This chapter is based on published work: "Tsuzuki S (2019). Economic consequences of Japanese schools' recovery certificate policy for seasonal influenza. BMC Public Health 2019 Vol. 19 Issue 1", doi: 10.1186/s12889-019-6600-0 [99].

Summary

Like other countries, Japan experiences a seasonal influenza epidemic every year. In order to return to school after an influenza-related absence, most Japanese students are required to submit a recovery certificate (chiyu-shoumeisyo in Japanese). The objective of this study was to estimate the economic consequences of this practice. A cost analysis was conducted to estimate the additional costs incurred by the issuance of recovery certificates from a restricted societal perspective. The estimated number of influenza patients under 15 years old from the 2013/14 season to the 2017/18 season, the proportion of working mothers were used to calculate the estimated total number of recovery certificates issued per year. The cost of return visits to physicians and the cost for issuing certificates were included in the direct costs. Productivity loss was estimated using the mean monthly salary of women and was included in indirect costs. The recovery certificate policy imposed an additional cost of 0.94 million USD per one million population. One-way deterministic sensitivity analysis demonstrated that the additional cost of the recovery certificate policy amounted to between 0.55 and 2.27 million USD per one million population. Probabilistic sensitivity analysis showed similar results. The recovery certificate policy has a substantial negative economic impact on the Japanese healthcare system and society from a restricted societal perspective.

4.1 Background

A large number of Japanese children suffer from symptomatic seasonal influenza infection every year [100]. It is desirable that influenza patients refrain from having contact with other people for several days in order to minimize the risk of secondary infection. Although the length of time that a symptomatic influenza patient can spread the virus varies from person to person [57,101–104], the Japanese government prohibits children from going to their school or nursery school until five days have passed from the onset day of influenza symptoms in accordance with the School Health and Safety Act [98]. In Japan, influenza is usually differentiated from influenza-like illness (ILI) with the use of rapid influenza diagnostic tests (RIDTs) [105]. Almost all patients who are suspected of having ILI are examined by RIDTs, especially during peak influenza season. If a child's RIDT is positive and they are diagnosed as having influenza, they must then stay at home for five days. If fever and other symptoms persist, the duration of attendance restriction is also extended until two days have passed after the decline of their fever. In addition, most children must submit a recovery certificate (*chiyu-shoumeisyo* in Japanese) to their school or nursery school in order for them to return. The recovery certificate is a document issued by a physician declaring that the individual is no longer contagious. At present, most schools in Japan do not permit students to return without a certificate [106].

This recovery certificate system involves various challenges. First of all, the five-day policy does not have sufficient scientific justification. Although a recent study reported that the mean duration of seasonal influenza's viral shedding was about five days [107], the duration of shedding was different for each strain and depended on the age of the patient [108]. Furthermore, the presence of a virus does not always mean that a patient is infectious [109]. Therefore, it is difficult to judge whether a five-day absence is appropriate or not. Additionally, the U.S. Centers for Disease Control and Prevention has concluded that the duration of viral shedding is not related to fever [104]. If this result can be applied to cases of influenza among students in Japan, two additional days of isolation after one's fever declines might not be appropriate.

Next, an additional challenge is that the documentation process seems to impose a societal and economic burden on both physicians and caregivers. This type of document must be issued by a medical doctor in Japan. Consequently, parents or other caregivers of children who have just had influenza must make an extra trip to their physician—a visit that comes attached with a fee. Healthcare costs for children are paid for by many local governments in Japan [110], but nevertheless, this process creates an economic burden from a healthcare payer's or a societal perspective because these costs are ultimately covered by the national health insurance system. In addition, it is necessary to take the indirect costs into consideration. Caregivers have to take their children to their physician once they have recovered from influenza. As a result, caregivers are forced to take time off from work. This leads to productivity loss that, while not severe at the individual level, becomes substantial at the national level.

In addition, the recovery certificate does not seem to have any practical effect on the prevention of secondary infection. Physicians judge the day of recovery from face-to-face history taking. All children who revisit their clinic or hospital for requesting a certificate have already recovered, but their physicians cannot know the exact time of recovery [111]. Consequently, the only thing physicians can do is to trust the caregiver's assessment of the recovery time. After this history taking process, physicians examine their patients and issue the certificate. There is almost no difference in this process from a self-assessment, as numerous Japanese infectious disease specialists have already pointed out [106,111–114].

Due to the increased burden causes for healthcare facilities, the Ministry of Health, Labour and Welfare does not recommend the recovery certificate system [115], yet many schools in Japan require their students to submit a certificate nevertheless. In this study, I aimed to estimate the economic consequences of this recovery certificate policy.

4.2 Methods

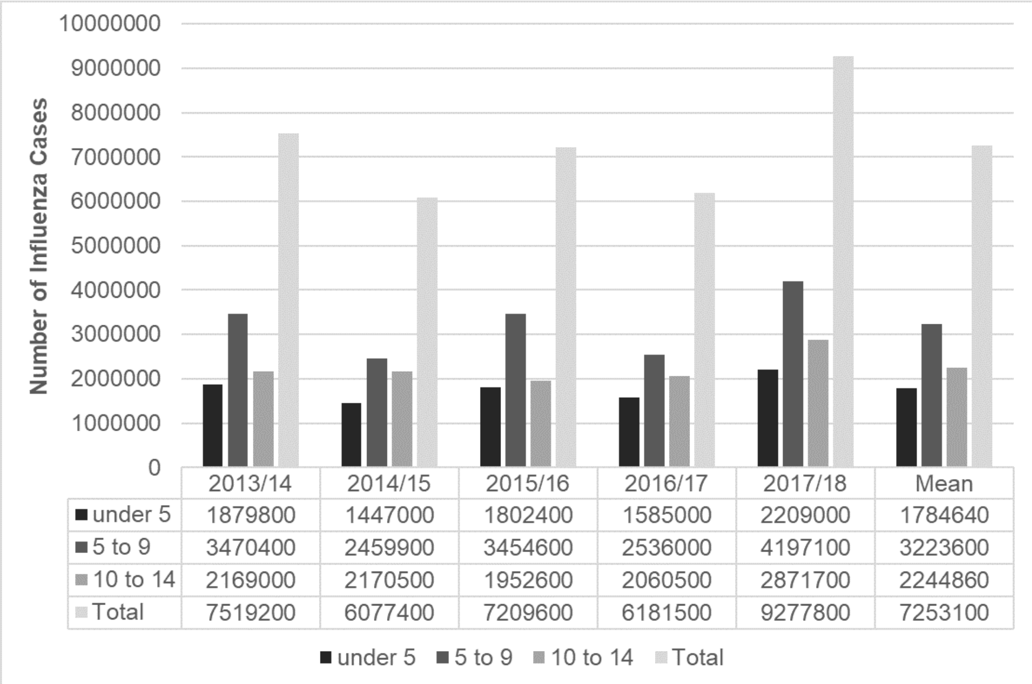
Direct and indirect annual costs of recovery certificates per 1,000,000 population at the national level were estimated from a restricted societal perspective. Direct costs include physician revisit consultation and documentation fees. Indirect costs include productivity loss estimated by the number of days of leave caregivers take for return doctor's visits. For simplicity, I assumed an exchange rate of 1 USD = 110 JPY, based on the average exchange rate in 2018. I used data from the National Institute of Infectious Diseases (number of influenza patients) [116], national statistics from the Ministry of Health, Labour and Welfare (demographic data and health insurance costs) [117,118], the National Institute of Population and Social Security Research (demographic data) [119], and the National Tax Agency (mean monthly salary) [120]. All data sources are freely available online.

The total number of recovery certificates issued each year was estimated by taking the total number of symptomatic influenza patients under 15 years old [116] combined with the proportion of households with children under 6 years old in which both parents work [117]. This is an important estimate because each household's demand for a nursery school depends on whether both parents work or not. If children under 6 years old do not attend nursery school or kindergarten, then a recovery certificate would not be required. Almost all schools in Japan, including elementary schools (elementary education starts at 6 years old in Japan), nursery schools, and kindergartens, require that students who caught influenza submit a recovery certificate. As a result, the total number of documents required can be estimated by the sum of: (1) the total number of influenza patients between 6 and 14 years old and (2) the number of influenza patients under 6 years old multiplied by the proportion of households in which both parents work. Since there are no national data about the number of patients per year according to age, I substituted 5-year age group data instead and then subdivided those data into one-year age groups, according to the age structure of the Japanese population [119]. Thus, I can describe the total number of certificates per year with the following equation (1):

$$N_t = \sum_{j=0}^{6}(N_j * R_j) + \sum_{k=7}^{14}(N_k) \quad \dots (1)$$

Where N_t represents the total number of recovery certificates, N_j and N_k represent the number of influenza patients among children j or k years old, and R_j is the proportion of households in which both parents work and their youngest child is j years old.

On average, Japan has about 7,253,100 influenza patients under 15 years old every year (Figure 4-1). According to the data from national statistics, 54.3% of mothers whose youngest child was under 6 work, and 21.1% were full-time workers. On the whole, as their children get older, a larger proportion of mothers tend to work. Although the proportion of mothers who work full-time is constantly about 20%, the proportion of part-time workers increases as their children grow up (Figure 4-2). In addition, 17.5% of households with children includes three or more generations. The average monthly salary of working women was 2,187.8 USD.



	2013/14	2014/15	2015/16	2016/17	2017/18	Mean
under 5	1879800	1447000	1802400	1585000	2209000	1784640
5 to 9	3470400	2459900	3454600	2536000	4197100	3223600
10 to 14	2169000	2170500	1952600	2060500	2871700	2244860
Total	7519200	6077400	7209600	6181500	9277800	7253100

Fig 4-1. Estimated number of influenza patients under age 15

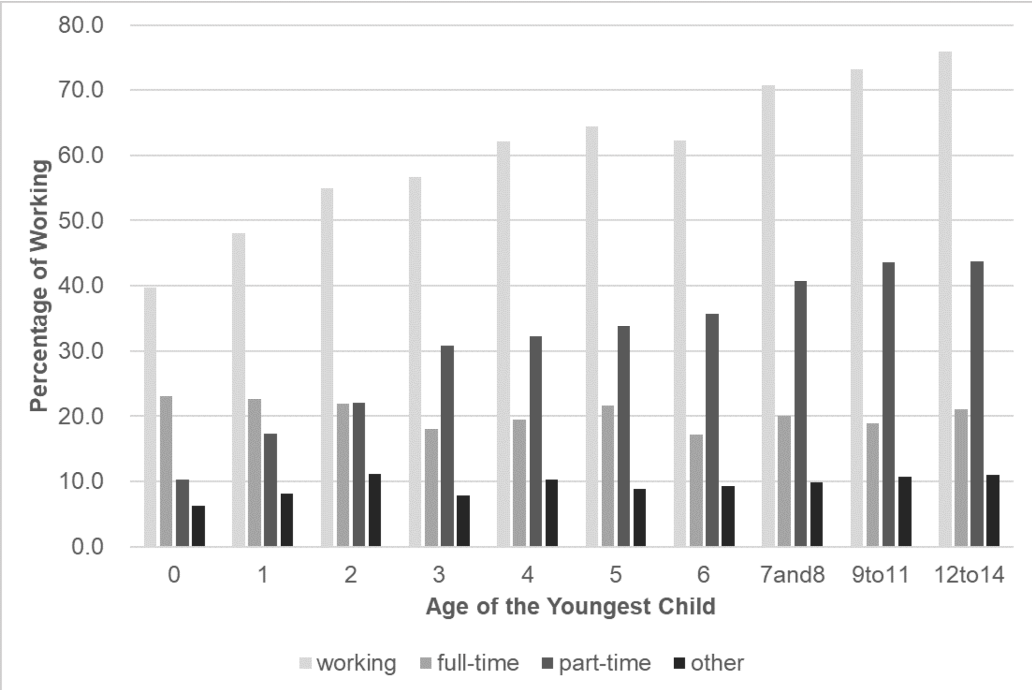


Fig 4-2. Proportion of working mothers classified by age of their youngest child

In Japan, the physician fee for a revisit is 10.1 USD per person for patients under 6 years old and 6.6 USD per person for children 6 and older, both of which are set by the Japanese government [118]. In contrast, price setting for documentation fees is left to the discretion of each healthcare facility. As such, I have assumed a documentation fee of 5 USD, an assumption which is supported by the expert opinion of Board Certified Pediatricians of Japan Pediatric Society. Additionally, some physicians do not claim any documentation and/or consultation fee from patients. Therefore the total number of certificates and revisit consultations were adjusted by the proportion of physicians who do not claim such fees [121]. This proportion was determined using an information website for healthcare professionals in which over 200,000 Japanese physicians are registered to participate in surveys. Of those, 1,277 physicians were randomly chosen by the website to participate in the survey and to answer a questionnaire about the recovery certificate. According to the survey results, 18% of physicians do not charge a fee to issue the certificate. In addition, 19% of physicians charge only a revisit consultation fee, while 63% charge both consultation fees and documentation fees.

Considering the survey results with equation (1), total direct costs of the recovery certificate policy can be described with the following equation (2):

$$total\ direct\ cost = N_t * (C_c * P_c + C_d * P_d) \dots (2)$$

Where C_c and C_d represent the cost for revisit consultation fees and documentation fees, respectively, and P_c and P_d represent the proportion of physicians who claim revisit consultation fees and documentation fees, respectively. N_t represents the total number of certificates.

In order to calculate productivity loss, I used the mean monthly salary of working women from 2013 to 2018 [120]. Most parents request a recovery certificate in the morning to minimize the duration of both their own and their children's absences from work and school, respectively. Then, after obtaining the document, they take their children to school, and go to work. Though it is difficult to estimate the exact duration of waiting time in outpatient clinics, the processes described above might be equivalent to a half-day of leave (from the beginning of work to lunch break). So, I estimated productivity loss corresponding to one half-day leave by taking half the amount of the mean monthly salary and dividing it by total working days.

Another important factor is how many caregivers must take off time from work to take their children to a physician. In the first place, stay-at-home parents and the unemployed can visit healthcare facilities without taking leave. Therefore, the total productivity loss caused by physician revisits can be represented as a product of the total number of certificates issued, the proportion of households in which both parents work, and a half-day of the mean daily salary.

Considering a caregiver's employment status (full-time or part-time), parents who work full-time jobs always have to take time off to visit a physician. Some part-time workers might be able to visit a physician without taking leave, but others might have to take time off. My equation averages out these differences at the population level because I use mean salary which includes both full-time and part-time workers.

Additionally, it is important to note the role of grandparents. In Japan, retired grandparents play an important role in childrearing. Indeed, 72% of parents can request that their own parents take care of their children when they become sick [122]. In such cases, it is the grandparents who take their grandchildren to a healthcare facility, allowing the children's parents to avoid taking time off from work. Also, I assumed that children aged 12 years and older (i.e., those who already have graduated from elementary school) can go to a healthcare facility by themselves, an assumption which is also supported by expert opinion of Board Certified Pediatricians of Japan Pediatric Society.

I did not include transportation fees in either the direct and indirect costs because there are a large number of private clinics in Japan and so people can usually visit a clinic near their home at little cost. In addition, a half-day of leave is assumed to be sufficient for obtaining a certificate because all patients are essentially healthy and require no further medical treatment or laboratory tests. I did not assume any discounting in my cost analysis because the outcomes are based only on costs themselves and analyses were conducted on the basis of a single-year assumption. Finally, I determined productivity loss caused by the recovery certificate policy by the equation:

$$total\ indirect\ cost\ = \sum_{j=0}^{12}(N_j * R_j) * (1 - P_{gp}) * W \ldots (3)$$

Where N_j represents the number of influenza patients among children *j* years old and R_j is the proportion of households in which both parents work and their youngest child is *j* years old; P_{gp} represents the proportion of parents who can ask grandparents to take care of sick children; and *W* represents the lost productivity from taking a half-day of leave.

I conducted one-way deterministic sensitivity analyses for each of the five variables influential for the result (i.e., document cost, total number of documents issued, proportion of grandparents who can help parents, length of leave that parents have to take, and mean salary of working women). The lower and upper values of the total number of documents issued and the mean salary of working women were set as ±30% of the original assumption following a previous study [92] because there was no information about their range. As for the range of document costs, I set it between 0 USD to 50 USD because there are some healthcare facilities which offer free documentation for recovery certificates, while others charge a higher fee similar to other types of medical certificates [121]. I assumed the range for the length of leave parents have to take was between one hour and one day. I also conducted a probabilistic sensitivity analysis (PSA) including 1,000 simulations with assumed distribution of parameter values (log-normal or triangular distribution). Values and distribution of each parameter are

shown in Table 4-1.

Table 4-1. Values and distribution of each parameter

Variable	Value (unit)	Range	Distribution	Reference
Document fee	5 (USD)	0-50 (USD)	lognormal	[121]

Consultation fee for children under 6	10.1 (USD)	Fixed	NA	[118]
Consultation fee for children 6 or older	6.6 (USD)	Fixed	NA	[118]
Proportion of grandparents who can take care of sick children	0.72	0.504-0.936	triangular	[122]
Length of leave taken	0.5 (day)	0.125-1.0 (day)	triangular	Assumption
Mean monthly wage	2,187.8 (USD)	1,531.5-2,844.2 (USD)	lognormal	[120]
Number of certificates issued*	5,937,692	4,156,384-7,719,000	triangular	[116,117,121]

***In the total population of Japan, per one season; NA: not applicable**

All analyses were performed with R, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) [91].

4.3 Results

Under the assumptions described in the previous section, the mean annual cost of the recovery certificate policy amounted to 939,872 USD per million population in Japan. Direct costs were estimated to be 430,737 USD and indirect costs were 509,135 USD per million population.

Deterministic, one-way sensitivity analyses demonstrated that the total additional costs ranged from 547,111 USD to 2,265,333 USD per million population (Table 4-2). Document fees played a comparatively important role in determining the total economic burden, but nevertheless, each variable did not change the results critically.

Table 4-2. Main result and results of deterministic one-way sensitivity analyses

	Direct cost	Indirect cost	Total cost
Original assumption	0.43	0.51	0.94
Document fees	1.76	0.51	2.27
	0.28	0.51	0.79
Number of documents issued	0.56	0.66	1.22
	0.30	0.36	0.66
Proportion of grandparents who can take care of sick children	0.43	0.12	0.55
	0.43	0.90	1.33
Length of leave taken	0.43	1.02	1.45
	0.43	0.13	0.56

Mean monthly wage	0.43	0.66	1.09
	0.43	0.36	0.79

Unit: million USD per million population

Upper rows represent results of the upper parameter value, bottom rows represent results of the lower parameter value.

Probabilistic sensitivity analysis demonstrated that the additional cost of the recovery certificate amounted to about million USD per million population in most cases (median: 847,193 USD, interquartile range: 610,724-1,235,824 USD). Figure 4-3 shows a histogram of 1,000 simulation results.

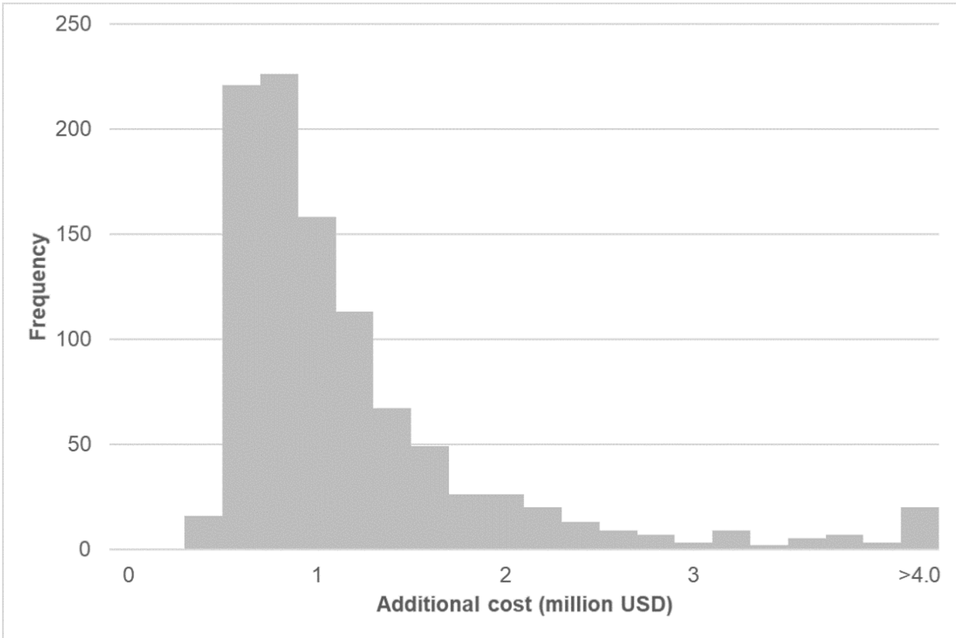


Fig 4-3. Results of probabilistic sensitivity analysis

A histogram of 1,000 simulations of the probabilistic sensitivity analysis

Y axis represents the frequency of trials.

4.4 Discussion

To my knowledge, this is the first study to measure the economic burden imposed on Japanese society by the recovery certificate system. The results of this study should create an opportunity to consider the impact of this long-standing custom.

Currently, Japan is experiencing the effects of a rapidly aging society, and its national medical expenses are growing larger and larger. In fiscal year 2015, annual expenses for medical costs in Japan amounted to 3,268 billion USD per million population and this figure is expected to rise [123]. Although 0.94 million USD is quite small compared to total medical expenses, it is nevertheless a substantial burden on Japanese society and the benefit of the recovery certificate practice is uncertain.

As detailed in this paper, there is no justifiable reason for schools to demand that children submit a certificate to return after recovering from influenza. On the contrary, there is a possibility that these recovery certificates do more harm than good. I should note that the situation, as it is now, sees healthy parents taking their already recovered children to healthcare facilities when they need certificates. Needless to say, there are a large number of sick people at these facilities. These sick people include patients with infectious diseases, which exposes the healthy caregivers and recovered children to new risks of infection. If it were possible to estimate the risk of secondary infection caused by obtaining a certificate, the total negative economic impact would become larger still and the additional disease burden could be visualized. Both from the perspective of economics and clinical medicine, the recovery certificate policy appears to have a net negative impact on our society. In fact, the government of Okinawa Prefecture has already declared that it does not recommend using recovery certificates as a requirement for returning to school [124].

Additionally, most schools in Japan have also adopted a recovery certificate policy for other infectious diseases (e.g., varicella, mumps, and so forth). This type of response probably derives from the Japanese aversion to risk. From the standpoint of school administrators, outbreaks of any infectious disease in their own schools are to be completely avoided. However, their attitude makes it difficult to conduct an appropriate risk assessment. Presumably, school administrators do not know the actual impact of recovery certificates and believe they are beneficial. I believe appropriate and regular information updates from the government and healthcare professionals is needed to improve the current situation.

As with all other research, our study has some limitations. First, I conducted my analyses with incomplete data. For example, data about the number of influenza patients only contained 5-year age groups. As a result, there might be some discrepancy between the real number of schoolchildren who need a certificate and the estimated one. As 98% of 5 year old children belong to some kind of kindergarten or nursery school [125], the estimated total number of documents is expected to be similar to the actual one. Furthermore, only point estimates were available for some parameters, so I had to set range of parameter values arbitrarily. This might also impair the robustness of the results.

Second, our assumptions include the possibility of some under/overestimation. I did not include any transportation fees for revisits even though some caregivers must use public transportation or private cars. In addition, some parents request that their physicians prescribe drugs for the common cold during the same visit. Antitussives and expectorants are not expensive drugs, but it is likely that these drugs would never be prescribed if parents did not have to revisit their physician to obtain a certificate. As for overestimation, I assumed that all schools and nursery schools require children to submit a certificate. Although the exact number is not known, a small number of schools do allow children to return to school without a recovery certificate. Nevertheless, my assumptions (e.g., some physicians issue certificates without charging a fee) and the wide range of sensitivity analyses should compensate for such under/overestimates.

Third, our analysis neglected the possibility that the recovery certificate policy has any positive impacts for preventing secondary transmission of influenza. If the duration of the infectious period lasts longer than 5 days, isolation at home for more than 5 days might be beneficial for preventing the spread of infection. However, as I have already explained, physicians issue certificates based on information from patients' caregivers. Consequently, patients could attend school on the same day if they did not need to submit any documents.

Considering these limitations, this analysis might sacrifice accuracy and robustness to some extent. Nevertheless, I believe that the results are reasonable, and worthy of note because quantitative analysis of the societal impact of the recovery certificate policy has been insufficient to date.

4.5 Conclusion

As I have shown, the recovery certificate system, which is unique to Japan, has some negative economic and societal consequences. Reconsideration of this policy may enable us to reduce excessive primary healthcare costs.

5. Chapter 3: Total disease burden caused by seasonal influenza in Japan and its optimal vaccination policy

This chapter is based on published work: "Tsuzuki S, Baguelin M, Pebody R and Van Leeuwen E (2020). Modelling the optimal target age group for seasonal influenza vaccination in Japan. Vaccine 2020 Vol. 38 Issue 4", doi: 10.1016/j.vaccine.2019.11.001 [126].

Summary

In Japan, the current influenza vaccination programme is targeting older individuals. On the other hand, epidemics of influenza are likely to be mainly driven by children. In this study, we consider the most cost-effective target age group for a seasonal influenza vaccination programme in Japan. We constructed a deterministic compartmental Susceptible-Exposed-Infectious-Recovered (SEIR) model with data from the 2012/13 to 2014/15 influenza seasons in Japan. Bayesian inference with Markov Chain Monte Carlo method was used for parameter estimation. Cost-effectiveness analyses were conducted from public health care payer's perspective. Totally, disease burden caused by seasonal influenza was estimated as 81,445.8 QALYs lost in total population of Japan (mean of 2012/13 - 14/15 season). A scenario targeting children under 15 was expected to reduce the number of cases 6,382,345 compared to the current strategy. A scenario targeting elderly population (age over 49 years) was expected to reduce the number of cases 693,206. The children targeted scenario demonstrated negative ICER (incremental cost-effectiveness ratio) value. On the other hand, elderly targeted scenario demonstrated higher ICER value than the willingness to pay (50,000 USD/QALY). A vaccination programme which targets children under 15 is predicted to have much larger epidemiological impact than those targeting elderly.

5.1 Background

Seasonal influenza is one of the major public health issues in Japan. It is estimated that the prevalence of seasonal influenza endemic in Japan amounted to over 10% every year [127]. Since the World Health Organization (WHO) has recommended vaccination as the most effective way of preventing infection and severe outcomes caused by influenza viruses [128], selecting the most cost-effective vaccination policy for seasonal influenza is important to obtain optimal health benefits with the same resources.

In recent years, most developed countries have put in place vaccination policies for seasonal influenza which target older individuals and those at higher risk of severe disease [129,130]. On the other hand, epidemics of influenza in the population are likely to be mainly driven by children [131–134], providing other potential vaccination strategies. For instance, the United Kingdom recently started the introduction of universal vaccination for children in 2013/14 and have already conducted quantitative assessment of their new vaccination policy [135,136]. So far, it seems appropriate that vaccination policy for seasonal influenza targets children, at least in the United Kingdom.

Turning to the present state of affair about vaccination policy in Japan, which recommends routine seasonal influenza vaccination for people aged 65 and older, and for high-risk population aged 60 and older, there is scarce quantitative evaluation of such vaccination policies. The current situation concerning the national vaccination programme is partly related to vaccine hesitancy amongst Japanese people [137]. This has led to a reduction in vaccine uptake compared to previous seasons, a so-called “vaccine gap” not only for seasonal influenza but also some other vaccine preventable diseases [138].

Thus, a formal evaluation of vaccine policy is required in Japan in order to establish the most cost-effective measures for reducing the disease burden due to vaccine preventable diseases like seasonal influenza.

The main objective of this paper is to determine the most effective and cost-effective target age group for a seasonal influenza vaccination programme in Japan, considering the local epidemiology of influenza and Japanese surveillance systems.

5.2 Methods

Overview

Epidemiology of seasonal influenza and the impact and cost-effectiveness of influenza vaccination policy in Japan were evaluated with a mathematical model. We used demographic, virological, clinical, and epidemiological data from the 2012/13 to 2014/15 influenza seasons to establish an age-stratified transmission model. We constructed a deterministic compartmental SEIR (susceptible-exposed-infectious-recovered) model to compare different vaccination scenarios. Bayesian inference with MCMC (Markov Chain Monte Carlo) was used for parameter estimation and model fitting. Cost-effectiveness analyses (CEA) were conducted for each vaccination scenario from a public health care payer's perspective.

Epidemiological and Virological Data

The epidemiological data consisted of the weekly surveillance report provided by National Institute of Infectious Diseases (NIID), Japan [127]. Weekly surveillance in Japan is based on sentinel surveillance of medically attended influenza (MAI), almost all of which is microbiologically diagnosed influenza by rapid influenza diagnostic test (RIDT). As Thomas pointed out [139], a large proportion of influenza-like illness (ILI) cases is infection other than influenza virus and ILI is difficult to be used directly as a proxy of total number of influenza cases. In Japan, the concept of ILI has not been used and microbiologically diagnosed cases are used as the proxy. Though RIDT is not popular as a diagnostic method in other countries, it is the prevailing method in Japan and shows high sensitivity and specificity [82]. Therefore, the number of MAI were an appropriate proxy for the total number of symptomatic cases. As for annual total number of MAI case, NIID provides an annual report about estimated total number of cases. Estimated total number of MAI cases are available in Table S5-1 in Supplementary information. NIID also reports virological test results every week and the absolute number of influenza positive strain is available. This data was used to estimate the proportion of each strain.

Demography and Contact Survey

For each of the three seasons of the study, age-structured population data were obtained from the Statistics Bureau Japan [140]. We considered 10 age groups (<5, 5-9, 10-14, 15-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70+ years of age). We stratified the population by risk for severe outcome of influenza infection based on the previous UK study [141] since this data is not available in Japan.

We introduced a contact matrix in our model to include the heterogeneity of social contact pattern instead of relying on a priori contact assumption. The contact matrix for the model was constructed from the contact survey data from Ibuka et al. [142]. They conducted a questionnaire survey that included 4331 respondents in 2011 and estimated the frequency of face-to-face conversation (talking within a two-meter distance) with age-specific mixing patterns, following the methodology of Mossong et al. [143]. For simplicity, we assume the same frequency of contacts in both weekdays and weekends and did not consider long school holidays. The same matrix was used for each of the three seasons.

Transmission Model

Previous studies have linked influenza transmission with the structure of contacts in the community [131,143]. A susceptible individual will be infected with probability q after contact with an infected individual. The mixing pattern in our model is described by a resampled subset of participants from the dataset from Ibuka et al. [142] using the methodology developed in previous studies [142–145].

Let T_j be the number of participants in class j, A_k and $\{N_k^i\}$ be respectively the age and number of contacts made in age group i for and by participant k. The re-normalised average number of contacts per day d_{ji} made by participants from age group j with persons in age group i standardised for age is

$$d_{ij} = \frac{\sum_{k:Ak \in j} N_k^i T_j}{\sum_{k:Ak \in j} T_j}$$

Contacts are symmetric, i.e., the number of contacts in the population resulting from people from age group i meeting with people from age group j is the same as the number of contacts made by people from age group j meeting with people from age group i. Therefore, if we call C_{ij} the probability that two randomly selected individuals in group i and j get in contact, we get by symmetry $C_{ij} = C_{ji}$. By using the direct formula $C_{ij} = d_{ij}/T_i$, symmetry will not usually be achieved because of reporting or participation biases. To achieve symmetry of the contact matrix $\{C_{ij}\}$, we thus set

$$C_{ij} = \frac{1}{2}\left(\frac{d_{ij}}{T_i} + \frac{d_{ji}}{T_j}\right)$$

We multiply this matrix by the transmission probability q, to obtain the transmission rate for each age group. The contact matrix is combined with the demographic data and updated in the MCMC (Markov Chain Monte Carlo) chain at each step, by resampling from the original data with replacement.

Vaccination

We assume that individuals are vaccinated annually from late October to December, evenly every week. Because seasonal influenza vaccine is not completely effective, only a proportion of the vaccinees were assumed to be protected. This proportion of vaccinees which do not get protected from vaccination is assumed to remain fully susceptible. We assumed that the vaccine efficacy depended on age and did not consider the match between vaccine and the circulating strain. We assume that the efficacy for children and younger adults be higher and that for elderly (50+ years of age) be lower, based on the recent other previous studies [146–148]. Vaccine coverage for each age group was derived from surveillance data from NIID [149].

Epidemiological Model

The epidemiological model applied to the present study is based on the R package “fluEvidenceSynthesis” maintained by Public Health England [150,151]. The model has a modified compartmental SEIR (Susceptible-Exposed-Infectious-Recovered) structure. Random mixing within population was assumed. To allow the latent and infectious periods to be gamma distributed, each of the E and I compartment were divided in two compartments (consequently the model has SEEIIR structure), with the same rate of loss of latency and infectiousness in both groups.

We assume that at the beginning of the epidemic a small fraction of individuals in each age class is infectious, and the remainder is susceptible. An age-dependent susceptibility profile is assumed, the parameters of which are estimated from the model-fitting process for all strains and years. We chose to limit the model to four age bands to avoid overfitting, then considered an average susceptibility for infants (0-4 years old), children and adolescents (5–19 years old), adults (20–69 years old), and elderly adults (70+ years old).

Our simulation was started at epidemiological week 36 in all three years according to the structure of data derived from NIID Japan. As for inputs for parameter inference, we combined freely available virological and sentinel surveillance data from the NIID website, as described in "Epidemiological and Virological Data" section [116]. Cases infected outside Japan were not considered.

We adapted the likelihood model to account for the difference in influenza monitoring between the UK and Japan. The most significant difference in Japan's surveillance system was the absence of syndromic surveillance. The total number of seasonal influenza patients in Japan is generally estimated using weekly sentinel surveillance data, which are based on the result of RIDT [152] (see the subsection "Epidemiological and Virological Data"). As for virological surveillance, while weekly data from NIID contain other respiratory viruses such as respiratory syncytial virus, rhinovirus, and so forth, we specifically estimated the proportion of each strain in the four major subtypes of seasonal influenza (A/H1N1, A/H3N2, B/Victoria, and B/Yamagata). Seasonal influenza viruses also bring asymptomatic infection with moderately high proportion [153,154], therefore we set the prior value of proportion of patients who visit health facilities according to the estimation by the previous study [155].

We assumed that a constant fraction (denoted by $\boldsymbol{\epsilon}$) of infected people went to the doctor and obtained the positive results of rapid swab test. Then the likelihood of a number of confirmed cases in a given week (C_w) is:

$$L(C_w;\, \epsilon,\, I) \;=\; B(C_w, \textstyle\sum_s \sum_a I^s_{a,\, w}\, , \epsilon)$$

where $B(\dots)$ denotes the binomial distribution, a the age group and s the subtype.

If it is age group dependent (which it most likely is), it should follow a Poisson-binomial-distribution. To simplify this, we loosen our assumption of a binomial distribution and instead use a Poisson distribution, which is then defined as follows:

$$L(C_w;\, \epsilon,\, I) \;=\; P(C_w, \beta \sum_s \sum_a \epsilon_a I^s_{a,\, w})$$

where β is the fraction of the population covered by the sentinel surveillance.

As for monthly subtype data, let define the fraction of a strain in a certain week as:

$$p_{s,\,w} \frac{\sum_a I_{a,\,w}^s}{\sum_{\boldsymbol{s},\boldsymbol{a}} I_{a,\,w}^s}$$

Since we have monthly data, we calculate the monthly values by summing over all the weeks in a certain month:

$$p_{s,\,m} \frac{\sum_w^m \sum_{\boldsymbol{a}} I_{a,\,w}^s}{\sum_w^m \sum_{\boldsymbol{s},\boldsymbol{a}} I_{a,\,w}^s}$$

Then the likelihood of the number of detected viruses per subtype $(n_{s,m})$ follows a multinomial distribution:

$$f(n_{H1N1}, m, n_{H3N2}, m, \dots;\ p_{H1N1}, m, p_{H3N2}, m, \dots)$$

For the next step, we have to estimate the yearly total number of patients to fit the model to the data. This process is quite similar to the summation of the swab results, but now summed over week, instead of over age group.

$$L(C_{a,y}\,;\,\epsilon,\ I) = B(C_{a,y}, \sum_{s}\sum_{w}^{y} I_{a,w}^{s}\,, \epsilon_a\,)$$

Assuming $\sum_s \sum_w^y I_{a,w}^s$ we can approximate the binomial distribution using a Poisson distribution;

$$L(C_{a,y};\,\epsilon,\ I) = P(C_{a,y}\,,\ \ \epsilon_a \sum_{s}\sum_{w}^{y} I_{a,w}^{s}\,)$$

Assessment of different vaccination scenarios

We compared estimated reduction rate of symptomatic cases, number of admissions and deaths reduced for seven different vaccination scenarios.

0. Current vaccination coverage
1. High coverage amongst 0-4 years of age (versus scenario 0)
2. High coverage amongst 0-9 years of age (versus scenario 0)
3. High coverage amongst 0-14 years of age (versus scenario 0)
4. High coverage amongst age over 50 years (versus scenario 0)
5. High coverage amongst age over 60 years (versus scenario 0)
6. High coverage amongst age over 70 years (versus scenario 0)

We set 90% of coverage for the target population in each imaginary scenario, similar to the highest level of influenza vaccination coverage achieved when it was legally mandatory [156].

As already pointed out in the previous studies, vaccination policy which targets children seems to be more effective than the current one which targets aged people [136,146,157], in view of epidemiological impact. The details of vaccine coverage for the scenarios are described in Table S5-2 in Supplementary information.

Cost-effectiveness analyses

The cost-effectiveness of each vaccination scenario was evaluated for each season, compared with the original vaccination coverage. In the present study, public health care payer's perspective was adopted in accordance with the Japanese guideline of economic evaluation [158]. We considered cost of vaccination programme, outpatient healthcare, inpatient care, and death after hospitalization. Each value was derived from a previous study [159]. All values were calculated with USD converted from Japanese Yen (JPY) with the rate of 1 USD = 110 JPY. We used the quality adjusted life years (QALYs) gain. We used the value of the burden of acute respiratory illness caused by influenza infection estimated in the previous study [96]. We set the willingness to pay (WTP) threshold to 50,000 USD/QALYs, when vaccination scenarios were not dominant against the current vaccination strategy.

The number of admissions and the number of deaths were calculated by the risk assessment derived from NIID Japan [160]. We set the discount rate value as 2.0% per year also in accordance with the Japanese guideline [32]. As for cost, we assume that all costs are incurred in the same year, because influenza is an acute disease, consequently, we did not discount cost. We discount the utility of life years gained by reduced mortality. Life years gained was calculated based on the mean period life expectancy of Japan, which was discounted every year (for example, if we prevent one death at two years of age, it means we can save 82 life years for the patient. But these 82 years were discounted every year with the constant rate 2.0%, then life years gained by this patient is about 40.9 years).

We ran univariate sensitivity analyses to examine the robustness of our results by increasing or decreasing key parameter values by 30% of their baseline or with a range of confidence intervals. When determining the range of each parameter, we referred to the Japanese guidelines for cost-effectiveness analyses as well as to the ISPOR and ISPOR SMDM guidelines [75,76]. In some cases, we have only one-point estimate for parameters due to insufficient data and references. In these cases, the Japanese guidelines do not make a specific recommendation. Thus, we regarded the ranges of parameters in the previous study (±30%) [33] as reasonable and used triangular sampling distributions. We additionally performed a probabilistic sensitivity analysis (PSA) by randomly and independently sampling economic model parameter values from probabilistic distributions with 2,000 simulations.

Economic model parameters and their distributions are described in Table S5-3 in Supplementary information.

No annual testing of vaccine efficacy is available from Japan. Therefore, we conducted a sensitivity analysis for vaccine efficacy with values from other countries [161]. Leval et al. reported yearly vaccine efficacy. According to their results, vaccine efficacy was comparatively high in 2012/13 and 2013/14 seasons (40% and 37% for young adults and 49% and 46% for elderly, respectively). On the other hand, the efficacy was quite low (15% for young adults and 18% for elderly) in 2014/15 season. Furthermore, the efficacy was higher in elderly than in younger adults. Although these values are not actual vaccine efficacy in Japan, they were appropriate for sensitivity analysis because they allow us to examine the cost-effectiveness of the same vaccination programme under more conservative assumptions. The vaccine efficacy for the sensitivity analysis is available in Table S5-4 in Supplementary information.

5.3 Results

Fitness of the model and baseline results

Each parameter in our mathematical model was estimated, and the fitted model managed to reproduce the detailed epidemiological patterns observed in the surveillance data. Figure 5-1-A, 5-1-B, and 5-1-C show the model fitting in weekly distribution of the number of influenza cases in each of the three seasons. Details of estimated and fixed values of parameters are available in Table S5-5, S5-6, and S5-7, and the estimated values of R_0 are shown in Table S5-8 in Supplementary information.

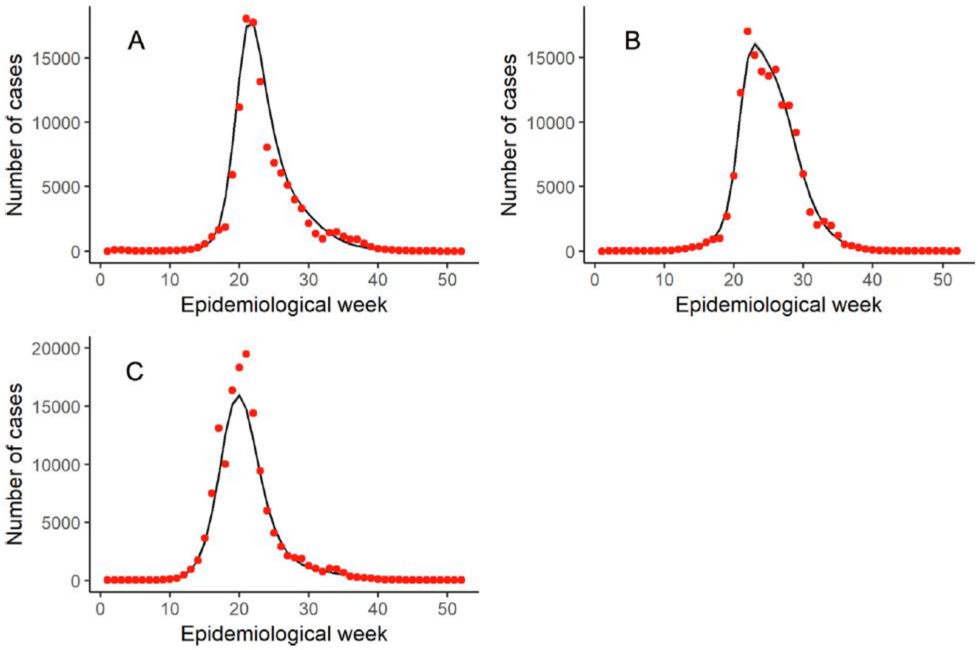


Fig 5-1. Model fitting in weekly distribution of medically attended influenza case in each season.

(A) 2012/13 season. (B) 2013/14 season. (C) 2014/15 season.

Dotted line represents observed sentinel surveillance data, solid line represents median value of model estimation, and grey area represent 95% credible interval of model estimation.

Totally, disease burden caused by seasonal influenza was estimated as 81,445.8 QALYs lost in total population of Japan (mean of 2012/13 - 14/15 season). Among all disease burden, 16,564.3 QALYs (20.3%) were derived from YLL. Per 100,000 population, 63.93 QALYs lost per year (mean of three seasons) was imposed on us.

Number of case reduction in each scenario

A scenario of high vaccine coverage (uptake of 90% at the end of the year) amongst children (0-14 years of age) demonstrated the largest reduction in MAI cases (6,382,345 cases reduced on average over one season). An elderly (age over 50 years) high coverage scenario reduced by 693,206 cases.

Detailed reduction in the number of consultations, number of admissions, and number of deaths are shown in Table 5-1, 5-2, and 5-3 respectively. Figure 5-2-A, 5-2-B, and 5-2-C depict violin plots about the results of 2,000 trials for each vaccination scenario, with median values, 95% credible intervals and frequency.

Table 5-1. Number of MAI reduction in each year*

Year	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6
2012	4,378,605 (4,288,392-4,468,448)	5,035,299 (4,937,225-5,139,837)	5,658,838 (5,548,215-5,777,042)	635,817 (613,912-663,344)	404,676 (382,841-436,184)	186,664 (173,243-201,086)
2013	6,484,863	8,272,079	9,194,932	521,027	305,423	70,915

	(6,327,225-6,602,801)	(8,081,733-8,426,922)	(9,006,101-9,350,908)	(503,469-544,544)	(292,964-330,776)	(68,699-76,599)
2014	1,126,848 (1,084,193-1,159,256)	3,262,586 (3,221,399-3,313,884)	4,293,938 (4,246,971-4,351,558)	922,101 (901,912-938,934)	710,294 (691,823-729,572)	436,576 (427,422-447,232)
Mean	3,996,366 (3,937,877-4,043,656)	5,523,228 (5,452,894-5,581,504)	6,382,345 (6,312,534-6,441,831)	693,206 (682,484-706,553)	474,180 (464,460-488,641)	231,574 (225,591-237,652)

*These numbers in the table represent the median value of 2,000 simulations and numbers in the brackets represent 95% credible interval.

Table 5-2. Number of admission reduction in each year*

Year	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6
2012	6,887 (6,743-7,025)	7,920 (7,765-8,072)	8,757 (8,577-8,928)	1,847 (1,791-1,929)	1,435 (1,379-1,435)	784 (741-833)
2013	9,224 (8,993-9,397)	11,682 (11,396-11,900)	12,743 (12,454-12,969)	1,257 (1,220-1,303)	898 (865-953)	269 (260-285)
2014	1,827 (1,754-1,884)	4,863 (4,786-4,966)	6,083 (5,993-6,202)	2,588 (2,544-2,627)	2,248 (2,200-2,291)	1,530 (1,504-1,556)
Mean	5,977 (5,882-6,053)	8,154 (8,040-8,245)	9,194 (9,073-9,290)	1,898 (1,873-1,927)	1,529 (1,504-1,560)	862 (843-880)

*These numbers in the table represent the median value of 2,000 simulations and numbers in the brackets represent 95% credible interval.

Table 5-3. Number of death reduction in each year*

Year	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6

2012	261 (254-267)	298 (290-306)	335 (325-344)	115 (111-120)	88 (85-94)	49 (46-52)
2013	270 (261-278)	330 (319-339)	362 (351-372)	76 (74-79)	54 (52-57)	17 (16-18)
2014	48 (45-51)	120 (117-126)	157 (153-164)	155 (152-157)	133 (130-136)	91 (90-93)
Mean	193 (189-196)	250 (245-254)	285 (279-289)	115 (114-117)	92 (91-94)	52 (51-53)

*These numbers in the table represent the median value of 2,000 simulations and numbers in the brackets represent 95% credible interval.

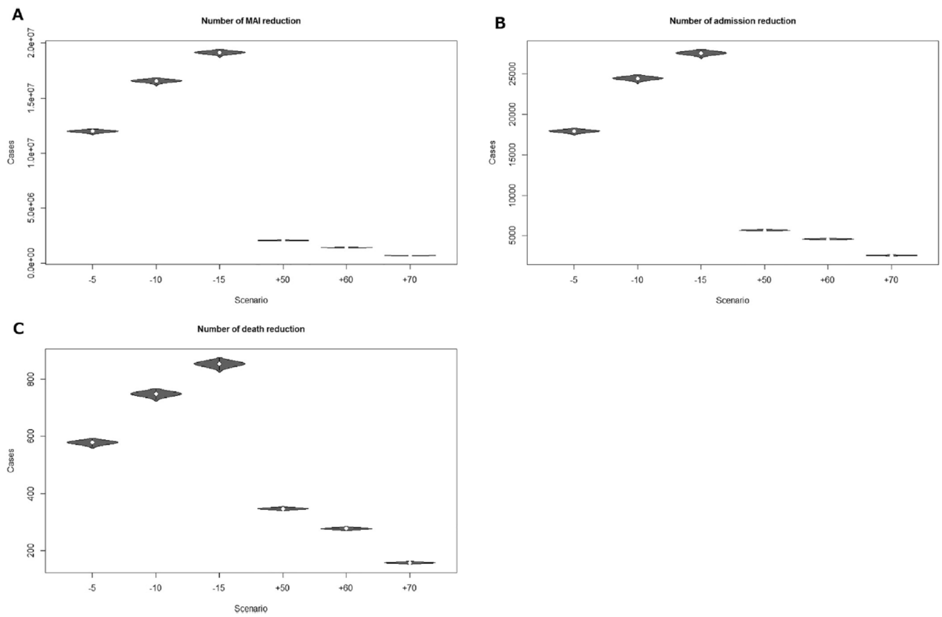


Fig 5-2-A. 3 years' mean number of medically attended influenza reduction for each scenario.

Fig 5-2-B. 3 years' mean number of admission reduction for each scenario.

Fig 5-2-C. 3 years' mean number of death reduction for each scenario.

Cost-effectiveness analyses (CEA)

The children targeted scenarios (all of 0-4, 0-9, 0-14) demonstrated negative value of three years' mean incremental cost and positive value of QALYs gain from public health care payer's perspective, which shows that the children targeted vaccination scenarios are dominant against the current vaccination policy. On the other hand, all the adult targeted scenarios (50+, 60+, 70+) showed incremental cost-effectiveness ratio (ICER) value larger than our willingness to pay (WTP, 50,000 USD/QALYs). Therefore, adult targeted scenarios might not be cost-effective although they bring us additional utility by preventing some influenza cases. The details of CEA results are shown in Table 5-4.

Table 5-4. Mean incremental cost, QALYs gain, and incremental cost-effectiveness ratio (ICER) of each vaccination scenario (thousand USD)*

	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6
Incremental cost	-456,826 (-448,657, -463,365)	-613,076 (-621,144, -603,278)	-647,607 (-655,884, -637,869)	728,314 (726,434, 729,819)	521,948 (519,921, 523,317)	217,455 (216,594 218,310)
QALYs gain	22,995 (22,641, 23,275)	31,321 (30,895, 31,664)	36,041 (35,613, 36,393)	5,453 (5,379, 5,545)	3,920 (3,850, 4,019)	1,955 (1,907, 2,000)
ICER	NA**	NA	NA	133.6 (131.0, 135.7)	133.2 (129.4, 135.9)	111.2 (108.3, 114.5)

ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

USD: United States dollar

*These numbers in the table represent the median value of 2,000 simulations and numbers in the brackets represent 95% credible interval.

**NA: Not applicable. Since scenario 1, 2, and 3 showed negative value of incremental cost, then these scenarios are regarded as "dominant" strategy.

Sensitivity analyses

Univariate deterministic sensitivity analyses showed that the costs for vaccination is the most influential variable in all the adult targeted scenarios. Costs for death cases had the least influence in all scenarios. The details of univariate sensitivity analysis results and tornado diagrams are described in Table 5-5, Figure 5-3-A and 5-3-B.

Table 5-5. Univariable sensitivity analyses for the annual mean of three years' incremental cost, QALYs gain, and incremental cost-effectiveness ratio (ICER) of each vaccination scenario (thousand USD)*

Parameter	Scenario 1 (incremental cost)	Scenario 2 (incremental cost)	Scenario 3 (incremental cost)
Cost for vaccination**	-427,388 (-433,926, -419,218)	-567,018 (-575,085, -557,219)	-576,313 (-584,591, -566,575)
	-486,265 (-492,803, -478,096)	-659,135 (-667,203, -649,337)	-718,901 (-727,178, -709,163)
Cost per outpatient**	-618,427 (-626,880, -607,891)	-836,423 (-846,851, -823,781)	-905,710 (-916,389, -893,148)
	-295,229 (-299,850, -289,429)	-389,720 (-395,437, -382,776)	-389,512 (-395,381, -382,590)
Cost per hospitalization**	-461,182 (-467,762, -452,943)	-619,016 (-627,144, -609,144)	-654,303 (-662,646, -644,471)
	-452,473 (-458,967, -444,373)	-607,130 (-615,144, -597,413)	-640,916 (-649,125, -631,266)
Cost per death**	-457,358 (-463,900, -449,179)	-613,765 (-621,839, -603,953)	-648,390 (-656,679, -638,642)
	-456,295 (-462,829, -448,136)	-612,386 (-620,449, -602,604)	-646,826 (-655,090, -637,096)
Parameter	**Scenario 1 (QALYs gain)**	**Scenario 2 (QALYs gain)**	**Scenario 3 (QALYs gain)**

Disease burden**	26,487 (26,080, 26,807)	36,114 (35,623, 36,507)	41,571 (41,080, 41,978)
	20,173 (19,861, 20,420)	27,441 (27,065, 27,744)	31,561 (31,183, 31,871)
Discount rate**	21,962 (21,624, 22,229)	29,988 (29,580, 30,316)	34,551 (34,143, 34,889)
	25,019 (24,637, 25,322)	33,930 (33,469, 34,298)	38,929 (38,467, 39,310)
Parameter	**Scenario 4 (ICER)**	**Scenario 5 (ICER)**	**Scenario 6 (ICER)**
Cost for vaccination**	179.1 (175.8, 181.8)	178.3 (173.5, 181.9)	149.8 (146.0, 154.0)
	88.1 (86.3, 89.5)	88.0 (85.3, 89.9)	72.7 (70.6, 75.0)
Cost per outpatient**	128.5 (125.9, 130.5)	128.3 (124.5, 131.0)	106.4 (103.5, 109.7)
	138.7 (136.2, 140.8)	138.0 (136.2, 140.8)	116.0 (113.1, 119.2)
Cost per hospitalization**	133.3 (130.8, 135.4)	132.9 (130.8, 135.6)	110.9 (108.0, 114.1)
	133.8 (131.3, 135.9)	133.4 (129.7, 136.2)	111.5 (108.6, 114.8)
Cost per death**	133.5 (131.0, 135.6)	133.1 (129.3, 135.8)	111.1 (108.2, 114.4)
	133.6 (131.1, 135.7)	133.2 (129.4, 136.0)	111.3 (108.4, 114.5)
Disease burden**	117.7 (115.5, 119.8)	117.3 (115.5, 119.6)	98.2 (95.7, 101.1)
	149.1 (146.3, 151.4)	148.5 (144.3, 151.5)	123.7 (120.5, 127.3)
Discount rate**	141.7 (139.0, 144.0)	141.0 (137.0, 144.0)	117.4 (114.3, 120.8)
	123.3 (121.0, 125.2)	123.4 (119.9, 126.0)	103.7 (100.9, 106.7)

ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

USD: United States dollar

*These numbers in the table represent the median value of 2,000 simulations and numbers in the brackets represent 1st quartile and 3rd quartile. Since scenario 1, 2, and 3 were “dominant” ICER is not applicable to these scenarios. Then Sensitivity analyses were conducted for incremental cost and QALYs gain separately.

**Upper and lower limitation of each parameter value were set as ±30% of original value or confidence intervals. As for discount rate, the range of the rate was set as 4.0% to 0%. Upper rows represent the incremental costs with upper value of each parameter, and lower rows represent those with lower value.

After changing all variables included in the sensitivity analyses, scenarios which target children were still dominant against the current coverage and those which target elderly were less cost-effective than the current coverage.

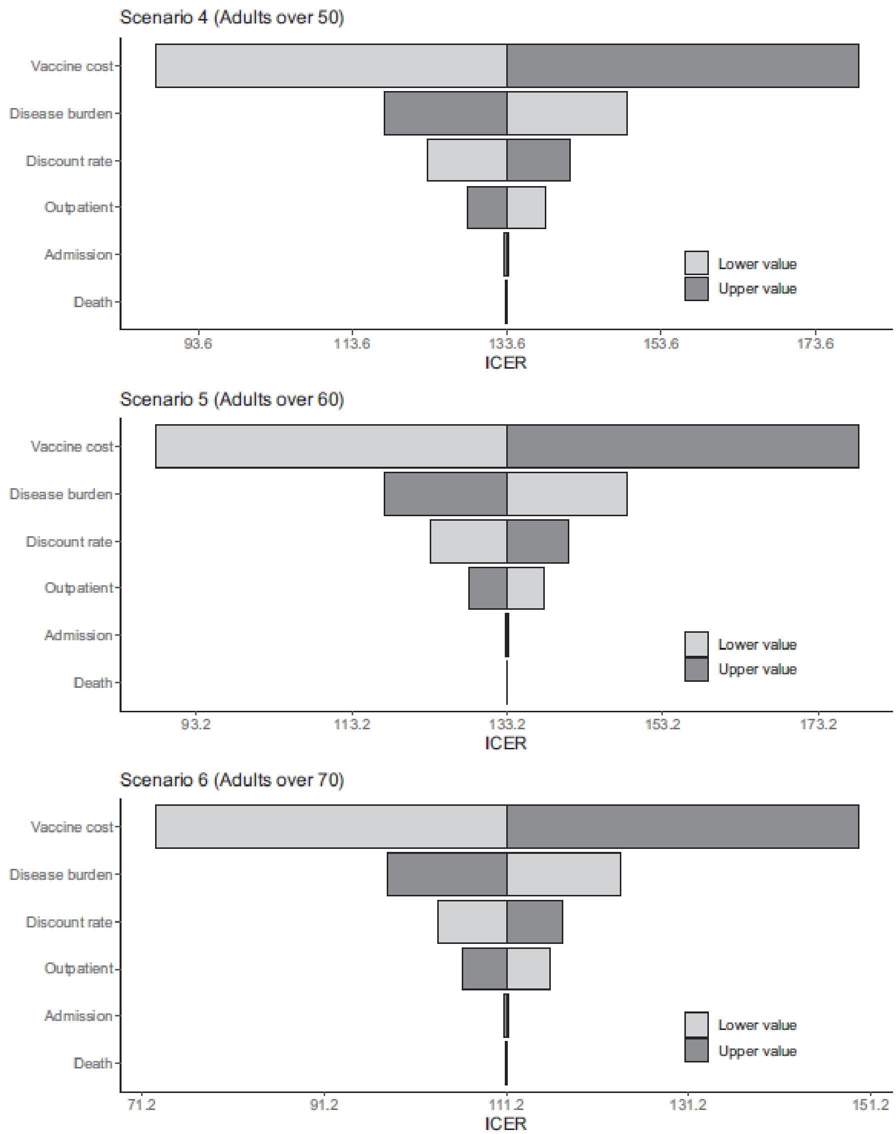


Fig 5-3-A. 3 years' mean of ICER for each scenario.

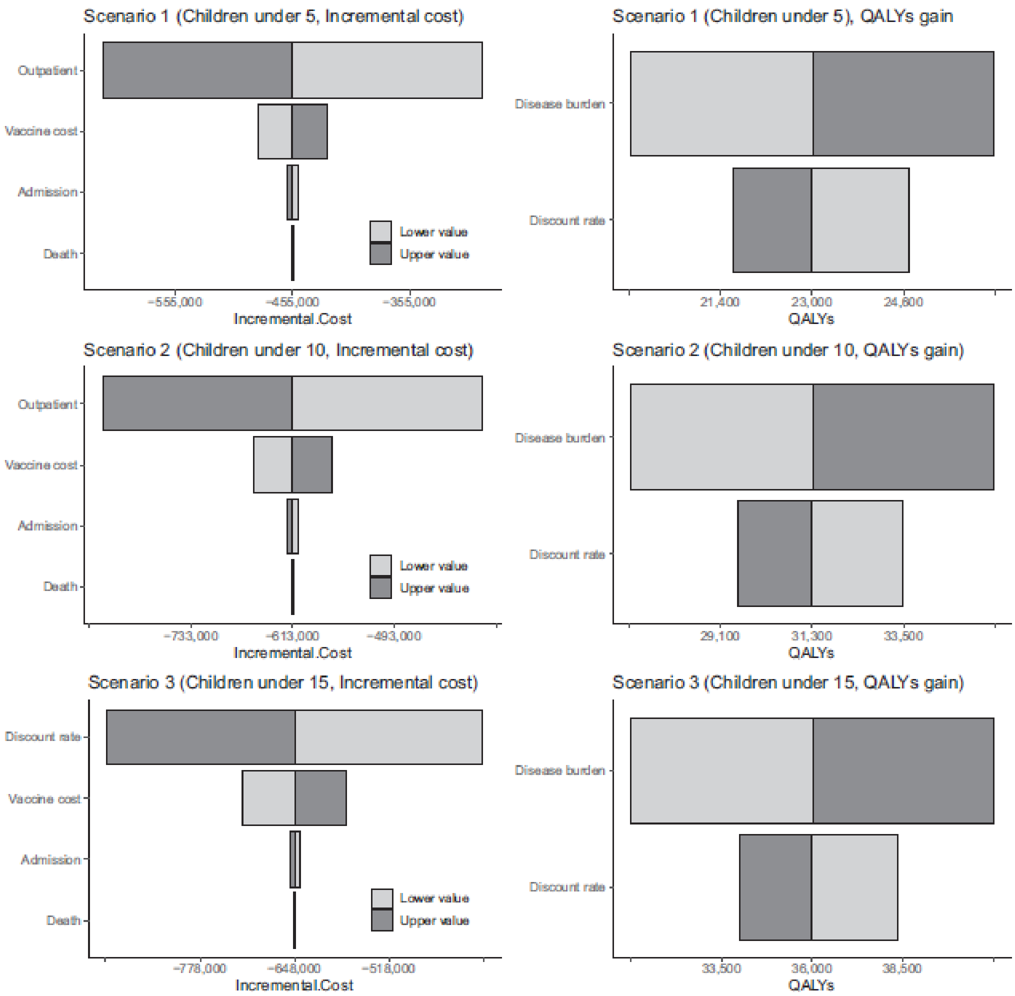


Fig 5-3-B. Tornado diagram of univariate sensitivity analysis in each scenario.

ICER: Incremental cost-effectiveness ratio; QALYs: Quality adjusted life years

USD: United States dollar

Sensitivity analysis with different vaccine efficacy

Even under the lower vaccine efficacy (15% for children and young adults, and 18% for elderly), the children targeted scenarios were dominant. The adult targeted scenarios were sometimes cost-effective (showed ICER value lower than 50,000 USD/QALY). The details of results are shown in Table 5-6.

Table 5-6. Sensitivity analysis for incremental cost, QALYs gain, and ICER in different vaccination efficacy (thousand USD)

Year	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6
Incremental cost						
2012	-566,906 (-584,143, -558,398)	-638,828 (-657,657, -630,775)	-684,682 (-706,142, -676,820)	180,111 (170,882, 198,256)	155,313 (145,360, 173,875)	15,188 (9,357, 24,986)
2013	-629,952 (-642,198, -603,954)	-813,653 (-848,622, -807,558)	-901,979 (-948,111, -895,885)	226,898 (220,336, 253,084)	184,907 (178,884, 203,403)	48,407 (46,383, 54,539)
2014	-165,556 (-177,294, -157,573)	-214,289 (-229,749, -204,743)	-250,493 (-270,314, -238,207)	297,747 (295,934, 299,544)	239,765 (238,092 240,600)	54,674 (53,918, 55,232)
Mean	-454,139 (-459,184, -448,296)	-555,276 (-577,452, -550,455)	-611,815 (-641,207, -606,074)	234,777 (230,348, 249,232)	192,497 (189,423, 205,082)	39,122 (37,315, 44,479)
QALYs gain						
2012	27,021 (26,628, 27,796)	30,721 (30,327, 31,569)	34,391 (34,019, 35,389)	12,174 (11,347, 12,569)	7,459 (6,567, 7,920)	3,779 (3,298, 4,078)
2013	28,166 (27,115, 28,703)	36,003 (35,730, 37,489)	41,079 (40,781, 42,897)	9,140 (7,819, 9,474)	5,311 (4,359, 5,626)	1,596 (1,270, 1,707)
2014	9,522 (9,146, 10,121)	12,074 (11,633, 12,850)	15,157 (14,596, 16,135)	5,478 (5,375, 5,584)	2,377 (2,320, 2,468)	1,388 (1,351, 1,430)

Mean	21,578 (21,318, 21,873)	26,247 (26,040, 27,222)	30,175 (29,928, 31,449)	8,938 (8,249, 9,135)	5,088 (4,467, 5,233)	2,269 (2,001, 2,364)
ICER						
2012	NA	NA	NA	14.8 (13.6, 17.5)	20.8 (18.4, 26.5)	4.0 (2.3, 7.6)
2013	NA	NA	NA	24.8 (23.3, 32.4)	34.8 (31.8, 46.7)	30.3 (27.2, 42.9)
2014	NA	NA	NA	54.4 (53.0, 55.7)	100.9 (96.5, 103.7)	39.4 (37.7, 40.9)
Mean	NA	NA	NA	26.3 (25.2, 30.2)	37.8 (36.2, 45.9)	17.2 (15.8, 22.2)

ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

USD: United States dollar; NA: not applicable

We also conducted probabilistic sensitivity analysis with 2,000 sets of parameter values drawn randomly according to each parameter's range and distribution. Scenario 1, 2, and 3 were cost-saving and dominant in all of these 2,000 simulations. Scenario 4, 5, and 6 are sometimes cost-effective and other times less cost-effective than the current coverage. Figure 5-4 shows the scatter plots of PSA results.

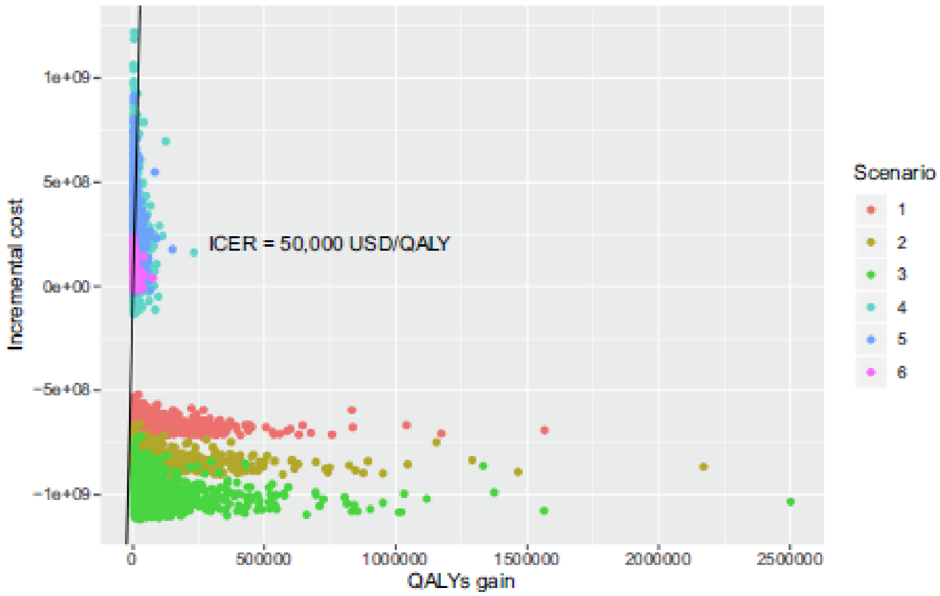


Fig 5-4. Scatter plot of probabilistic sensitivity analysis results.

ICER: Incremental cost-effectiveness ratio; QALY: Quality adjusted life year

USD: United States dollar

5.4 Discussion

Our model showed that vaccination programmes which target children were more effective and they might be dominant against the current vaccination coverage. Other vaccination programmes which target children (under 5, under 10) would also be more effective than the current coverage. On the other hand, programmes which target elderly people seem to be less effective than the current coverage. These results suggest that our effort to increase vaccination coverage among children might be beneficial. Univariable and probabilistic sensitivity analyses also support the presented results.

Sensitivity analysis for different vaccine efficacy estimates suggested that vaccination programmes which target children are more effective even under low vaccine efficacy. The results also suggested that programmes which target elderly might be cost-effective under the assumption of higher vaccine efficacy than that of younger age groups, nevertheless, the superiority of programmes which target children never changed.

As mentioned earlier, the current coverage achieved by the present vaccination policy of seasonal influenza in Japan targets elderly people who are 65 or older years of age, or at high risk of severe influenza infection due to their underlying conditions or illnesses [162]. It aims to prevent disease burden of influenza in those at higher risk following infection [163], rather than aiming for building additional herd immunity. In this sense, the result of the present study suggests reasonable alternatives for future vaccination strategies.

In a historical context, Japanese vaccination policy has experienced a significant recession since Japanese government lost a lawsuit around the adverse effects of the measles, mumps and rubella (MMR) vaccine [137,138]. The MMR vaccine was withdrawn from the market in fear of aseptic meningitis in 1993 based on the government's decision. After that, only 4 out of 20 types of vaccine approved in the UK were approved in Japan until March 2012 [164].

With regard to seasonal influenza vaccine, this serious recession had great impact on political decision making. In 1980s, Japanese Immunization Act demanded compulsory vaccination. However, after MMR vaccine withdrawal, Japanese government also withdrew their recommendation about seasonal influenza vaccines. As a result, vaccination coverage of seasonal influenza declined from about 90% to almost zero, at least transiently [30]. It was already reported that this sudden decline of vaccine coverage brought an increase in excess mortality due to influenza [165,166].

Nevertheless, the Japanese "vaccine gap" has been shrinking through recent decades and various vaccines (i.e. pneumococcal conjugated vaccine) were approved and an immunization programme of seasonal influenza was also re-implemented [167,168]. It can thus be regarded as an appropriate time to re-consider another, more efficient vaccination policy.

The absence of quantitative assessment of vaccination policy in Japan also has had impact on the delayed approval of novel vaccines and modification of vaccination strategies [137,138,168]. There are only a few economic analyses studying seasonal influenza vaccine [159,169] in Japan, but these studies were based on static epidemiological models, therefore dynamics of herd immunity effect might be underestimated. Considering these results, it can be said that our results might offer reasonable evidence for examining the new vaccination strategy based on the latest epidemiological findings.

As stated above, the present study might offer novel and promising findings for decision making of Japanese vaccination policy. However, we should be careful when we interpret the results because they include several limitations.

First, we have to be aware that Japanese epidemiological data were not completely sufficient to evaluate seasonal influenza epidemiology precisely. The most important difference between the UK data and Japanese data was that Japan has no syndromic surveillance data. Notably Japanese sentinel surveillance does not provide the data about the total monitored population under the sentinel surveillance system and these surveillance data are not stratified by age group. Consequently, there might be discrepancy between the actual number of patients and the estimated number of patients to some extent.

Virological data also have limitations. We have no data about the total number of specimens examined in public health institutes and could not know how frequently these specimens contain other respiratory viruses. Furthermore, virological data are not stratified by age group. Due to these limitations, we could just "infer" the proportion of each four strains (A/H1N1, A/H3N2, B/Victoria, and B/Yamagata).

Additionally, vaccination coverage might be biased because Japanese national surveillance about vaccination coverage was based on answers from voluntary people. It is conceivable that voluntary respondents do not represent the general population of Japan and have some preference for taking vaccination.

Japanese original vaccine coverage was comparatively higher than European countries [157,170–172].

Second, the results of the cost-effectiveness analyses also contain some uncertainties. Because we have no data about the proportion of the high-risk population, we assumed the proportion of high-risk population based on a foreign study. Nevertheless, it is worth considering that number of severe outcome (admission and death) due to influenza has comparatively smaller impact on CEA results than the disease burden generated by outpatient cases. Therefore, the proportion of high-risk population might have little influence on the total effectiveness of vaccination programme.

Third, we conducted CEA only from public health care payer's perspective. However, previous studies suggest that considerable part of the disease burden of seasonal influenza can be attributed to societal productivity loss [92,96]. Nevertheless, the present study demonstrated that achieving high vaccination coverage might be cost-effective even from public health care payer's perspective.

Last, we should take note that we focused on only three epidemiological years from 2012/13 season to 2014/15 season. However, it might not be sufficient to estimate the true burden of influenza epidemic due to high variability of seasonal influenza [173,174].

5.5 Conclusion

The present study suggested that vaccination programmes which target children are predicted to have larger epidemiological impact than those targeting elderly populations and the current coverage, both in view of incidence reduction and cost-effectiveness, then children can be regarded as an appropriate target population for seasonal influenza vaccination in Japan.

Although constructing more appropriate mathematical model with better epidemiological data and more detailed cost-effectiveness analysis would be our future challenges, our results might offer another acceptable choice of vaccination policy to Japan.

6. Chapter 4: Indirect burden of COVID-19 on our society

This chapter is based on published work: "Tsuzuki S, Ohmagari N and Beutels P (2022). The burden of isolation to the individual: a comparison between isolation for COVID-19 and for other influenza-like illnesses in Japan. Epidemiology and Infection 2022 Vol. 150", doi: 10.1017/S0950268821002569 [175].

Summary

At present, there is scarce evidence about the burden associated with isolation of COVID-19 patients. We aimed to assess the differences between COVID-19 and other influenza like illnesses in disease burden brought by isolation. We conducted an online survey of 302 respondents who had COVID-19 or other influenza-like illnesses (ILIs) and compared the burden of isolation due to sickness with one-to-one propensity score matching. The primary outcomes are the duration and productivity losses associated with isolation, and the secondary outcome is the Health-Related Quality of Life (HRQoL) valuation on the day of the survey. Acute symptoms of outpatient COVID-19 and other ILIs lasted 17 (interquartile range [IQR] 9-32) and 7 (IQR 4-10) days, respectively. The length of isolation due to COVID-19 was 18 (IQR 10-33) days and that due to other ILIs was 7 (IQR 4-11) days, respectively. The monetary productivity loss of isolation due to COVID-19 was 1424.3 (IQR 825.6-2545.5) USD and that due to other ILIs was 606.1 (IQR 297.0-1090.9) USD, respectively. HRQoL at the time of the survey was lower in the COVID-19 group than in the "other ILIs" group (0.89 and 0.96, $p = 0.001$). COVID-19 infection imposes a substantial disease burden, even in patients with non-severe disease. This burden is larger for COVID-19 than other ILIs, mainly because the required isolation period is longer.

6.1 Background

Coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus, has become a global health threat [47,48,176]. More than half a year after the roll-out of highly effective vaccines against COVID-19, the pandemic remains difficult to control [177].

COVID-19 can be regarded as one of the influenza-like illnesses (ILIs) because it causes upper respiratory symptoms like seasonal influenza and its severity is mild in most cases [178–180]. However, there are several distinctive characteristics which differentiate COVID-19 from other ILIs.

First, COVID-19 is more likely to result in severe illness and death than other ILIs do. Previous studies suggested that the infection-fatality rate of COVID-19 was about ten times higher than that of seasonal influenza [178,181]. Although patients may recover with only mild symptoms, COVID-19 infection should be another important cause of excess mortality [50].

Second, the transmission dynamics of COVID-19 is quite different from other ILIs, in that pre- and asymptomatic transmission is more common than for other ILIs [182–184]. Additionally, both incubation period and infectious period of COVID-19 were regarded as longer than those of other ILIs [185,186]. These facts suggest that COVID-19 required a longer duration of isolation as a countermeasure in order to slow down its spread.

Presumably, we need to strengthen our isolation policy in order to prevent further spreading of COVID-19 due to the reasons mentioned above. However, at the same time, we have to consider the societal burden of such interventions including productivity loss because its appropriate duration should be determined by a kind of trade-off between disease prevention effect and societal loss.

At the early stage of the pandemic, the Japanese government determined the duration of isolation for COVID-19 patients as two weeks [187], following the recommendation published by World Health Organization (WHO), Centers for Disease Control and Prevention (CDC) and other organizations [188–190]. This recommendation was updated to “10 days after symptom onset, plus at least 3 additional days without symptoms” in June 2020 [187], based on the updated recommendation published by WHO and other organizations [188–190].

However, these recommendations were defined based on clinical insights. It would be relevant to try and define the duration of isolation with clinical, economic and societal aspects taken into consideration because such long duration of isolation may present a substantial burden for the patients.

At present, there is scarce evidence about the socio-economic burden imposed by isolation of COVID-19 patients. The few previous studies examining the burden caused by isolation, focused on narrow psychological impact [191–193]. The main objective of the present study is to estimate its burden in a way that it might inform health economic evaluation and policy making from a societal perspective.

6.2 Methods

Settings

We conducted an online questionnaire survey recruiting people who had been diagnosed with COVID-19 or other influenza-like illnesses (ILIs) at any time between 1st October 2019 and 28th February 2021 in Japan. Most of the 302 respondents had already recovered but 12 participants had symptoms at the time of the survey. The participants were voluntarily and randomly recruited from registrants of NEO MARKETING INC, a Japanese marketing research company. The participants were asked to provide information on the latest episode of isolation due to having ILIs during the study period and stratified them into (a) COVID-19 group and (b) other ILIs group. We defined ILIs as these diseases diagnosed by physicians: COVID-19, seasonal influenza, adenovirus infection, respiratory syncytial virus (RSV) infection, hand, foot and mouth disease, pertussis, and other common colds. We did not use the definition of ILI [88] because asymptomatic infection is common in COVID-19 and other ILIs, in which case not symptoms, but diagnoses provide the rationale for isolation. The respondents had to be at least 20 years old, the legal age for adulthood in Japan at the time of the study. Informed consent was given before the start of the survey.

Statistical analysis

We collected data on sex, age, number of household members, education level, household and individual income per month, duration of symptoms and isolation, and Health-Related Quality of Life (HRQoL) at the time of questionnaire survey. As for HRQoL, we used the 15-D questionnaire [19] to estimate HRQoL value at the time the survey was conducted. The questionnaire assesses the 15 dimensions of HRQoL by each of 15 questions (Mobility, Vision, Hearing, Breathing, Sleeping, Eating, Speech, Excretion, Usual activities, Mental function, Discomfort and symptoms, Depression, Distress, Vitality, and Sexual activity). We can obtain HRQoL value between 0 and 1 as the sum of the scores of 15 dimensions. Categorical variables were presented as absolute number and percentage, continuous variables as median and interquartile range (IQR).

We compared the COVID-19 group with the "other ILIs" group by the matched data using one-to-one, nearest neighbour propensity score matching (caliper = 0.2) [193]. Age, sex, education level and presence of underlying medical conditions were adjusted. The primary outcome is duration and productivity loss of isolation evaluated as monetary value; the secondary outcome is HRQoL value. We compared the outcomes (not normally distributed) between two groups using Mann-Whitney U test. Monetary value of productivity loss was calculated by multiplication of duration (days) and wage of each participant (per day equivalent). We transformed Japanese Yen (JPY) to USD as 110 JPY = 1 USD, according to the exchange rate in 2021. The

HRQoL values were compared after excluding participants who presented any symptoms at the time of the survey.

Two-sided p values of < 0.05 were considered to show statistical significance. All analyses were conducted in the R environment, version 4.0.5 [91].

Ethics approval

This study was approved by the Ethics Committee of National Center for Global Health and Medicine (NCGM-G-004001-01). Written informed consent was obtained from each participant before starting the survey through an electronic form and the ethical review board approved this form of consent.

6.3 Results

Table 6-1 shows the demographic characteristics of participants. Of the 302 respondents, 138 were classified into COVID-19 group and 164 were other ILIs group. The basic characteristics of two groups were similar (Table 6-1). The median duration of symptoms (from the onset to the end of symptom presentation) and isolation (from the onset until the end of the isolation period) for the other ILIs group were 7 days each, while those for the COVID-19 group were 15.5 and 17.0 days.

Table 1. Demographic characteristics of the participants

	COVID-19 group	Other ILIs group
Number of participants	138	164
Male	97 (70.3)	110 (67.1)
Age (median [IQR])	45.5 [37.0, 55.0]	46.0 [36.0, 56.0]
Number of household members		
1	33 (23.9)	35 (21.3)
2	23 (16.7)	29 (17.7)
3	35 (25.4)	49 (29.9)
> 4	47 (34.1)	51 (31.1)
Diagnosis		
COVID-19	138 (100.0)	0 (0.0)
Seasonal influenza	0 (0.0)	122 (74.4)
RSV infection	0 (0.0)	1 (0.6)
Hand, foot, mouth disease	0 (0.0)	1 (0.6)
Pertussis	0 (0.0)	1 (0.6)
Common cold	0 (0.0)	39 (23.8)
Comorbidities		
Asthma	37 (26.8)	30 (18.3)
Allergic rhinorrhea	46 (33.3)	45 (27.4)
Atopic dermatitis	25 (18.1)	20 (12.2)
Neurological disorder	11 (8.0)	3 (1.8)
Respiratory diseases	16 (11.6)	5 (3.0)
Cardiovascular diseases	17 (12.3)	7 (4.3)
Diabetes mellitus	23 (16.7)	8 (4.9)
Renal diseases	16 (11.6)	7 (4.3)
Liver diseases	10 (7.2)	8 (4.9)
Metabolic diseases	13 (9.4)	2 (1.2)
Immunodeficiency	14 (10.1)	4 (2.4)
Pregnancy	4 (2.9)	0 (0.0)
No comorbidities	58 (42.0)	72 (43.9)
Place of isolation		

Home	86 (62.3)	157 (95.7)
Hotel	51 (37.0)	12 (7.3)
Hospital	51 (37.0)	7 (4.3)
Duration of work restriction	14 [10, 23]	5 [4, 10]
Monthly wage (USD)	2272.7 [1818.2, 4545.5]	2272.7 [1363.6, 3636.4]
Proportion of wage covered during isolation	80.0 [50.0, 100.0]	95.0 [50.0, 100.0]
Education level		
Secondary school	0 (0.0)	3 (1.8)
High school	22 (15.9)	42 (25.6)
Vocational school	29 (21.0)	15 (9.2)
University	71 (51.4)	91 (55.5)
Graduate school	16 (11.6)	13 (7.9)
Ongoing symptoms	11 (8.0)	1 (0.6)

ILI; influenza-like illness, RSV; respiratory syncytial virus, USD; United States Dollar (110 Japanese Yen = 1 USD)

Numbers with brackets represent absolute number and percentage

Numbers with square brackets represent median value and interquartile range

Table 6-2 describes the details of data after propensity score matching. Standardized mean difference (SMD) larger than 0.1 was regarded as significant imbalance.

Table 6-2. Demographic characteristics of data after propensity score matching

	COVID-19 group	Other ILIs group	SMD
Number of participants	128	128	

Male	92 (71.9)	89 (69.5)	0.052
Age (median [IQR])	44.0 [37.0, 54.0]	46.0 [36.0, 55.0]	0.019
Diagnosis			
COVID-19	128 (100.0)	0 (0.0)	
Seasonal influenza	0 (0.0)	94 (73.4)	
RSV infection	0 (0.0)	1 (0.8)	
Hand, foot, mouth disease	0 (0.0)	1 (0.8)	
Pertussis	0 (0.0)	1 (0.8)	
Common cold	0 (0.0)	31 (24.2)	
Comorbidities			0.016
Asthma	36 (28.1)	24 (18.3)	
Allergic rhinorrhea	44 (34.4)	38 (29.7)	
Atopic dermatitis	25 (19.5)	15 (11.7)	
Neurological disorder	2 (1.6)	11 (8.6)	
Respiratory diseases	15 (11.7)	3 (2.3)	
Cardiovascular diseases	13 (10.2)	4 (3.1)	
Diabetes mellitus	22 (17.2)	5 (3.9)	
Renal diseases	15 (11.7)	4 (3.1)	
Liver diseases	9 (7.0)	6 (4.7)	
Metabolic diseases	12 (9.4)	2 (1.6)	
Immunodeficiency	13 (10.2)	2 (1.6)	
Pregnancy	3 (2.3)	0 (0.0)	
No comorbidities	53 (41.4)	55 (43.0)	
Place of isolation			
Home	79 (61.7)	123 (96.1)	
Hotel	48 (37.5)	11 (8.6)	
Hospital	47 (36.7)	74(3.1)	
Education level			0.019
Secondary school	0 (0.0)	0 (0.0)	
High school	27 (21.1)	21 (16.4)	
Vocational school	27 (21.1)	12 (9.4)	

University	66 (51.6)	80 (62.5)
Graduate school	14 (10.9)	9 (7.0)

ILI; influenza-like illness, SMD; standardized mean difference, RSV; respiratory syncytial virus, USD; United States Dollar (110 Japanese Yen = 1 USD)

Numbers with brackets represent absolute number and percentage

Numbers with square brackets represent median value and interquartile range

Table 6-3 shows the outcome comparison between the COVID-19 group and the "other ILIs" group. The COVID-19 group showed longer median duration of symptoms (18 days versus 7 days) and isolation (16 days versus 7 days). Productivity loss of isolation due to COVID-19 was greater than that due to other ILIs (1424.3 USD versus 606.1 USD). The HRQoL value of the COVID-19 group was lower than that of the other ILIs group (0.89 versus 0.96).

Table 6-3. Comparison of outcomes between two groups

	COVID-19 group	**Other ILIs group**	***p* value***
Duration of symptoms	17 [9, 32]	7 [4, 10]	< 0.001
	18 [10, 33]	7 [4, 11]	< 0.001
Duration of isolation	15.5 [11, 25]	7 [5, 12]	< 0.001
	16 [11, 25]	7 [5, 12]	< 0.001
Productivity loss due to isolation (USD)	1393.9 [742.4, 2575.8]	540.9 [289.4, 1075.8]	< 0.001
	1424.3 [825.6, 2545.5]	606.1 [297.0, 1090.9]	< 0.001
Health-Related Quality of Life	0.89 [0.73, 0.97]	0.95 [0.84, 0.99]	0.003
	0.89 [0.72, 0.97]	0.96 [0.86, 0.99]	0.001

ILI; influenza-like illness, USD; United States Dollar

*Results of Mann-Whitney U test

Numbers with square brackets represent median value and interquartile range

Numbers in upper rows represent the results before matching

Numbers in lower rows represent the results after matching

Table 6-4 shows the difference in each dimension of HRQoL in 15-D questionnaire. While most of 15 dimensions were lower in the COVID-19 group, Vision, Depression, Distress and Vitality were not substantially different.

Table 6-4. Difference in each dimension of Health-Related Quality of Life between two groups by matched data

	COVID-19 group	Other ILIs group	*p* value*
Mobility	0.07 [0.04, 0.07]	0.07 [0.04, 0.07]	0.009
Vision	0.05 [0.05, 0.05]	0.05 [0.05, 0.05]	0.146
Hearing	0.06 [0.05, 0.06]	0.06 [0.65, 0.06]	0.004
Breathing	0.07 [0.06, 0.08]	0.08 [0.06, 0.08]	< 0.001
Sleeping	0.06 [0.06, 0.07]	0.06 [0.06, 0.07]	0.016
Eating	0.07 [0.04, 0.07]	0.07 [0.07, 0.07]	0.005
Speech	0.07 [0.05, 0.07]	0.07 [0.07, 0.07]	< 0.001
Excretion	0.06 [0.04, 0.06]	0.06 [0.06, 0.06]	0.001
Usual activities	0.08 [0.05, 0.08]	0.08 [0.08, 0.08]	< 0.001
Mental function	0.09 [0.04, 0.09]	0.09 [0.09, 0.09]	0.001
Discomfort and symptoms	0.04 [0.04, 0.06]	0.06 [0.04, 0.06]	0.002
Depression	0.05 [0.05, 0.05]	0.05 [0.05, 0.05]	0.289

Distress	0.05 [0.03, 0.06]	0.05 [0.05, 0.06]	0.468
Vitality	0.06 [0.04, 0.08]	0.06 [0.06, 0.08]	0.169
Sexual activity	0.89 [0.72, 0.97]	0.96 [0.86, 0.99]	0.009

*Results of Mann-Whitney U test

Figure 6-1 shows the probability density curve of duration of symptoms and isolation, productivity loss, and Quality of Life at the day of questionnaire survey.

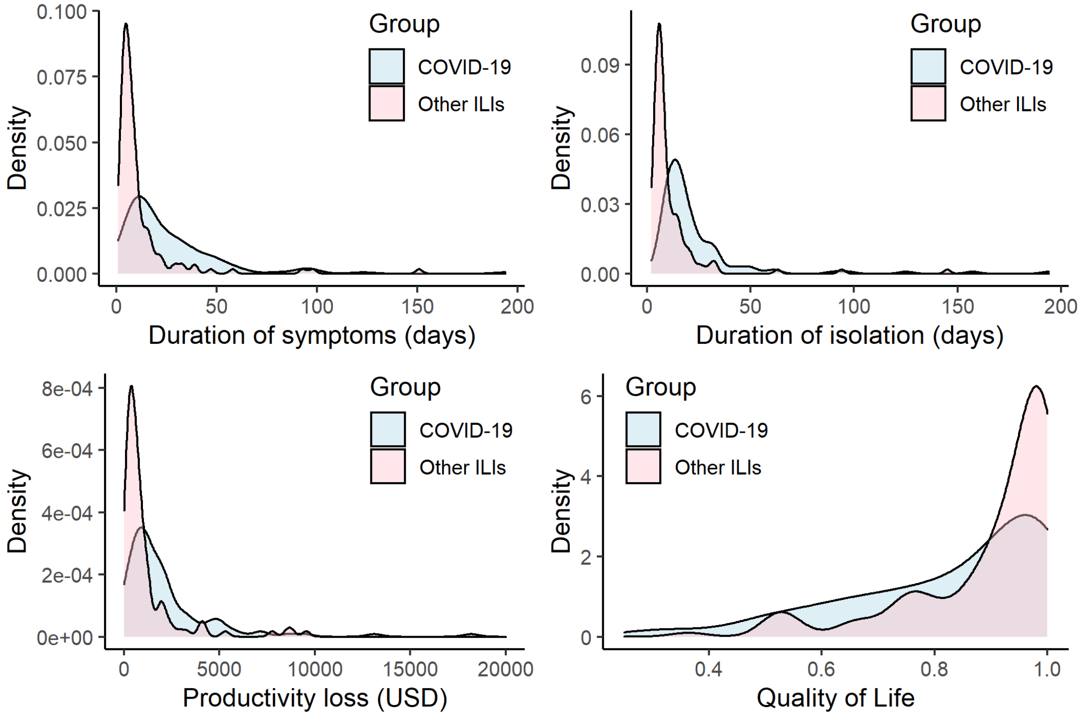


Figure 1. Probability density curve of duration of symptoms and isolation, productivity loss and Quality of life

Top left panel shows duration of symptoms. Top right panel shows duration of isolation. Bottom left panel shows productivity loss. Bottom right panel shows Health-Related Quality of Life.

ILI; influenza-like illness, HRQoL; Health-Related Quality of Life

Red area represents COVID-19 group and blue area represents other ILIs group.

6.4 Discussion

We showed the difference between COVID-19 and other ILIs in relation to the individual HRQoL, economic impact and duration of isolation. As expected, COVID-19 imposes a heavier burden on society than other ILIs do in various aspects. To our knowledge, there are no previous studies which compare the economic impact and duration of isolation between persons infected by SARS-CoV-2 and by other ILIs.

First, the longer duration of isolation comes with greater absenteeism from work. It is noteworthy that the median duration of isolation (16 days by the data after propensity score matching) was longer than 14 days. As described above, its duration in Japan was initially determined as 14 days at the early stage of the pandemic and reduced to 10 days later by Ministry of Health, Labour and Welfare (MHLW) [187]. The Japanese government also adopted the additional isolation time defined by WHO [188], i.e., “plus at least 3 additional days without symptoms (including without fever and without respiratory symptoms)”. This means that longer duration of symptoms will consequently result in longer duration of isolation.

In the “other ILIs” group (excluding COVID-19), the most frequent diagnosis was seasonal influenza (74.4%). The large proportion of seasonal influenza in this group was probably due to the isolation policy specific to Japan [67]. The responsibility for defining the duration of isolation for school children infected with seasonal influenza, lies with the Ministry of Education, Culture, Sport, Science and Technology, and not the MHLW. This is based on the School Health and Safety Act [98]. This law defines a five-day isolation period for seasonal influenza with the day of symptom onset as day 0. It is the main cause of the comparatively long isolation period for seasonal influenza in Japan [67]. Therefore, the burden caused by isolation due to seasonal influenza in Japan seems heavier than that in other countries, nevertheless, that caused by COVID-19 imposes a heavier burden than other ILIs.

As a result of this longer duration of isolation, the productivity losses should become larger in the COVID-19 group than in the other ILIs group. In addition, our results showed the economic loss from the patients’ perspective and as such it represents an underestimate of the societal economic burden. From the societal perspective, productivity losses, arising to employers and other third parties may exceed the sum of individual employee losses, if many employees are simultaneously isolated. Furthermore, in contrast to other ILIs, COVID-19 patients were often isolated in a designated hotel and not at home, especially when the patients have no risk factors of severe diseases and their cohabitants also have no apparent risk factors

[187]. Their accommodation fee and professional healthcare personnel costs are covered by the government and these costs should be included in the total costs from a societal perspective. Such cost data were not available and therefore not included here. Additionally, an infection in any household, even if it is a single member of the household, often consigned the whole household to isolation especially if they could not provide additional accommodation to isolate the infected person. Therefore, the number of jointly isolated household members is another important factor to consider when estimating costs.

In short, our results suggest that the longer duration of the isolation period associated with COVID-19 imposed a greater burden than that associated with other ILIs, and it might be even underestimated. The optimal duration of the isolation period for epidemic control should ideally be considered jointly with the socioeconomic consequences of isolation.

Also, after adjusting for the participants' background, there were significant differences in HRQOL value at the day of the survey between the COVID-19 group and the "other ILIs" group (0.89 and 0.96, respectively). This result might suggest that, even if patients were not aware of it, COVID-19 had long-term effect on their psychosocial health status. Although most of the COVID-19 group feel that they have already recovered and have no symptoms, actually they showed lower value of HRQoL on most dimensions of the 15-D questionnaire (Table 4). For instance, these results suggest that some participants of the COVID-19 group had more difficulty with breathing and mental functioning.

Although so-called “long COVID syndrome” or “post COVID syndrome” is not conclusively defined in previous studies [194,195], it covers important clinical manifestations that are specific to COVID-19, as compared with other ILIs. Therefore, it increases the additional burden on society. In our survey, more than a half of participants who had COVID-19 infection indicated that their symptom(s) lasts more than four weeks. Conversely, only 7.9% in the other ILIs group reported a duration of symptoms longer than four weeks. The proportion of patients who reported “long COVID syndrome” in previous studies varies, including between another study in Japan [196] and a review of previous studies in other countries [197]. Although our study was not designed to study long-COVID specifically, our estimate is not substantially different from these previous findings [196–198]. Considering this, even after its acute phase, COVID-19 may continue to have a negative impact on HRQoL and productivity, more frequently and longer than other ILIs.

Our study includes several limitations. First, our data were based on an online survey, and therefore requires participants to have basic internet literacy. That is, participants of our survey might have more interest in their health status and better basic computational skills than the general Japanese population. However, this form of survey was preferred because in the case of COVID-19, minimising contact between the interviewers and the patients is important to contribute to breaking transmission chains.

Second, as already discussed in this section, productivity loss was evaluated only from the participants' viewpoint, and insufficient data are available to inform the broader societal perspective (accommodation fee, healthcare professional personnel, etc.). Third, HRQoL was assessed at the day of the survey and not assessed at different time points over the periods of symptomatic disease and isolation. Note that the 15-D questionnaire does not include a recall period. More elaborate quantitative evaluation of productivity losses and health-related HRQoL remains a subject for future research.

6.5 Conclusion

Our results showed that COVID-19 imposes a heavier burden in Japan than other ILIs do, not only due to its symptoms but also due to the productivity losses during the longer period of isolation. These findings are preliminary, but could be useful to inform future research and healthcare policy makers to determine the optimal duration of isolation. The health and economic impact of epidemic mitigation through isolation could then be estimated, considering not only the benefits in terms of mitigating the epidemic spread, but also the costs of lost productivity. The challenge will be to identify the economic optimum for society, where the marginal benefits equal the marginal costs of isolating an average infected person for an extra day.

7. Chapter 5: Disease burden caused by long-COVID

This chapter is based on published work: "Tsuzuki S, Miyazato Y, Terada M, Morioka S, Ohmagari N and Beutels P (2022). Impact of long-COVID on health-related quality of life in Japanese COVID-19 patients. Health and Quality of Life Outcomes 2022 Vol. 20 Issue 1", doi: 10.1186/s12955-022-02033-6 [199].

Summary

The empirical basis for a quantitative assessment of the disease burden imposed by long-COVID is currently scant. We aimed to assess the disease burden caused by long-COVID in Japan. We conducted a cross sectional self-report questionnaire survey. The questionnaire was mailed to 526 eligible patients, who were recovered from acute COVID-19 in April 2021. Answers were classified into two groups; participants who have no symptom and those who have any ongoing prolonged symptoms that lasted longer than four weeks at the time of the survey. We estimated the average treatment effect (ATE) of ongoing prolonged symptoms on the EuroQol's Visual Analogue Scale (EQ-VAS) and EQ-5D-3L questionnaire using inverse probability weighting. In addition to symptom prolongation, we investigated whether other factors (including demography, lifestyle, and acute severity) were associated with low EQ-VAS and EQ-5D-3L values, by multivariable linear regression. Among all, 349 participants reported no symptoms and 108 reported any symptoms at the time of the survey. The participants who reported any symptoms showed a lower average value on the EQ-VAS (69.9 vs 82.8, respectively) and on the EQ-5D-3L (0.85 vs 0.96, respectively) than those reporting no symptoms considering the ATE of ongoing prolonged symptoms. The ATE of ongoing prolonged symptoms on EQ-VAS was -12.9 [95% CI -15.9 to -9.8], and on the EQ-5D-3L it was -0.11 [95% CI -0.13 to -0.09], implying prolonged symptoms have a negative impact on patients' EQ-VAS and EQ-5D-3L score. In multivariable linear regression, only having prolonged symptoms was associated with lower scores (-

11.7 [95% CI -15.0 to -8.5] for EQ-VAS and -0.10 [95% CI -0.13 to -0.08] for EQ-5D-3L). Due to their long duration, long-COVID symptoms represent a substantial disease burden expressed in impact on health-related quality of life.

7.1 Background

Coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus, has become a global health threat [48,200]. Not only its acute phase of disease, but so-called "long-COVID" is also a cause of substantial disease burden [194,201]. A systematic review reported that 80% of patients developed one or more long-term symptoms and the prevalence of 55 long-term effects of COVID-19 [202].

There is no clear definition of long-COVID so far, however, the National Institute for Health and Care Excellence (NICE) in The UK defined it as "signs and symptoms that develop during or following an infection consistent with covid-19 and which continue for more than four weeks and are not explained by an alternative diagnosis" [203]. This term includes ongoing symptomatic COVID-19, from four to 12 weeks post-infection, and post-COVID-19 syndrome, beyond 12 weeks post-infection [204].

The symptoms of long-COVID are various and often different from the acute phase of COVID-19. Miyazato and colleagues reported that the mean time from COVID-19 symptom onset to the emergence of alopecia was 58.6 days and one of patients presented dysosmia after 92 days after symptom onset [196]. Other symptoms such as general fatigue [205,206], respiratory symptoms [207,208], cognitive and mental health disorder [209,210], and so forth [211,212] have been reported as long-COVID.

Considering its chronic phase, the disease burden of COVID-19 should be larger than that of other respiratory infections due to length and variety of the symptoms. However, the empirical basis for a quantitative assessment of the disease burden imposed by long-COVID is currently scant.

As already mentioned, COVID-19 is one of the greatest global health crises, of an infectious disease that will eventually become endemic, quantitative evaluations of its disease burden are necessary to appropriately assess the impact of interventions. The burden of Long-COVID-19 should be assessed separately from acute COVID-19 because it has clearly distinct characteristics, as part of the disease burden caused by COVID-19.

Malik and colleagues reported a meta-analysis about post-acute COVID-19 syndrome and the health-related quality of life (HRQoL) [213]. However, their results did not include HRQoL between 0 and 1, as single indicator of health utility. Tran and colleagues investigated the validity of impact tools of long-COVID, and they evaluated the impact of long-COVID quantitatively [214], nevertheless, their main interest is not HRQoL itself but to validate their own tool. Although Tabacof and colleagues also assessed the HRQoL of long-COVID patients [215], they focused on rather each component of EQ-5D and had no control group. Fink and colleagues evaluated the correlation between persistent symptoms of pediatric COVID-19 and HRQoL then the target population was different [216].

As described above, the quantitative evaluation of HRQoL for long-COVID adults as a single indicator of health utility which can easily be applied to more comprehensive study such as cost-effectiveness analysis is still scarce. Our study aims to estimate an important part of the disease burden caused by COVID-19, in order to appreciate the potential impact of interventions against it.

7.2 Methods

Settings

We conducted a cross-sectional, retrospective survey in which a self-report questionnaire was mailed in April 2021 with two reminders 2 weeks and 1 month later to eligible participants. Potential participants were recruited from the people who visited the outpatient service of the Disease Control and Prevention Center (DCC) in National Center for Global Health and Medicine (NCGM) between 1st February 2020 and 31st March 2021, in order to obtain pre-donation screening test for COVID-19 convalescent plasmapheresis (Another study named “Collection and antibody measurement of Convalescent plasma foreseeing the use for COVID-19 treatment”). i.e., although the questionnaire survey was conducted in April 2020, all the participants have a documented history of COVID-19 at least eight weeks before they visited the outpatient service. The visitors of the outpatient service were voluntarily recruited and 526 participants were included in the study. Visitors who were younger than 20 years old were excluded from the survey. The minimum time from symptom onset or diagnosis of COVID-19 to the questionnaire survey was 56 days. Participants were requested to complete and return the questionnaire and 457 of 526 (86.9%) participants completely answered the questionnaire and were included in the analysis.

Ethics approval

According to local ethical guidelines, providing responses to the questionnaire was considered as providing participant consent. This study was reviewed and approved by the Ethics Committee of the Center Hospital of the NCGM (NCGM-G-004121-00).

Measures

EQ-5D-3L questionnaire comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression and each dimension has three levels: no problems, some problems, and extreme problems. The subject is asked to answer each question, and the decision results into a score between -0.6 and 1.0, with 0 corresponding to death, and some exceptional health states having negative values, i.e., being considered by the average person as worse than dead.

We collected information about demographics (age, sex, height, weight, smoking, drinking, pregnancy, and past history of diseases), clinical course of the acute phase of COVID-19 infection (day of onset and/or diagnosis, admission status during the acute phase, use of antivirals/systemic steroids, requirement of supplementary oxygen/mechanical ventilation/extracorporeal membrane oxygenation during admission), and symptoms since onset to the questionnaire survey (fever, fatigue, shortness of breath, joint pain, myalgia, chest pain, cough, abdominal pain, dysgeusia, dysosmia, runny nose, red-eye, headache, sputum, sore throat, diarrhoea, nausea, appetite loss, hair loss, depression, loss of concentration, and memory disturbance). All symptoms were recorded based on self-reporting, with their onset date and duration.

We included age, sex, Body Mass Index (BMI), smoking, drinking, hypertension, diabetes, chronic obstructive lung diseases, malignancy, use of antivirals, use of systemic steroids, admission status, and severe COVID-19 disease during admission (use of mechanical ventilation or extracorporeal membrane oxygenation during admission), according to the definition by a report of national registry data in Japan [180]) as confounding factors.

Statistical analysis

The sample size for the linear regression model was calculated by F test [217]. The F test has numerator and denominator degrees of freedom. The numerator degrees of freedom, u, is the number of coefficients (minus the intercept). In our case, $u = 12$ however at the time of calculation, we set $u = 15$. The denominator degrees of freedom, v, is the number of error degrees of freedom:

$$v = n - u - 1$$

This implies

$$n = v + u + 1.$$

The effect size, f^2, is $R^2/(1 - R^2)$, where R^2 is the coefficient of determination, in other words, the "proportion of variance explained". We used $f^2 = 0.15$ which was recommended by Cohen [217]. and set the level of significance at 0.05 and power at 0.80. As a result, we obtained $v = 122.4$ and the required sample size was $122.4 + 15 + 1 \cong 139$.

Two-sided *p* values of <0.05 were considered to show statistical significance. All analyses were conducted by R, version 4.0.5 [91].

Answers were classified into two groups; participants who have no ongoing prolonged symptoms and those who have any ongoing prolonged symptoms. "Ongoing prolonged symptom" was defined as symptoms lasted longer than four weeks from the onset of acute phase of COVID-19 infection (i.e., "long-COVID" condition defined in [203]), and, presented at the time of the survey. We evaluated the average treatment effect of ongoing prolonged symptoms on EuroQol's Visual Analogue Scale (EQ-VAS), which is a measurement instrument that tries to measure the self-reported health status with the range between 0 and 100. and HRQoL values estimated by the EQ-5D-3L questionnaire [218] using the Japanese value set [219].

We used inverse probability weighting (IPW) method with propensity score which was calculated by multivariate logistic regression model predicting the likelihood of having ongoing prolonged symptoms [90,220]. The standardized mean difference and variance ratio were used to measure covariate balance, and an absolute standardized difference above 10% and variance ratio over 2.0 was interpreted as a meaningful imbalance [221].

Additionally, we investigated factors associated with low EQ-VAS and EQ-5D-3L index values other than ongoing prolonged symptoms by linear regression model. Multicollinearity was examined by variance inflation factor (VIF) and VIF ≥ 2.5 as an indicator of multicollinearity [222].

7.3 Results

The left side of Table 7-1 shows the basic characteristics of the participants. 457 participants recovered from acute phase of COVID-19 and 108 of them presented at least one ongoing prolonged symptom(s). The proportion of female was larger in "Any symptom" group than that in "No symptom" group. There was no substantial difference between the two groups in terms of their age, medical history, admission status and days from symptom onset/diagnosis to the survey. About a half of participants once admitted to hospitals due to acute phase COVID-19. Crude comparison of EQ-VAS and EQ-5D-3L index showed that "Any symptom" group had lower EQ-VAS and EQ-5D-3L index than the "No symptom" group did (EQ-VAS: 70

vs 85, EQ-5D-3L index: 0.81 vs 1.0, respectively). The right side of Table 7-1 describes the characteristics of the data after propensity score weighting. 95 of “Any symptom” group and 296 of “No symptom” group were included, and other participants were discarded because of missing items.

Table 7-1. Characteristics of participants before and after propensity score weighting

	All				Propensity score weighted			
	No symptom	**Any symptom**	**SMD**	**Variance ratio**	**No symptom**	**Any symptom**	**SMD**	**Variance ratio**
Number	349	108			296	95		
Age	47 [48, 39-55]	47 [47, 40-54]	0.001	1.207	46.3 [11.0]	46.0 [10.0]	0.028	1.198
Male	188 (53.9)	38 (35.2)	< 0.383	1.083	147.7 (49.9)	47.4 (49.9)	0.003	1.0
BMI	23.7 [23.2, 21.1-25.6]	23.9 [23.4, 20.9-26.9]	0.163	1.646	23.8 [4.1]	23.6 [4.4]	0.037	1.165
Smoking	130 (37.2)	38 (35.5)	0.036	1.014	103 (34.8)	33.4 (35.2)	0.004	1.0
Drinking	290 (83.1)	86 (79.6)	0.089	1.162	246 (83.1)	79.7 (83.9)	0.008	1.0
Hypertension	52 (14.9)	14 (13.0)	0.056	1.117	39.1 (13.2)	12.5 (13.2)	0.0	1.0
Diabetes	23 (6.6)	5 (4.6)	0.085	1.385	16.6 (5.6)	4.9 (5.2)	0.004	1.0
COPD	3 (0.9)	0 (0.0)	< 0.132	NA	0 (0.0)	0 (0.0)	NA	NA
Malignancy	6 (1.7)	0 (0.0)	0.187	NA	3.8 (1.3)	0 (0.0)	0.013	1.0

Days from symptom onset / diagnosis to the survey*	248.9 [249.0, 148.0-357.0]	250.8 [243.0, 150.0-367.0]	0.018	1.125	NA	NA	NA	NA
Inpatient*	195 (56.0)	63 (58.3)	0.046	1.007	NA	NA	NA	NA
Use of antivirals	62 (18.8)	22 (20.8)	0.049	1.085	49.7 (16.8)	16.7 (17.6)	0.007	1.0
Use of steroids	40 (12.8)	13 (13.3)	0.013	1.037	39.4 (13.3)	12.7 (13.4)	0.001	1.0
Severe disease†	7 (2.1)	6 (5.6)	0.183	2.619	7.1 (2.4)	2.2 (2.3)	0.001	1.0
Oxygen support*	44 (12.6)	13 (13.3)	0.027	1.10	NA	NA	NA	NA
EQ-VAS	85 [85, 75-90]	70.4 [70, 60-80]	0.810	**1.412**	82.8 [13.0]	69.9 [17.3]	**0.891**	**1.773**
EQ-5D-3L index	0.98 [1.0, 1.0-1.0]	0.91 [0.81, 0.77-1.0]	0.845	**2.659**	0.96 [0.09]	0.85 [0.16]	**0.914**	**3.190**

Mean [median, interquartile range/standard deviation] for continuous variables, number (%) for categorical variables.

†Use of mechanical ventilation or extracorporeal membrane oxygenation during admission.

SMD: standardized mean difference, BMI: Body Mass Index, COPD: chronic obstructive pulmonary disease, EQ-VAS: EuroQol Visual Analogue Scale,

*Not included in calculating propensity score

Table 7-2 describes the characteristics of prolonged symptoms. We defined "long-COVID" as the status in which any symptoms attributed to SARS-CoV-2 infection last longer than four weeks in our study, regardless of their continued presence at the time the survey was completed. As such, prolonged symptoms in this study indicate "long-COVID" symptoms as defined in [203]. In total 201 of 457 (44.0%) participants reported at least one symptom longer than four weeks after COVID-19 symptom onset. Among these, 73 (16.0%) reported one symptom, 46 (10.1%) two, 47 (10.3%) three, and 35 (7.7%) four or more symptoms. The most common of these prolonged symptoms was general fatigue, which was reported by 58 of 457 (12.7%) participants. The second most common symptom was alopecia, as 55 of 457 (12.0%) participants experienced worse than usual hair loss.

Table 7-2. Details of symptoms lasted longer than four weeks in the participants

	Number	Duration (days)
Fatigue	58 (12.7)	50 [30-60]
Hair loss	55 (12.0)	60 [30-90]
Cough	54 (11.8)	40 [30-60]
Dysosmia	47 (10.3)	45 [30-60]
Dysgeusia	47 (10.3)	35 [30-60]
Shortness of breath	36 (7.9)	42.5 [30-60]
Loss of concentration	34 (7.4)	40 [30-90]
Depression	29 (6.3)	40 [30-60]
Chest pain	18 (3.9)	60 [40-98]
Appetite loss	17 (3.7)	30 [30-60]
Headache	17 (3.7)	44 [30-60]
Memory disturbance	15 (3.3)	60 [30-90]
Sputum	14 (3.1)	43 [30-60]
Fever	11 (2.4)	30 [30-45]

Joint pain	8 (1.8)	48 [30-98]
Myalgia	5 (1.1)	40 [30-60]
Sore throat	5 (1.1)	30 [30-50]
Runny nose	5 (1.1)	30 [30-31]
Red-eye	4 (0.9)	60 [58-75]
Diarrhoea	2 (0.4)	33 [31-34]
Nausea	1 (0.2)	30 [30-30]
Abdominal pain	0 (0.0)	NA

Absolute number (%) for the number of participants, median [interquartile range] for the duration of symptoms.

Figure 7-1 shows the distribution of propensity scores before and after weighting. Figure 7-2 shows the balance of covariates before and after weighting. The balance of covariates in both groups improved after IPW weighting. The two groups differed mainly in terms of gender and BMI, which could give rise to confounding factors when comparing their HRQoL measurements. Figure 7-2 demonstrates that the standardized mean difference in these two factors decreased.

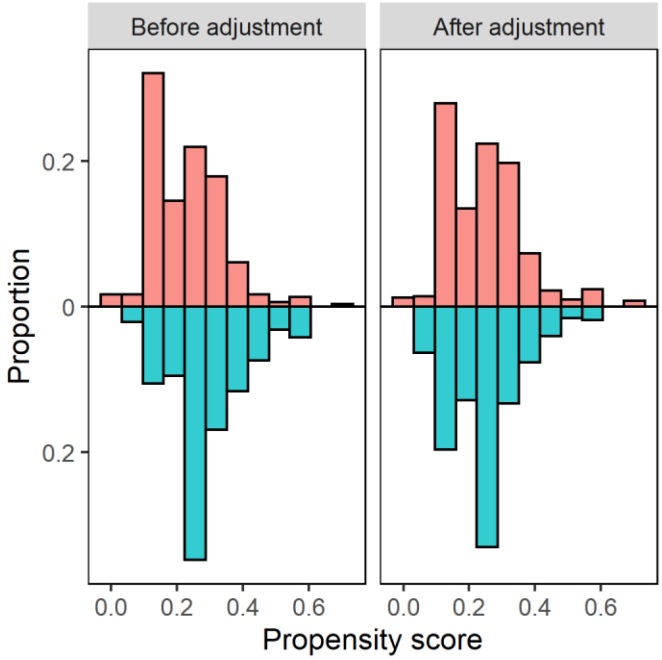


Figure 1. Distribution of propensity score before and after weighting

Red colour represents “No symptom” group and blue colour represents “With symptom” group.

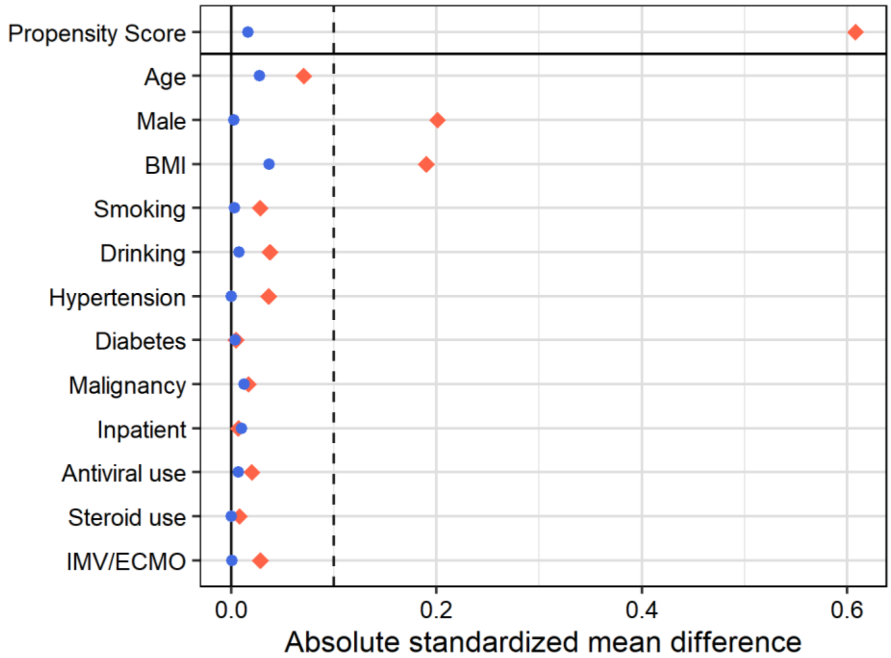


Figure 2. Balance of covariates before and after inverse probability weighting

Red squares represent before adjustment and blue circles represent after adjustment.

Adjusted EQ-VAS and EQ-5D-3L score comparisons were similar to the unadjusted crude comparisons (Table 7-3). The ATE of ongoing prolonged symptoms was -12.9 (95% confidence interval [CI] -15.9 to -9.8) on the EQ-VAS, and -0.11 (95% CI -0.14 to -0.09) on the EQ-5D-3L. The differences attributed to the symptoms were larger than the minimally important difference estimated in a previous study (0.048, 95% CI 0.046 to 0.051) [223]. Therefore, prolonged symptoms can be regarded as having clinically significant negative impact on patients' EQ-VAS and EQ-5D-3L scores.

Table 7-3. Average treatment effect of ongoing prolonged symptoms on EQ-VAS and EQ-5D-3L index

	Intercept	ATE	*P* value
EQ-VAS	82.8 [80.6 to 84.9]	-12.9 [-15.9 to -9.8]	< 0.001
EQ-5D-3L index	0.96 [0.95 to 0.98]	-0.11 [-0.13 to -0.09]	< 0.001

Values are median [95% confidence intervals].

ATE: average treatment effect, EQ-VAS: EuroQol Visual Analogue Scale

Table 7-4 shows the results of linear regression analysis about covariates associated with the EQ-VAS (4-a) and EQ-5D-3L (4-b). Both analyses showed that ongoing prolonged symptoms substantially influence the EQ-VAS and EQ-5D-3L values. Although male sex and steroid use during admission were associated with not lower EQ-VAS scores, no other variable than having ongoing prolonged symptoms was associated with the EQ-5D-3L scores. In both models, all VIF values were below 2.5.

Table 7-4-a. Results of linear regression analysis about EuroQol Visual Analogue Scale value

Variable	Coefficient	95% confidence interval	*P* value
Intercept	85.7	[75.1, 96.4]	**< 0.001**
Ongoing prolonged symptoms	-11.7	[-15.0, -8.5]	**< 0.001**

Age	0.03	[-0.11, 0.17]	0.642
Male	3.2	[0.2, 6.2]	**0.038**
BMI	-0.3	[-0.6, 0.1]	0.125
Smoking	0.2	[-2.8, 3.2]	0.882
Drinking	2.6	[-1.1, 6.2]	0.171
Hypertension	-0.2	[-4.6, 4.2]	0.924
Diabetes	-4.7	[-11.0, 1.6]	0.142
Malignancy	-4.1	[-16.2, 8.0]	0.507
Inpatient	-2.9	[-5.9, 0.2]	0.066
Use of antivirals	-1.3	[-5.7, 3.2]	0.577
Use of steroids	5.3	[0.3, 10.2]	**0.036**
Severe disease†	5.4	[-4.8, 15.6]	0.30

†Use of mechanical ventilation or extracorporeal membrane oxygenation during admission.

Table 7-4-b. Results of linear regression analysis about Health-related Quality of Life

Variable	Coefficient	95% confidence interval	*P* value
Intercept	0.97	[0.89, 1.05]	**< 0.001**
Ongoing prolonged symptoms	-0.10	[-0.13, -0.08]	**< 0.001**
Age	0.00002	[-0.00001, 0.00003]	0.969
Male	0.02	[-0.01, 0.05]	0.052
BMI	0.0008	[-0.001, 0.002]	0.560
Smoking	-0.01	[-0.03, 0.01]	0.383
Drinking	0.02	[-0.01, 0.05]	0.255
Hypertension	-0.003	[-0.04, 0.03]	0.860
Diabetes	-0.05	[-0.1, 0.01]	0.068
Malignancy	0.002	[-0.1, 0.1]	0.959
Inpatient	-0.02	[-0.04, 0.01]	0.144
Use of antivirals	0.02	[-0.02, 0.05]	0.301

Use of steroids	0.02	[-0.02, 0.06]	0.386
Severe disease†	0.05	[-0.03, 0.13]	0.264

†Use of mechanical ventilation or extracorporeal membrane oxygenation during admission.

7.4 Discussion

Our results demonstrated that people suffering from the phenomenon we called "long-COVID" showed lower HRQoL. This would be another important aspect of COVID-19 to consider because it implies a heavier disease burden than other influenza like illnesses (ILIs), not only due to its severity but also the characteristics of its chronic phase. In the first place, COVID-19 showed higher case-fatality than other ILIs [178,181,224]. Additionally, it might cause a substantial burden through accumulated mild disease only.

Furthermore, the frequency and the duration of symptoms due to "long-COVID" are also noteworthy. Our results showed that nearly half of the participants who recovered from acute COVID-19 (201/457) experienced any symptoms lasting more than four weeks. As for participants who required supplementary oxygen support, 32 out of 70 (45.7%) presented any symptoms longer than four weeks. The precise duration of such symptoms was not obvious because more than 100 participants reported that their symptoms were still ongoing. Nevertheless, the symptoms attributed to "long-COVID" often continue for several months. Although the HRQoL valuations for participants who had any “long-COVID” symptoms was better than those previously reported during the acute phase of other ILIs in Japan (0.81 vs 0.66, respectively) [67], the HRQoL losses attributable to “long-COVID” should exceed those due to the acute phase of other ILIs because of its duration.

There are several strengths in this study. First, we evaluated the disease burden of long-COVID using standardised HRQoL instruments yielding HRQoL weights, which can be used as inputs for cost-effectiveness analysis with Quality Adjusted Life Years (QALY) as outcome of interest. This characteristic will be beneficial for further research about COVID-19.

Second, we compared the burden of long-COVID symptoms with the “control” participants who have past histories of the acute phase of COVID-19 infection and no ongoing symptoms due to long-COVID. As described in Background, albeit there are a few studies which investigate the association between HRQoL and long-COVID, most of them did not compare HRQoL of people suffering from long-COVID with healthy controls.

Additionally, our results suggest that prevention is more important in COVID-19 countermeasures than other ILIs because effective treatment of “long-COVID” is not clearly established yet [204,225]. Although there is no doubt that vaccination against SARS-CoV-2 will reduce the risk of fatal and severe COVID-19 [226–228], its effectiveness against “long-COVID” is not demonstrated yet. This may provide an additional incentive to prevent SARS-CoV-2 infection even in the absence of known risk factors of severe illness.

As our linear regression models demonstrated, there were no definite factors which have negative influence on HRQoL other than ongoing prolonged symptoms. This suggests that lower HRQoL of long-COVID patients can be attributed to these symptoms, and therefore palliative methods against them would be important. With regard to EQ-VAS, male sex and systemic steroid use during admission showed a positive impact on EQ-VAS values. The positive impact of male sex might be attributed to the finding that female COVID-19 patients experience long-COVID more often than male patients [196]. The effect of steroid use during admission is not clear. If treatment during the acute phase of COVID-19 is associated with milder burden than long-COVID, then even mild cases should be treated with appropriate drugs. The impact of treatment during the acute phase of infection on its chronic phase (long-COVID) is an important challenge to address in future research.

In short, symptoms due to long-COVID may be a cause of low HRQoL. Since long-COVID might be an important contributor to future disease burden, effective countermeasures should be considered. At present, there is no established treatment of long-COVID. In anticipation of therapeutic agents for long-COVID, both pharmaceutical (e.g., vaccination) and non-pharmaceutical (e.g., social distancing) preventive interventions remain important.

There are several limitations in our study. First, since our results are based on the questionnaire survey there are some cognitive biases in participants' responses. The participants answer the questionnaire at least eight weeks after they visited the outpatient service. Given the circumstances, memory recall of the participants might be affected. However, since this study aims to assess the burden of "ongoing" prolonged symptoms, this kind of influence could be trivial.

Second, the potential participants were enrolled from the visitors of outpatient department at the national center hospital of infectious diseases in Japan, implying the study population tend to have had mild disease in their acute period and are comparatively young. Although this can be regarded as a selection bias, long-COVID in relatively young age groups is a serious issue in society, meriting attention in the current social context.

Third, since the participants of this study voluntarily agreed with answering the questionnaire, they can be regarded as having more interest in their own health than that of the general population in Japan. This volunteer bias might be a cause of overestimation in assessment of their prolonged symptoms. In addition, our data about participants' symptoms were based on self-reported information and not validated by any healthcare professionals. However, we believe that this will not impair the value of our findings substantially because most symptoms attributable to long-COVID are subjective ones such as fatigue, and they are difficult to be validated objectively even if they are assessed by healthcare professionals.

Fourth, there is possible bias caused by non-responders. We do not know why some of participants did not complete the survey. The disease burden of long-COVID could be under/overestimated although the response rate of our survey was quite high (86.9%).

Fifth, we should be careful about the representativeness of the data when we interpret the results because our survey includes a comparatively small number of participants. However, our sample size calculation supported that the number of participants had a sufficient power to detect differences in HRQoL.

As discussed above, there are several sources of bias and we should take care when interpreting the results, nevertheless, also take note that the impact of these limitations can be regarded comparatively small in this study.

Next, we could not take “new variants” into consideration. The difference in severity, infectiousness, and so forth between such new variants and old ones were already reported [228–230], however, there is no solid evidence about the frequency and the severity of “long-COVID” symptoms in new variants. This should be the subject of future study.

The statistical model we chose also includes its own limitation. Since we compared EQ-VAS and EQ-5D-3L scores after adjusting participants’ background by IPW method with propensity score, we could include most of the participants in the main analysis. Nevertheless, we had to exclude some of them due to missing items, and these missing values might have some impact on the result. Additionally, variables we collected from the survey was limited, then there might be other factors which we could not take into consideration in this study. These limitations will be future challenges to be addressed. Nevertheless, we can consider our results were robust to some extent because both ATE evaluation and linear regression analysis showed similar results. They both indicate that the symptoms caused by long-COVID might impair our quality of life.

7.5 Conclusion

What we call "long-COVID" brings us substantial disease burden in addition to the burden attributed to the acute phase of COVID-19. This additional burden makes the whole disease burden of COVID-19 heavier, making prevention strategies all the more important. The influence of acute phase treatment, vaccination, and variants on "long-COVID" should be examined in the near future.

8. Chapter 6: Behavioural change in social contact after emergence of COVID-19

This chapter is based on published work: "Tsuzuki S, Asai Y, Ibuka Y, Nakaya T, Ohmagari N, Hens N and Beutels P (2022). Social contact patterns in Japan in the COVID-19 pandemic during and after the Tokyo Olympic Games. Journal of Global Health 2022 Dec 3;12:05047. doi: 10.7189/jogh.12.05047.

Summary

Social contact data in Japan have not been updated since 2011. The main objectives of this study are to report on newly collected social contact data, to study mixing patterns in the context of the COVID-19 pandemic, and to compare the contact patterns during and after mass gathering events like the 2020 Olympic Games, which were held in 2021. We compared the number of contacts per day during and after the Olympic Games and on weekdays and weekends; we also compared them with a pre-COVID-19 pandemic social contact study in Japan. Contact matrices consisting of the age-specific average number of contacted persons recorded per day were obtained from the survey data. Reciprocity at the population level was achieved by using a weighted average. The median number of contacts per day was 3 (interquartile range (IQR) = 1-6). The occurrence of the Olympic Games and the temporal source of data (weekday or weekend) did not change the results substantially. All three matrices derived from this survey showed age-specific assortative mixing patterns like the previous social contact survey. The frequency of social contact in Japan did not change substantially during the Tokyo Olympic Games. However, the baseline frequency of social mixing declined versus those collected in 2011.

8.1 Background

Mixing patterns in the population are key determinants for explaining the spread of infectious diseases and for assessing the possible impact of non-pharmaceutical interventions like school closure, travel restrictions, and city lockdowns on outbreaks of emerging infectious diseases transmitted from human to human through the respiratory or close-contact route, like COVID-19 [52,59,61,144,231–234].

Since Mossong et al. constructed social contact matrices of European countries from the POLYMOD contact survey [143], they have been utilized in many studies [146,235–237].

Social mixing patterns differ by country and change over time. For instance, Ibuka et al. [142] developed a social contact matrix based on a questionnaire survey of the Japanese general population conducted in 2011. They reported that the Japanese population had a greater frequency of contacts than Europeans, although the overall age-specificity of the mixing patterns was similar. According to Prem et al., contact matrices for children in African countries showed more frequent contact among children than for those in European countries, although they showed similar age assortativity [238]. Additionally, the timing of the survey might potentially determine its results, even in the same country. A previous study from Belgium did not show fundamental differences in contact patterns between 2006 and 2010/2011 [239]. Two surveys from Hong Kong showed a large difference in the frequency of contact between two seasons (8.1 in the 2015/2016 and 18.0 in the 2009/2010 season) [240,241].

Coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus has become a global threat to public health [47,48]. In Japan, as in other countries, various non-pharmaceutical interventions have been implemented in the early stage of the COVID-19 pandemic, including school closure, reduced opening hours in restaurants and bars, and the promotion of remote working [242]. Consequently, the daily social behaviour of the Japanese population changed drastically. The government repeatedly declared a state of emergency and recommended avoiding "Three Cs (closed spaces, crowded places, and close-contact settings)" [243]. Given the circumstances, we hypothesized that the number of contacts in Japan is expected to have decreased compared to the pre-COVID-19 pandemic period. While European countries have already updated their information about social mixing patterns [244], there has been no updated information in Japan since 2011. The first objective of this study is to update the social mixing patterns of Japan in the context of the COVID-19 pandemic.

Furthermore, we should note that Japan organised the Tokyo 2020 Olympic Games, which were held in 2021 [245]. The event can be regarded as one of the largest scale mass gatherings during the pandemic, presenting a greater risk for the spread of COVID-19 [246–248]. Nevertheless, we have very little quantitative evidence about how social mixing patterns vary by large international mass gathering events such as the Olympic Games, though we hypothesise that the Games increased the frequency of contact. Therefore, the second objective of this study is to compare the mixing patterns and frequency of social contact in Japan during and after the Tokyo Olympic Games.

8.2 Methods

Study population and data

We conducted an online survey between August 4, 2021, and August 17, 2021. The participants were voluntarily and randomly recruited from registrants (respondents) of INTAGE RESEARCH INC, a Japanese marketing research company. The same number of invitation emails was sent to the registrants in both survey periods, "during" the Olympic Games period (August 4 – August 9) and "after" the Olympic Games period (August 10 – August 17). Each period included one set of weekends (Saturday and Sunday). In addition, participants were recruited according to quota for age, gender (sex-ratio = 1), and population in each prefecture based on Japan's 2015 census. An additional survey was conducted for obtaining more detailed information about the age of persons they contacted on the day of the first survey (i.e., between August 4 and August 17, 2021) between September 10 and September 13, 2021 We included only participants who responded to both surveys (n = 3337). Among them, 1953 were enrolled during the Tokyo Olympic Games (between July 23, 2021, and August 8, 2021) and 1384 responded to the survey after the Olympic Games were closed.

Following the previous study on social contacts in Japan [142], respondents answered survey questions online, about social contacts for themselves and for household members who were under the age of 20 at the time of the survey. Those asked about their household members were given the option of taking a break to consult with their household members before specifying contacts of household members. We defined respondents and participants separately. Respondents were individuals who answered the survey directly and participants were respondents' household members who did not answer the questionnaire directly. For example, if a mother responded on behalf of a child, the mother was a respondent while the child was a participant. Participants were instructed to make their best guess when they did not know the exact information about the age of their contacts.

Information about the participants' basic demographics and each age group's frequency of contacts was collected. The survey was conducted as a single-day point prevalence survey, like many other contact studies, including the study by Ibuka et al. [142]. As a result, respondents gave the details of their contacts on the day preceding the one on which they completed the questionnaire. The English version of the questionnaire is available in Supplementary information 1.

A contact was defined as 1) a conversation of three or more sentences within two meters distance, 2) a direct conversation with others (indirect ones such as via telephone were excluded), 3) conversations with face coverings or partitioning, 4) a dinner with other people, where all those present at the table are considered contacts, 5) more than one conversation with the same person (counted as one contact), and 6) physical contact with a person (counted as one contact). The basic definition of a contact was similar to the previous study but explanations about face covering, partitioning, and how to count group contacts were added.

Sample size calculation

First, we assumed that the frequency of contact in this study had decreased compared to previous studies by Ibuka et al. [142]. In this case, we have no data about standardized differences between the data obtained by the previous study and the ones obtained by our survey. Therefore, we set the power at 0.9 and the effect size at 0.2, constituting a small difference [217,249]. Consequently, power calculation by a student’s t test demonstrated that 527 samples in each group (the previous study and the present study) were required.

Next, we assumed that the frequency of contacts in the weekends was smaller than that on weekdays, as the previous study reported. We set the power at 0.9 and the effect size (Cohen's d) of weekends was calculated as 4.26 from the previous study [142]. This difference can be regarded as "huge", and therefore we set the effect size at 0.8 so as not to overlook smaller differences between weekdays and weekends [249,250]. As a result, power calculation by a student's t-test demonstrated that 34 samples in each group (weekdays and weekends) were required.

Data analysis

The descriptive analysis of the participants' basic demographic characteristics is presented with continuous variables summarised by their median and interquartile range (IQR) and factors of categorical variables by their absolute number and percentage. The normality of continuous variables was examined by the Shapiro-Wilk test, yielding a non-normal distribution for all continuous variables presented in the results.

Factors associated with the number of contacts were examined using random forests [251], which is a class of ensemble methods that generate many classifiers or predictions and aggregate their results, specifically designed for classification or regression trees. We used the feature selection algorithm from the Boruta package

[252] in R for constructing a variable importance list. The Boruta algorithm is a wrapper implemented in the R package randomForest [253]. The details of its algorithm are described in Supplementary information 2.

Further, we examined the relative number of contacts in different age groups, between genders, during or after the Olympic Games, and among other factors selected by the Boruta process by a negative binomial regression model. Two-sided p-values of <0.05 were considered statistically significant.

Contact matrices

We established contact matrices from the questionnaire data consisting of the average number of contact persons recorded per day. Reciprocity was obtained by averaging the population-level number of contacts of the corresponding cells [131,254]. Additionally, we made another contact matrix based on the year 2011 data derived from Ibuka et al. [142] For this pre-COVID-19 matrix, we determined a weighted average d_{ij} of the number of contacts in age group j made by participants of age group i. We made four matrices using our year 2021 data; a weekday (from Monday to Friday) matrix (W), a weekend (Saturday and Sunday) matrix (H), a matrix after the Olympic Games (A), and a matrix during the Olympic Games (O). This gave the elements of the contact matrix $\varphi_{ij} = c_{ij}$, scaled by the time period T over which contacts were measured (in this study, per day then $T = 1$). All analyses were conducted using R, version 4.1.2 [91].

8.3 Results

The basic characteristics of the participants are shown in Table 8-1. As described in the previous section, 1953 participants were enrolled during the Olympic Games, while 1384 were enrolled after the Olympic Games. Among them, 1600 (47.9%) were male and 1713 (51.3%) were from urban areas. 2198 (65.9%) were enrolled on weekdays. During the Olympic Games, only 79 (4.0%) went to the venue and 26 (1.3%) watched the games at sports bars, because many of the games took place without live spectators.

Table 8-1. Basic characteristics of the respondents

	During the Olympic Games (n = 1,953)	After the Olympic Games (n = 1,384)	Total (n = 3,337)
Age (years)	37 [12-50]	37.5 [14–51]	37 [13–50]
Male	970 (49.7%)	630 (45.5%)	1,600 (47.9%)

Residents in urban area*	980 (50.2%)	733 (53.0%)	1,713 (51.3%)
Working status			
Full time	1,062 (54.4%)	729 (52.7%)	1,791 (53.7%)
Part time	349 (17.9%)	220 (15.9%)	569 (17.1%)
Job seeking	50 (2.6%)	41 (3.0%)	91 (2.7%)
Others (students etc.)	492 (25.2%)	394 (28.5%)	886 (26.6%)
Education			
Secondary	45 (2.3%)	25 (1.8%)	70 (2.1%)
High school	623 (31.9%)	414 (29.9%)	1,037 (31.1%)
University	1,277 (65.4%)	938 (67.8%)	2,215 (66.4%)
Others	8 (0.4%)	7 (0.5%)	15 (0.4%)
Number of household members	3 [2-4]	3 [2-3]	3 [2-3]
Participated in weekdays	1,518 (77.7%)	680 (49.1%)	2,198 (65.9%)
Remote working on the day of survey	173 (8.9%)	57 (4.1%)	230 (6.9%)
Watching the Olympic Games		NA	NA
On site	79 (4.0%)		
At sports bar	26 (1.3%)		
Commute to workplaces	1,246 (63.8%)	840 (60.7%)	2,086 (62.5%)
Frequency of dining out per month			

Before pandemic	1 [0-2]	1 [0-3]	1 [0-2]
During pandemic	0 [0-0]	0 [0-0]	0 [0-0]

Numbers in brackets represent percentage and interquartile range.

NA, not available; Urban area; ordinance-designated cites, prefectural capital and other cities of similar size

The random forests approach using the Boruta method showed that age was the most important factor influencing the total number of contacts made. Additionally, contacts at work and permittance of remote work were also important. Notably, the timing of the survey (weekday or weekend, during or after the Olympic Games) was not found to be an influential factor. Visiting a sports bar or being onsite during the Olympic Games were also not influential. The results of the random forest approach are described in Figure S8-1 in Supplementary information 2.

The results of a negative binomial regression model for the total number of contacts are presented in Figure 8-1. People younger than 20 years of age reported a smaller number of contacts compared with adults. Participants who visited sports bars during the Olympic Games reported a larger number of contacts, but those who visited the site of the Olympic Games reported a lower number of contacts.

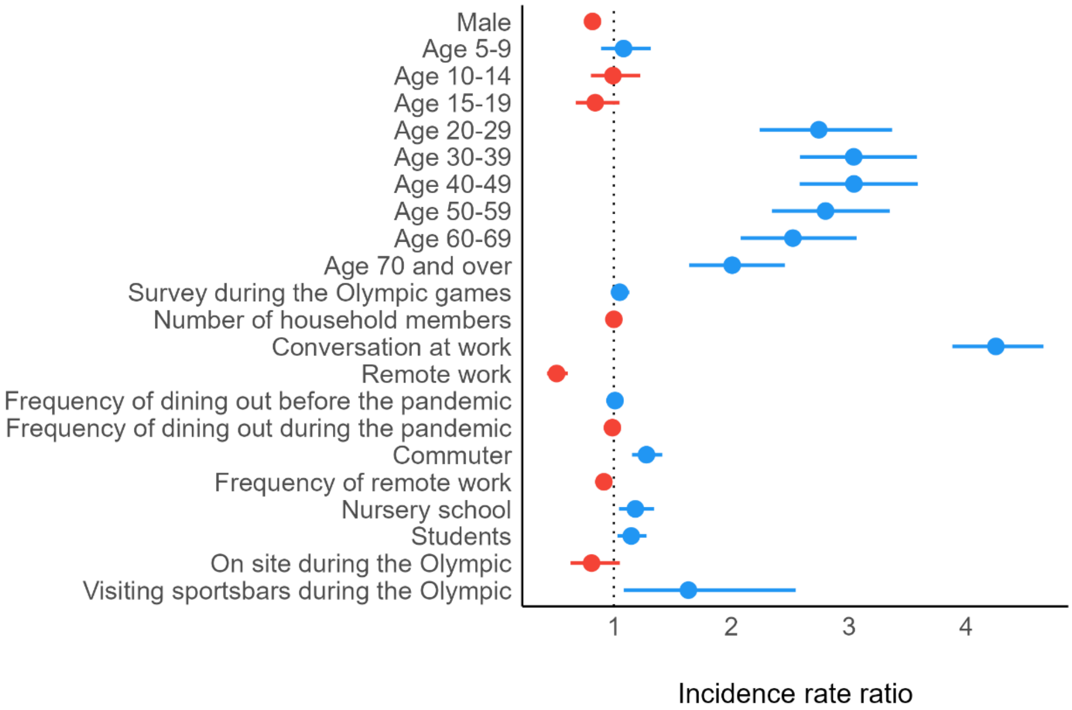


Figure 8-1. Results of a negative binomial regression model for the total number of contacts

Blue circles represent positive impact on the total number of contacts. Red circles represent negative impact on the total number of contacts. The lines on either side of the circles represent 95% confidence intervals.

IRR: Incidence rate ratio

The median and mean number of contacts per day was 3 (IQR = 1-6) and 8.92 (standard deviation (SD) = 25.45), respectively. Whether the Olympic Games were held or not, and the timing of survey (weekday or weekend) did not change these results substantially.

Figure 8-2 (Panel A-D) and Figure S8-2 in Supplementary information 2 are social contact matrices based on the weekday survey data, the weekend survey data, the survey data “after the Olympic Games” period, the survey data “during the Olympic Games” period, and a re-constructed matrix derived from Ibuka et al. [142]. All four matrices derived from this survey showed an age-specific assortative mixing pattern like the re-constructed matrix derived from Ibuka et al. While the latter matrix showed more frequent contact among children than among adults, our survey results showed the opposite. Furthermore, it was difficult to find obvious differences among the four matrices derived from this survey.

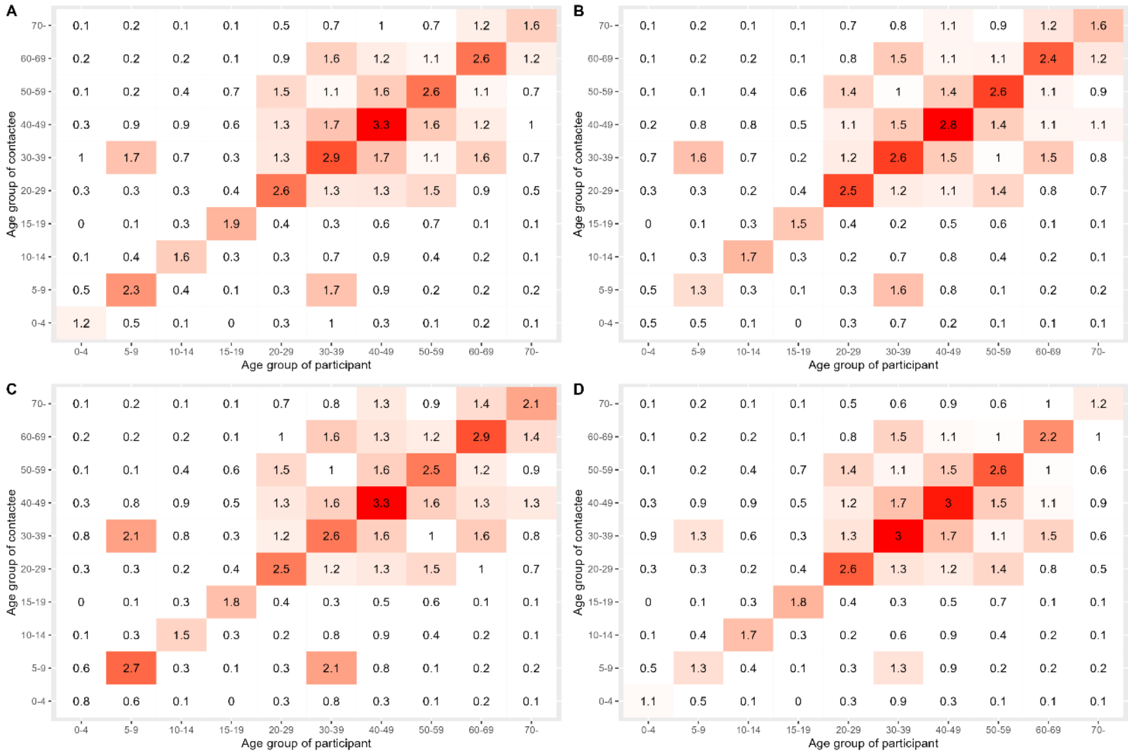


Figure 8-2. Contact matrices

Panel A. Contact matrix based on the weekday survey data

Panel B. Contact matrix based on the weekend survey data

Panel C. Contact matrix based on the survey data "after the Olympics"

Panel D. Contact matrix based on the survey data "during the Olympics"

Average number of contacts per day between age groups. Red colour indicates higher contact numbers compared to white cells, with darker colour signifying higher number of contacts.

8.4 Discussion

To the best of our knowledge, this is the first study to explain the change of social mixing patterns during and after the Olympic Games in the context of the COVID-19 pandemic.

One of our hypotheses that the COVID-19 pandemic decreased the frequency of contacts in Japan seems reasonable because the average number of contacts per day shown by this study was substantially smaller than that reported by the previous study [142].

Meanwhile, large-scale mass gathering events such as the Olympic Games are expected to increase the chance of social contact among the general population [255,256]. However, our findings demonstrated that their frequency of contact did not change significantly during or after the Olympic Games period. This might be explained by the fact that the Tokyo Olympic Games were held under strict conditions with hardly any live spectators. For instance, traffic regulation was strengthened around Tokyo and the tolls for the Metropolitan Expressway were raised during the Olympic Games. These interventions could have possibly contributed to reducing human flow.

The number of contacts among children was lower than in the previous study (1.6 vs 12.9 in the 10-14 age group) because of the summer vacation period in August. However, even if we exclude children from the survey data, the frequency of social contacts among Japanese adults was substantially lower compared to the pre-COVID-19 period (the median number of contacts per day was 3 vs 12, respectively) [142]. This large difference might be attributed to the current COVID-19 pandemic even when taking the weekend effect into consideration because the difference in contacts between weekdays and weekends in Japan was not that large (14 and 8, respectively) [142]. Since April 10, 2021, the Japanese government declared the third state of emergency for four prefectures including, the Tokyo metropolitan area [257]. After that, the declaration was made for some other prefectures, only to be lifted on June 20 for all, except for the Okinawa Prefecture. However, the state of emergency was declared for Tokyo again on July 12, and the Tokyo metropolitan area had been under a state of emergency until the end of September. The Tokyo Olympic Games were conducted from July 23 to August 8, 2021, and therefore all of the games were done during the declaration [257]. Considering these conditions, the state of emergency declaration may have had a substantial impact on social mixing behaviour of the Japanese general population, although the declaration did not imply legal enforcement.

Our results also showed that weekends did not have a clear influence on mixing behaviour in the COVID-19 pandemic period. This finding can also be attributed to the declaration because it recommended avoiding unnecessary outings and trips. The random forest analysis supports this hypothesis, showing that the most important factor for the increase in the number of contacts other than age was contacts at work. The variation in contacts was determined by work-related behaviour, and not substantially by contacts in the private sphere.

Our study has several limitations. First, it included only the participants who answered two rounds of online surveys. This may impair the reliability of the results because the second online survey was conducted after a month has passed since the Olympic Games had finished, possibly complicating comparisons with similar studies [258,259] due to differences caused by people not participating in the second round. Nevertheless, the survey design can be regarded as appropriate for the study's main objective since the previous study in Japan was also reported based on the point prevalence survey [142]. Second, our survey was fully internet-based, implying participants had to have basic knowledge of the internet, which could lead to selection bias. However, as most previous studies reported, young adults and children are the main sources of frequent contacts, and thus the selection bias might be less influential. Additionally, the Hoang et al.'s systematic review of contact studies pointed out that no clear relationship in the number of contacts had been found when comparing online diaries with paper diaries [260]. Third, like other previous studies, we could not obtain information directly from children. In our survey, we requested respondents who had children younger than 20 years old living in their household to indicate the number of contacts made by their children, which could lead to biases in reporting, especially in younger children who are primary school students or utilize nursery schools/kindergartens. Fourth, we did not consider the effect of seasonality, vacation, other non-pharmaceutical countermeasures, and other factors. Since August is the summer vacation season in Japan, it is likely that their mixing behaviour is different from other seasons. Furthermore, many Japanese adults take “Obon” vacation in the latter half of August, which exactly corresponds to the period just after the Olympic Games. Further study would be desirable to assess the effect of these social factors on the number of social contacts.

8.5 Conclusion

The frequency of social contacts in Japan did not change substantially during the Tokyo Olympic Games. However, the baseline frequency of social mixing decreased compared with that reported previously, and this might be attributed to the COVID-19 pandemic and the state of emergency declaration.

9. Chapter 7: Total disease burden caused by COVID-19 in Japan from the beginning of 2020 to the end of 2021

This chapter is based on unpublished work: "Tsuzuki S and Beutels P (2022). The estimated disease burden of COVID-19 in Japan from 2020 to 2021. Submitted to Journal of Infection and Public Health and currently under review.

Summary

To date, it is not fully understood to what extent COVID-19 has burdened society in Japan. This study aimed to estimate the total disease burden due to COVID-19 in Japan during 2020-2021. We stratify disease burden estimates by age group and present it as absolute Quality Adjusted Life Years (QALYs) lost and QALYs lost per 100,000 persons. The total estimated value of QALYs lost consists of (1) QALYs lost brought by deaths due to COVID-19, (2) QALYs lost brought by inpatient cases, (3) QALYs lost brought by outpatient cases, and (4) QALYs lost brought by long-COVID. QALYs lost due to COVID-19 was estimated as 286,781.7 for two years, 114.0 QALYs per 100,000 population per year. 71.3% of them were explained by the burden derived from deaths. Probabilistic sensitivity analysis showed that the burden of outpatient cases was the most sensitive factor. The large part of disease burden due to COVID-19 in Japan from the beginning of 2020 to the end of 2021 was derived from Wave 3, 4, and 5 and the proportion of QALYs lost due to morbidity in the total burden increased gradually. The estimated disease burden was smaller than that in other high-income countries. It will be our future challenge to take other indirect factors into consideration.

9.1 Background

Coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus, has become a global health threat since the beginning of 2020 [47,48,176]. In Japan, it was first detected in early 2020 [261].

This emerging infectious disease became one of the most pressing concerns for the Japanese general population and the Ministry of Health, Labour and Welfare (MHLW) Japan in early 2020 and the Prime Minister of Japan declared the state of emergency on 7th April 2020 for seven prefectures including the Tokyo metropolitan area [63,180,242]. MHLW recommended to avoid Three Cs (Closed spaces, Crowded places, and Close-contact settings) to prevent COVID-19 transmission [243] and behaviour of the general population drastically changed. The number of healthcare facility visits and the consumption of antimicrobials decreased substantially after the emergence of COVID-19 in Japan [262,263]. In short, the COVID-19 pandemic changed the Japanese way of life substantially.

To date, it is not fully understood to what extent this novel emerging disease has burdened society. A quantification of the observed burden, despite the great efforts that were made to minimise it, is a first step towards understanding how pandemic management can be improved.

Compared with other high-income countries, the cumulative incidence of

COVID-19 cases, hospitalisations and deaths has been comparatively small in Japan, at least until the end of the year 2021 [264]. For instance, the United Kingdom reported 952.6 cumulative hospitalizations per 100,000 population [265] and the US reported 11,700.6 cumulative hospitalizations per 100,000 population at the end of 2021 [266], while Japan reported 1,706.1 cumulative hospitalizations per 100,000 population in the same period. As for deaths, Japan reported lower rates (14.6 deaths per 100,000 population) compared with the UK and the US (218.1 and 247.8 deaths per 100,000 population, respectively) and the average of the world (69.1 deaths per 100,000 population) [267]. On the other hand, it should be noted that several other countries such as Australia presented lower mortality rates (9.5 deaths per 100,000 population) [264].

In order to learn from the crisis and be better prepared for future pandemics, we aim to assess the burden caused by COVID-19 in more detail. We can classify the disease burden directly caused by COVID-19 into four categories;

(i) Quality Adjusted Life Year (QALY) losses caused by fatal cases
(ii) QALY losses caused by outpatient cases
(iii) QALY losses caused by mild to severe inpatient cases
(iv) QALY losses caused by long-COVID[201]

Since they can be both interpreted as indicators of pandemic management, here we aim to document both the cumulative and the chronological, per-wave, disease burden caused by COVID-19. The COVID-19 epidemic in Japan was characterised by five waves in 2020 and 2021. We adopted a previously proposed classification of waves observed in Japan [268], as follows (see also Figure 2):

(i) First wave (Wave 1), 01/01/2020-05/31/2020;

(ii) Second wave (Wave 2), 06/01/2020-10/31/2020;

(iii) Third wave (Wave 3), 11/01/2020-03/31/2021;

(iv) Fourth wave (Wave 4), 4/1/2021-6/30/2021;

(v) Fifth wave (Wave 5), 7/1/2021-12/31/2021

The Japanese government had implemented different non-pharmaceutical interventions (NPIs) in each period and the guidelines for clinical management of COVID-19 cases grew gradually, implying the characteristics of the burden in each wave are expected to be different.

The main objective of this study is to assess the disease burden caused by COVID-19 in Japan between the beginning of 2020 and the end of 2021 in order to enable comparisons over time, with other diseases and with other countries.

9.2 Methods

Settings

We constructed a progression pathway model of COVID-19 infection (Figure 9-1), in which two types of infection; symptomatic and asymptomatic, and three degrees of severity were defined; outpatient cases, inpatient cases (mild), and inpatient cases (severe). The definition of "severe" inpatient cases varied by prefecture because each prefecture defined the severity of inpatient COVID-19 cases by its own criteria. A large part of prefectures defined "severe" cases as patients admitted to an intensive care unit (ICU) or patients requiring mechanical ventilation. Additionally, we assumed that any type of symptomatic infection could lead to long-COVID. In line with previous studies [196,199], we defined long-COVID patients as presenting with COVID-19 symptoms for longer than four weeks from symptom onset. The final stage of each infected case was "Death" or "Recovery". We assumed that all symptomatic infections (both outpatient and inpatient cases), including long-COVID episodes, and deaths contributed to the disease burden, whereas asymptomatic infections did not.

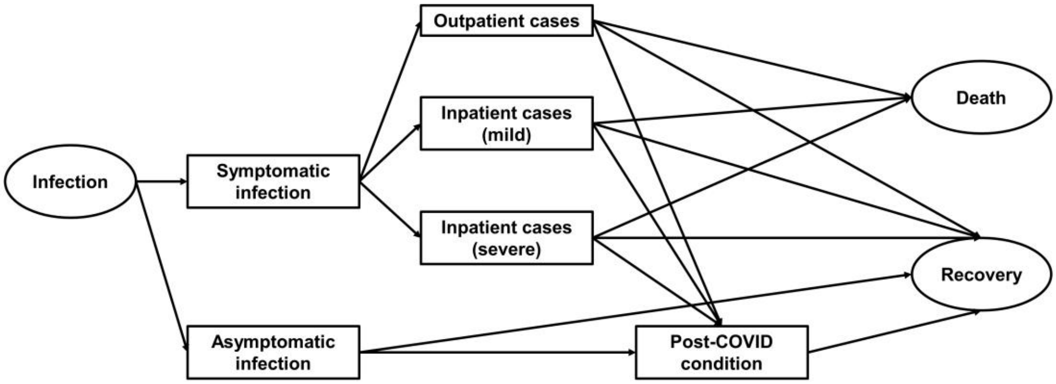


Figure 9-1. Progression pathway diagram of COVID-19 infection

We estimated the disease burden due to COVID-19 in Japan for the period from the beginning of 2020 to the end of 2021 because the first case of COVID-19 in Japan was detected on 15th January 2020 [261], and by the end of 2021 80.4% of the population had received their primary course of COVID-19 vaccination. Additionally, the less severe Omicron variant of concern (VOC), became dominant early in 2022, and its clinical, detection and epidemiological characteristics were quite different from other strains.

Data sources

We used open data sources for the daily number of confirmed cases and deaths caused by COVID-19. Demographic data were sourced from official statistics [119]. Disutility of each health status was presented as QALYs lost per episode and defined according to values from the literature [175,199,269]. We assumed the proportion of acute symptomatic COVID-19 cases that gives rise to long-COVID was 16.6% in adults and 3.9% in children [270,271]. An overview of these parameters is shown in Table 9-1.

Table 9-1. Detail of parameters included in the model

Parameters	Value	Distribution	Reference
Disutility (QALYs lost)			
Outpatient case	0.033	Lognormal (mean = -5.187, SD = 0.034)	[175]
Inpatient case	0.439	Normal (mean = 0.439, SD = 0.027)	[269]
Long-COVID	0.129	Lognormal (mean = -4.209, SD = 2.597)	[199]
Proportion with long-COVID			
In adults	0.166	Binomial	[270]

In children (under 20)	0.039	Binomial	[271]

Estimation of disease burden

We stratify the disease burden estimates by age group and present it as absolute QALYs lost and QALYs lost [272,273] per 100,000 persons. QALYs lost due to premature mortality were calculated as the remaining period life expectancy at the time of death per fatal case, i.e., the number of life years lost (LYL). We used nine age groups, in accordance with available COVID-19 mortality statistics: < 10 years, 10-19 years, 20-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years, 70-79 years, 80-89 years, and ≥ 90 years, and assumed deaths reported within a given age group occurred at the mid-point of the age interval, in line with previous studies [92,126].

QALYs lost due to inpatient cases were calculated by multiplying the total number of mild/severe inpatient cases with the disutility per COVID-19 inpatient case. Similarly, QALYs lost due to outpatient and long-COVID cases were calculated by multiplying the total number of outpatient and long-COVID cases with the respective disutilities per case (see table 9-1).

The total disease burden of COVID-19 was expressed as the sum of the above, i.e., the QALYs lost due to disease in inpatient cases, outpatient cases and due to premature deaths.

Two-sided p values of < 0.05 were considered to show statistical significance. All analyses were conducted by R, version 4.1.3 [91].

Sensitivity analysis

We conducted probabilistic sensitivity analysis to acknowledge uncertainty and examine the robustness of our results. We ran 1,000 simulations of the disease burden estimation with different sets of parameter values derived from the defined ranges and distributions. The range of each parameter, distribution, and the references we used to determine it are available in Table 9-1. The influence of each parameter on the total disease burden was evaluated by a linear regression analysis with 1,000 simulation results as an independent variable and 1,000 parameter sets as dependent variables.

Ethics approval

All data used in this study are publicly available. As such, the datasets used in our study were de-identified and fully anonymized. Therefore, this study did not require specific ethical approval.

9.3 Results

In total, 1,728,228 COVID-19 cases were confirmed in Japan from the beginning of 2020 to the end of 2021. Among them, 232,495 cases were observed in 2020 and 1,495,733 cases in 2021. A relatively small number of cases was observed in Waves 1 and 2 (99,959 cases and 1,765 deaths) in Japan, and more than half of the total cases between 2020 and 2021 were observed in Wave 5 (931,393 cases), although the number of deaths in Wave 5 was comparatively small (3,762 deaths). Similarly, the maximum number of cases requiring hospitalization in Wave 1 was 6,250, while in Wave 5 it was 231,596. Figure 2 shows the epidemic curve of confirmed cases and number of cases requiring hospitalization from 2020 to 2021. When the life years lost were adjusted by the age-specific population norm for health-related quality of life (as shown in the Supplementary file), the interpretation of these results did not change.

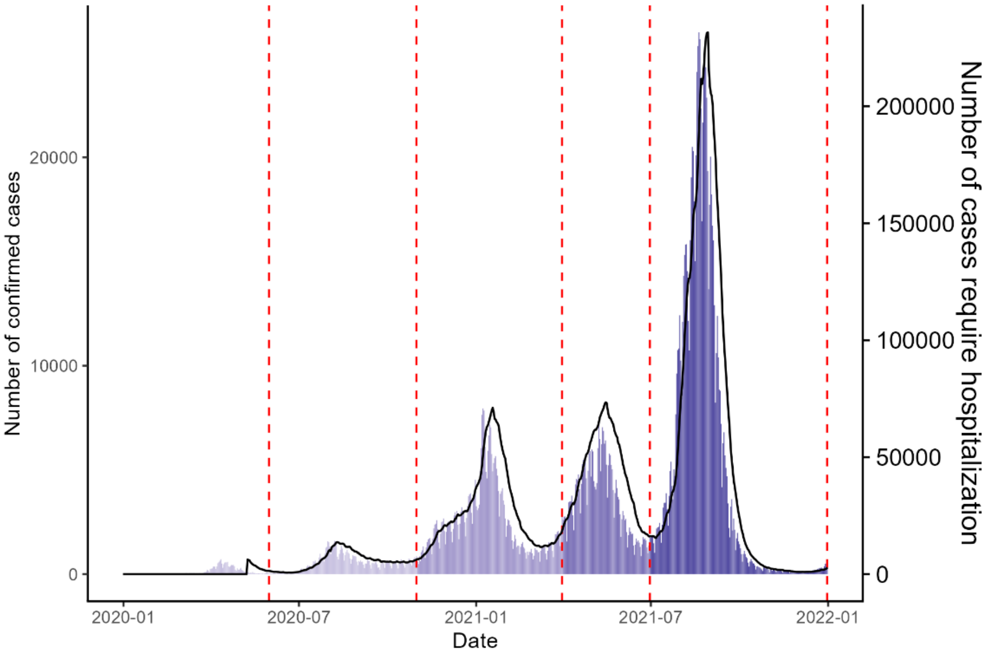


Figure 9-2. Daily number of confirmed COVID-19 cases and hospitalisations

Wave 1; 01/01/2020-05/31/2020, Wave 2; 06/01/2020-10/31/2020, Wave 3; 11/01/2020-03/31/2021, Wave 4; 4/1/2021-6/30/2021, Wave 5; 7/1/2021-12/31/2021

Bars represent the daily number of confirmed cases. The black line represents the number of cases requiring hospitalization. Vertical lines represent the delimitation of five epidemic waves.

More than a half of total cases were observed in Wave 5 (931,393 cases). The Delta variant of concern (VOC) was dominant in this period30,31, as it outcompeted the less transmissible Alpha VOC in July 2021.

The number of fatal cases was 3,095 in 2020 and 14,520 in 2021. The case-fatality ratio (CFR) was 0.013 in 2020 and 0.0097 in 2021, respectively. The estimated average age of fatal cases was 80.2 (Wave 1 and 2), 82.3 (Wave 3), 81.5 (Wave 4), and 75.8 (Wave 5) years.

QALYs lost due to COVID-19 were estimated as 286,781 over two years, or an average of 114.0 QALYs per 100,000 population per year. The observed disease burden differed substantially between waves: from 8.5 QALYs per 100,000 population in Wave 1, up to 96.2 QALYs per 100,000 population in Wave 5. Figure 9-3 shows the evolution of QALYs lost per 100,000 population in the total population and by broad age group (under 40, 40-69, and over 69) over the waves. The disease burden in younger age groups gradually increased during the study period with 36.4%, 47.6%, 36.6%, 45.0% and 68.2% of the QALYs lost occurring in the age groups younger than 70 in Waves 1 through 5, respectively. When life years lost are adjusted for quality these percentages become38.7%, 50.7%, 39.6%, 48.3%, and 70.7%, respectively. As for the number of cases, the proportion of younger age groups increased slightly (87.3% in Wave 1 and 92.2% in Wave 5, respectively).

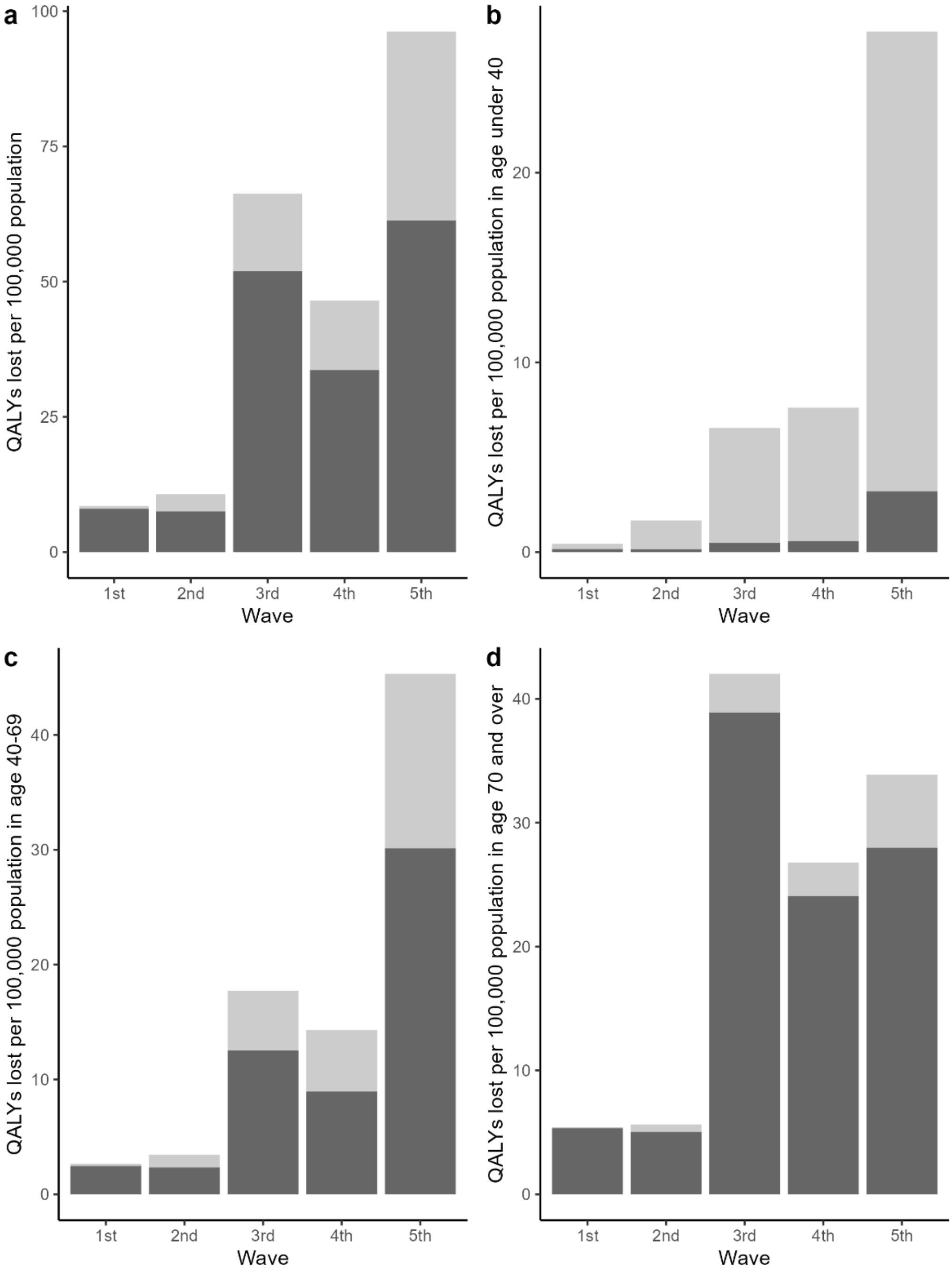


Figure 9-3. Comparison of QALYs lost per 100,000 population in each epidemic wave

Wave 1; 01/01/2020-05/31/2020, Wave 2; 06/01/2020-10/31/2020, Wave 3; 11/01/2020-03/31/2021, Wave 4; 4/1/2021-6/30/2021, Wave 5; 7/1/2021-12/31/2021

Light grey bars represent QALYs lost due to morbidity and dark grey bars represent QALYs lost due to mortality.

QALYs; Quality-adjusted life years

Panel a: Disease burden in total population

Panel b: Disease burden in population under 40

Panel c: Disease burden in population between age 40 and 69

Panel d: Disease burden in population 70 and over

More than 70% of QALYs were lost due to premature mortality (204,437.2 out of 286,781.7, 71.3%), while nearly 20% were lost due to morbidity in outpatient cases (57031.5 QALYs lost, 19.9%), and only a small part of the burden came from morbidity in severe cases (422.5 QALYs lost, 0.1%). Long-COVID accounts for 3.4% of the total disease burden (9,791.7 QALYs lost). Figure 9-4 shows the breakdown of disease burden attributed to each clinical status.

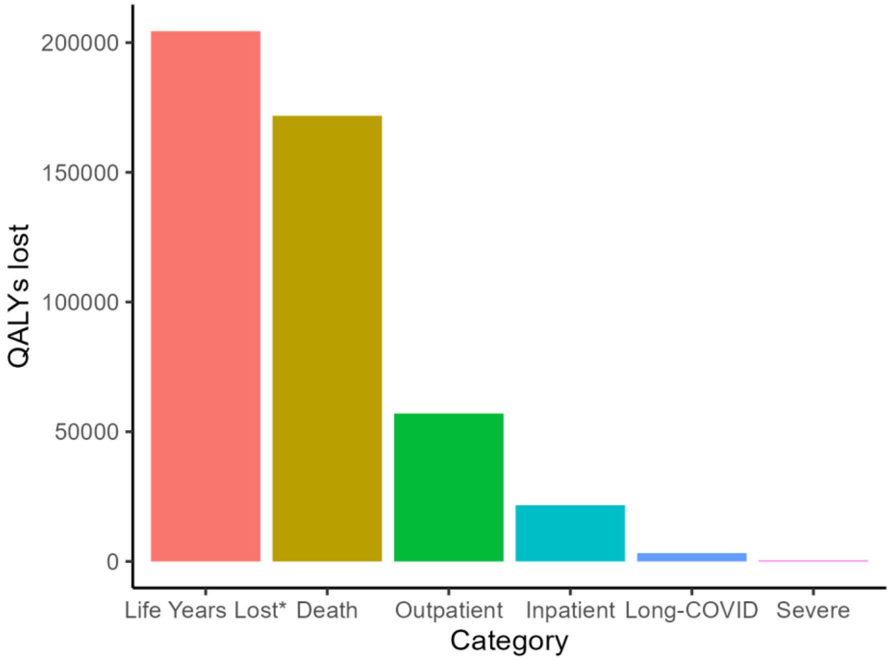


Figure 9-4. Breakdown of disease burden by clinical manifestation of COVID-19

QALYs; Quality-adjusted life years

*Count without quality adjustment (i.e., assuming life years lost due to premature mortality would have been lived in perfect health).

Probabilistic sensitivity analysis showed the disease burden directly due to COVID-19 ranged between 226,883 and 512,236 (median 242,834, IQR 236,108 to 254,488) QALYs, or between 90.1 and 203.6 (median 96.5, IQR 93.8 to 101.1) QALYs per 100,000 population. The disutility per outpatient case was the most influential parameter for the estimated QALY losses due to morbidity, whereas the disutility per long-COVID patient was the second most influential. Figure 9-5 shows the influence of these and the other input parameters by their coefficient in a linear regression analysis using 1,000 input parameter sets and 1,000 associated QALY estimates. Clearly, accurate estimates for the disutilities per outpatient and per long-COVID patient are important to estimate the burden of disease from COVID-19.

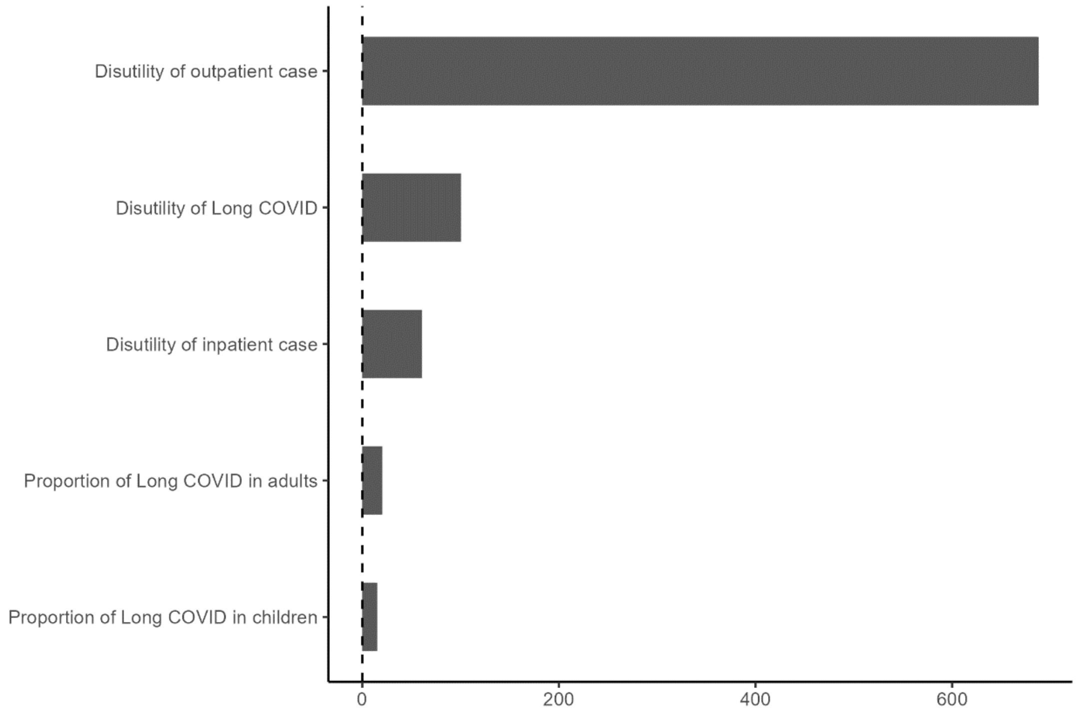


Figure 9-5. Linear regression coefficient of each parameter included in the probabilistic sensitivity analysis

X axis represents coefficient value of each parameter.

9.4 Discussion

To the best of our knowledge, this is the first study which estimated the disease burden directly due to COVID-19 in Japan in the first two years of the pandemic. The disease burden brought by this emerging infectious disease during the first two years was smaller than in most other high-income countries (HICs). For instance, McDonald and colleagues reported that the total disease burden per-capita in the Netherlands in 2020 due to COVID-19 was 1,640 Disability-adjusted life-years (DALYs) per 100,000 population [56]. This number is more than ten times higher than that of our study. Other countries, e.g., Scotland and Malta, also reported similar size of burden in 2020 [274,275]. Germany and Denmark reported smaller burden, however, the results were still much larger than ours (368 and 520 DALYs/100,000, respectively) [65,276].

An obvious difference between previous studies and ours is that we used QALY losses instead of DALYs to express burden of disease. Many guidelines advocate the use of a combined measure of morbidity and mortality as preferred outcome in economic evaluation, and the majority of country-specific guidelines, including those for Japan, prescribe the use of QALYs [277], although some influential generic guidelines such as the IDSI [278] and the 2019 WHO guide for economic evaluation of vaccinations [279] indicate that the choice between these outcome measures may depend on the analyst's preference and of the specific intervention under study.

QALYs were used in our study to include the disease burden attributable to long-COVID based on a previous observational Japanese study using the EQ-5D-3L questionnaire [199]. Although this choice may limit the comparability with studies using DALYs as an outcome, it allows us to attain our primary objective, i.e., assessing the disease burden by clinical manifestation, wave and age group, and have a basis to start from to assess the QALY impact of interventions (as one would for economic evaluation). Furthermore, DALYs were conceived in a very similar manner as QALYs, and applied studies using both measures have reported relatively small differences, although the former used life expectancy tables to determine the years of life lost component and the latter used normative utility to assume the utility of general population [272].

As for the total disease burden, this could be simply attributed to the relatively small number of confirmed cases and deaths per population, and low case fatality rate in Japan [264]. Mortality of COVID-19 cases was smaller in Japan than in most other HICs during the study period [178,280–282]. With regard to the number of deaths, the total number of all-cause excess deaths from the beginning of 2020 to the end of 2021 was estimated at between 11,014 and 58,905, while all-cause exiguous deaths in the same period was between 9,069 and 45,185 [283]. Considering these numbers included the influence of diseases other than COVID-19, the number of indirect deaths due to COVID-19 might not change the total burden estimates substantially. One can speculate about the reasons why the COVID-19 case and death toll tended to be lower in Japan than in many other HICs. Basically, people who presented fever or any symptoms suspicious of COVID-19 were required to visit one of the designated medical facilities and physicians who diagnosed COVID-19 had to report all COVID-19 cases they diagnosed, implying the potential risk of underestimating the number of cases was low. The cumulative number of COVID-19 cases in Japan increased most steeply after the emergence of the Omicron VOC, and the proportion of the Japanese population with non-vaccine induced immunity against COVID-19 remained low, even in 2021 [284].

Considering the breakdown of QALYs lost, the part of the burden attributable to fatal cases was smaller than that in previous studies. Although only 71.3% of QALYs lost was attributed to fatal cases in our study, more than 90% of the total burden was attributed to LYL in previous studies in other countries [64,65,274–276]. It may be partly explained by some studies not including the burden of long-COVID. Furthermore, we have used a simplified approach by counting each lost life year as one, implying that each of these life years was assumed to be lived in perfect health. We also made estimates accounting for a quality adjustment in the life years gained, and as expected, this leads to lower estimates of the QALYs lost due to premature mortality.

The probabilistic sensitivity analysis acknowledges parametric uncertainty and indicates a relatively wide range for the total disease burden. This might be attributed to uncertainty in the estimation of the burden of outpatient cases and long-COVID because we defined the range of disease burden caused by these two statuses according to empirical data in our previous studies [175,199], then small sample sizes affected their uncertainty. Additionally, it would also be due to the fact that there is no single established definition of long-COVID. Tsuzuki et al defined long-COVID as four weeks or longer duration of symptoms after diagnosis of COVID-19 [199], however, WHO defines post COVID-19 condition as the status "usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis" [285]. With changing definitions, the proportion of symptomatic cases incurring long-COVID varies significantly. In addition, disutility of each long-COVID case varies substantially by study [213,286,287] which will bring further uncertainty.

There are several limitations in this study, similar to the previous studies. First, our results did not consider how many cases were unreported. As described above, all diagnosed COVID-19 cases including asymptomatic ones had to be reported in Japan, nevertheless some level of underreporting seems inevitable. For instance, McKenzie and colleagues insisted that there might be 1.77 times higher number of cases than reported during the same period (from the beginning of 2020 to the end of 2021) [288]. It is difficult for us to estimate the precise cumulative incidence of COVID-19 because we have very little evidence on the seroprevalence of SARS-CoV-2 in Japan[284,288]. However, most of such unreported cases were expected to be "asymptomatic" because they had to be reported if they presented any suspicious symptoms. Since our objective is to assess the disease burden directly attributable due to COVID-19, we can ignore such cases, although they may have given rise to anxiety, especially in 2020, and have an impact on mental wellbeing in both the infected person and their direct contacts in and outside the household.

Second, we did not take the burden to the healthcare systems into consideration. Japanese government decided to admit all the patients diagnosed with COVID-19 regardless of its severity in the early phase of the pandemic [63]. As a result, a large number of tertiary hospitals could not offer normal healthcare due to high burden of the management of COVID-19 cases. This would have brought additional burden to society as previous studies reported[289,290]. Nevertheless, we believe that this additional burden to the healthcare system did not contribute to increase the total disease burden, because excess mortality attributable to the causes other than COVID-19 was smaller than before during the study period [283], and no large catch-up effect due to postponed care has been detected in mortality statistics to date.

Third, we could not consider the impact of non-pharmaceutical interventions (NPIs). The Japanese government had implemented a "state of emergency" declaration as a kind of recommendation to avoid social contact like capital lockdown in other countries [291]. In addition, new entries from several countries such as China were restricted in April 2020, and from abroad were to be fully restricted at the beginning of 2021. This restriction was lifted transiently in October 2021, however, almost no one could enter Japan from abroad during 2021. Such interventions might contribute to decrease the number of COVID-19 cases in exchange for the economic burden. We have scarce evidence about both the economic aspects of these non-pharmaceutical countermeasures so far and a counterfactual scenario about the burden of disease and the economic impact in case we had not implemented such NPIs. Although it seems clear that the total disease burden due to COVID-19 in Japan was relatively smaller than in most other HICs, the impact of the indirect effects of NPIs on the overall disease burden remains a topic on research, as it is in many other countries.

Fourth, we did not distinguish between primary and secondary infections in unvaccinated persons and breakthrough infections in vaccinated persons. The cases reported in 2021, included breakthrough infections, but we lacked the information to specify these cases. Al-Aly et al. showed that the risk of death and post-acute sequelae were higher in unvaccinated cases than breakthrough infections [292], and the total burden might become slightly smaller if we consider the impact of breakthrough infection. Nevertheless, the number of breakthrough infection can be considered smaller than the normal ones, then its impact also should be a small one.

Fifth, in line with all other studies known to us, we exclude other indirect aspects of the disease burden such as that caused by isolation, imposed on patients' family members, and so forth, because the number of isolated persons and the number of patients' household members are not well documented. Although our previous studies had estimated the per-patient impact of these aspects [67,175], future work will attempt to combine these results with the estimated number of isolated people and household members of infected cases as part of a more general assessment of the indirect burden.

9.5 Conclusion

Most of the disease burden due to COVID-19 in Japan from the beginning of 2020 to the end of 2021 was incurred in 2021 during waves 3, 4, and 5. The proportion of the total burden due to non-fatal disease increased gradually and this was probably due to the lower mortality by COVID-19 in the latter half of the study period, especially in the elderly. It also shows that younger people contributed more to the disease burden as SARS-CoV-2 circulated more in the general population from 2021 onwards. The estimated disease burden in Japan was smaller than in most other HICs and this can be attributed to the small number of confirmed cases in Japan. Future research may further explore the underlying reasons for the lower cumulative incidence of COVID-19 cases in Japan, while taking contextual factors into consideration.

10. Chapter 8: General discussion

10.1 Main findings of the thesis

As we have seen, both seasonal influenza and COVID-19 had imposed substantial disease burden on Japanese society. According to GBD 2019 Diseases and Injuries Collaborators, DALYs due to lower respiratory tract infection in 2019 in Japan was 993.6 per 100,000 population [293]. Similarly, Diabetes and schizophrenia brought 728.9 and 229.8 DALYs per 100,000 population, respectively [293].

It is difficult to compare DALYs with QALYs directly because each indicator showed wide range of results in previous studies. In addition, the methodological differences between them make them more difficult to be compared. As mentioned in the previous chapters, QALYs are originally not linked to any particular disease or condition and rather based on the values of individuals' own health status. In contrast, DALYs have been linked to specific diseases, and its objective was to quantify the burden of disease [21]. For example, the use of life table in the calculation of DALYs can cause a substantial difference between its estimate and QALYs [272]. Cassini and colleagues estimated that DALYs per 100,000 population per year due to seasonal influenza from 2009 to 2013 in EU/EEA countries [294], while Dolk and colleagues reported that QALYs lost due to seasonal influenza in Germany was 119 per 100,000 population [295] and 43.3 QALYs lost per 100,000 population in England in 2010/11 season, according to a previous study from UK [97]. This might be attributed to each study's setting (year, country, and so forth) because one study usually set its primary outcome any one of QALYs or DALYs, then it makes difficult for us to compare them directly when we consider the disease burden of influenza. As for COVID-19, the estimated disease burden in 2020 in Netherlands was 1,640 DALYs per 100,000 population [64], while 350.0 QALYs lost per 100,000 population [296], although this discrepancy can be attributed not to the difference between DALYs and QALYs, but to their methods to calculate QALYs because the latter one estimated the burden of fatal cases only. This means that the disease burden due to non-fatal COVID-19 cases accounts for a substantial part of the total disease burden caused by COVID-19. There are only a few previous studies that have estimated the disease burden due to COVID-19 at the population level using QALYs. It is also difficult to compare DALYs with QALYs directly in the context of COVID-19. Although this might be a limitation, if we assume that the value of DALYs and that of QALYs are interchangeable to some extent [267], these two ILIs can be regarded as the cause of about 20% of disease burden due to lower respiratory infection in Japan.

Whether this figure should be considered high or low might be controversial. However, we can justify the implementation of various NPIs in 2020 and 2021 because the QALYs lost due to COVID-19 was estimated as 114.0 QALYs per 100,000 population per year (Chapter 7), which is significantly greater than that of seasonal influenza (63.93 QALYs per 100,000 per year, mean of 2012/13, 2013/14, and 2014/15 season [126]). In other words, even with strict NPI implementation, such as the declaration of a state of emergency, the disease burden caused by COVID-19 could hardly be restrained to levels equivalent to twice those of seasonal influenza. An important question is whether the burden caused by the NPIs themselves (e.g., mental wellbeing from restrictions in social life) would be higher in Japan than in other countries [297]. One systematic review revealed that help-seeking behaviour had changed dramatically during the COVID-19 pandemic, and the delay in seeking help might have resulted in lost opportunities to link patients with appropriate treatment in many countries [298]. Although no evidence has been reported so far, it is not difficult to imagine that a similar situation occurring in Japan.

Compared with other developed countries, Japan had suffered from a smaller disease burden both due to influenza and COVID-19. For instance, QALYs lost caused by influenza in England and Wales was estimated at 109.94 per 100,000 population [299]. According to one of the latest studies from Germany, it was calculated as 210.35 QALYs lost per 100,000 population per year [300]. As for COVID-19, Japan had experienced a much smaller disease burden compared with other countries. McDonald and colleagues estimated it in Netherlands as 1,640 DALYs per 100,000 population in 2020, and Wyper and colleagues reported it in Scotland as about 1,800 DALYs per 100,000 population in the same year [64,274]. Despite differences in the unit of indicator (DALYs and QALYs), the disease burden experienced by Japanese society was significantly lower than that of other developed countries. For example, in

Germany and some other countries, the burden was compared to Netherlands and Scotland, however, estimates for all of these countries were still substantially higher than the estimate for Japan, which was 10 times smaller (114.0 QALYs lost per 100,000 population per year) [65,275,276].

Although the reasons for the lower burden of these two diseases in Japan compared to other countries are likely multifactorial, premature death is an important contributor, and we can compare CFRs to investigate this. Our findings showed that only 846.0 deaths per year were attributed to influenza during the three seasons from 2012/13 to 2014/15 [126], which is consistent with the official statistics of the Japanese government [162,301]. We estimated that we had 13,607,079 medically attended influenza cases per year in the same period, implying the CFR of seasonal influenza in Japan was only 0.0062%, while it was 0.028% and 0.25% in England and Wales and in Germany, respectively [299,300]. This difference may be partially explained by differences in the definition of death because we used the number of deaths directly associated with influenza, while the previous study used the number of influenza-associated deaths. Additionally, our data from Japan used the number of medically-attended influenza cases as the denominator, whereas the previous study from Germany used the number of inpatient cases. This may explain the large difference between the CFR in Japan and that in Germany. The relatively small difference between the CFR in Japan and that in England and Wales may be due to the difference in numerator. As deaths accounted for only 20.3% of the QALYs lost due to influenza in Japan, this difference may not result in a substantial difference.

However, the low CFR of COVID-19 in Japan should be noted. Only 17,615 deaths were recorded during 2020 and 2021, and the CFR was 1.02% (Chapter 7). Although this figure was somewhat higher than that of seasonal influenza, it was substantially lower than that of other countries (1.50%, 1.65%, 1.35%, and 1.37% in the US, Germany, Belgium, and the UK in the same period, respectively) and the world average (1.89% in the same period) [264]. As for the reporting of fatal cases, the Japanese government asked physicians to report all fatal cases with diagnosis of COVID-19 as deaths due to COVID-19, which means that it is more likely to be overestimated, than underestimated, an observation that was confirmed when we compared these death notifications to overall excess mortality in Japan in Chapter 7.

In addition, the low number of confirmed cases in Japan is likely to be another important factor explaining its lower disease burden. As mentioned above, 1.73 million confirmed cases were reported during 2020 and 2021. In the same period, US and the UK had 54.91 million and 12.94 confirmed cases, respectively [264]. In fact, despite many developed countries experiencing a decline in life expectancy during the 2019/20 season [302], life expectancy in Japan has reached an all-time high in 2020 (81.64 years for men and 87.74 years for women, respectively) [140].With regard to the reason why such a small number of cases had been confirmed in Japan, we may attribute it to the poor capacity of the COVID-19 diagnostic test in community at least in the early stage of the pandemic [303,304], then therefore the chance of underreporting might be greater than that in other countries. Nevertheless, we may consider that our NPIs and high adherence to them in the general population contributed to this low incidence. For example, the proportion of people wearing face coverings was extremely high throughout the pandemic [305], social contact behaviour in Japan changed drastically after the emergence of COVID-19 (Chapter 6), and so forth.

Furthermore, we have taken sufficient account of the disease burden of long-COVID sufficiently into consideration. We used the definition of “long-COVID” in the early phase of the pandemic, when cases with symptoms lasted more than four weeks [203], and therefore we emphasized its burden more seriously. Despite the high burden of long-COVID, the total burden due to COVID-19 in Japan was lower than that reported in previous studies.

Considering these findings, the Japanese countermeasures against COVID-19 could be considered a success, at least in view of health indicators, although these results do not prove causality. With smaller number of confirmed cases compared with that of a similar size country (the UK), a lower CFR and a lower disease burden, these indicators suggest that Japan may be doing well to mitigate the damage caused by COVID-19.

Nevertheless, at the same time, we may have to withhold the evaluation of our countermeasures against COVID-19 in a sense, because we have not yet sufficiently assessed their economic burden. In other words, we do not know whether these good results with regard to health indicators were really what we wanted or not, at the cost of great economic loss that we have recently experienced.

As described in Chapter 6, the frequency of social contact in Japan drastically decreased in 2021, despite the presence of large mass gathering events such as the Olympic Games (Chapter 6). It is easy to imagine that such a behavioural restriction should have had a significant negative impact on the Japanese economy. Indeed, according to the Cabinet Office Japan, the annual GDP growth rates for 2019 and 2020 were 0.3% and -4.8% respectively [306]. Inoue and Todo estimate that the economic loss of a one-month lockdown of Tokyo would be 27 trillion JPY, or 5.2% of the country's annual GDP [307].

To sum up, this thesis has shown that the disease burden due to COVID-19 in Japan during 2020 and 2021 was greater than that due to seasonal influenza, but less than that in other countries. It is possible that our NPIs against COVID-19 implemented during the study period might have a positive impact on health outcome, however, they should be evaluated in more detail, taking into account the economic loss caused by them. This will be discussed in more detail under "Future challenges".

10.2 Strengths and limitations

Though the current researches presented in this thesis had some strengths and added several novel insights to the field of infectious disease epidemiology, they also had some limitations that should be taken into account when interpreting their findings.

One of the main strengths of our research is that most of their main findings were the only ones from Japan. The methodologies applied to each chapter were not completely original ones and were derived from previous studies, and evidences in the field of infectious disease epidemiology and health economics was scarce in Japan. Our findings presented the disease burden of the emerging infectious disease which is one of the most important global health threats in Japan, in a comparable way and then allowed us to compare them with those of other ILIs and/or other countries. Without these findings, it may be difficult to make appropriate health policy decisions about COVID-19.

Additionally, our researches added value to Japanese society because they included some novel findings specific to Japan. For instance, the high proportion of MAI among seasonal influenza infection, RIDT examination, and antiviral prescription was very specific to Japan [67]. The disease burden caused by the isolation policy usually varies between countries because the duration and conditions of isolation differ between countries, so the results that take into account the situation in each country would be more favourable [99,175]. Consequently, our results became more reliable because they were based on the context of Japanese society.

Although this was not the intended outcome from the outset, and a result somewhat removed from the original aim (to assess the disease burden due to COVID-19), we found that large-scale mass gathering events such as the Olympic Games can be conducted under appropriate behavioural restrictions and circumstances (Chapter

7). We also updated the contact matrix based on the experience of the COVID-19 pandemic. These findings can contribute to the field of infectious disease epidemiology, as many modelling studies that can capture the transmission dynamics of infectious diseases require information on social contacts.

The methodological limitations of each study have already been discussed in the individual chapters. Nevertheless, the main arguments described in this chapter should also be interpreted with caution, taking these limitations into account. First, many of our findings are based on the Internet-based questionnaire survey [67,175,199] (and Chapter 7). Therefore, all subjects who participated in these surveys had basic internet skills, which led to a bias in the age distribution and educational level. In addition, some of these surveys included comparatively small number of samples, which may increase the uncertainty of the results, and we should be concerned about the representativeness of the data.

Second, the empirical data were often insufficient for a robust analysis. For example, in Chapter 3 we estimated the total burden of seasonal influenza and assessed the optimal vaccination policy against it [126]. As explained in that chapter, we had to make several assumptions where we could not obtain any data from Japanese surveillance systems or where there was no previous report from Japan. We used the vaccine efficacy from the previous systematic reviews or previous studies from other developed countries, assumed that the same proportion of the population was at high risk of severe disease, and defined the costs of hospitalised and fatal cases somewhat arbitrarily. These facts may affect the robustness of the results, although we conducted sensitivity analyses with wide range of parameter values.

Third, we estimated the disease burden due to COVID-19 without the burden caused by heavy pressure on the capacity of healthcare facilities. This may be more important in estimating the disease burden in Japan, because almost all COVID-19 cases had to be admitted to the designated (mostly tertiary) healthcare facilities, then the pressure on the capacity of the healthcare system may be greater than in other countries [187,243]. For instance, 37,187 patients were admitted at the time of 1st January 2021, but only 711 cases were classified as severe [280]. This suggests that healthcare professionals in Japan were busy managing mild cases. As a result of this case management policy, each local authority had to strictly prioritise the order in which COVID-19 cases were admitted to healthcare facilities, and additional disease burden might be generated [308–311].

Fourth, we did not consider the disease burden in 2022. The Omicron VOC has different characteristics from those of previous strains, especially in terms of infectivity and clinical severity [229,230,312,313]. The Japanese COVID-19 surveillance data do not include information on the virus strain of each case, so the proportion of the Omicron VOC among all cases is not available. Additionally, the frequency of long-COVID is likely to be different [314,315]. As a result, the disease burden of each case should be quite different between the Omicron VOC and previous strains, so we decided to limit our research period of interest to 2020 and 2021 only.

Fifth, we did not estimate a "counterfactual" scenario of COVID-19 during 2020 and 2021 in Japan. We did not include the estimate of disease burden due to COVID-19 in the counterfactual scenario under assumption of no NPIs during the study period in the current research plan, and this would be another future challenge that will be discussed in more detail in the next section.

10.3 Future challenges

As discussed in the previous sections, we have endeavoured to estimate the disease burden caused by two types of ILI, seasonal influenza and COVID-19. Although our findings added some novelty to the field of infectious disease epidemiology, there are still many future works that should be addressed.

First, the disease burden due to seasonal influenza should be updated. After the emergence of COVID-19, we have experienced two consecutive seasons with extremely low prevalence of seasonal influenza. Under such conditions, its disease burden must be lower and its optimal target for prioritised vaccination may change. This update will be an important contribution on determining which disease (e.g., seasonal influenza or COVID-19) should be prioritised in health policy decision making.

Second, we need to extend the study period in order to include the disease burden of the Omicron VOC. Due to the low CFR and low prevalence of long-COVID, the disease burden per case will be smaller, however, the number of confirmed cases in Japan has been rapidly increasing as of the end of September 2022. The cumulative number of confirmed cases in the UK and Japan at the time of 22nd September 2022 was 23.62 million and 20.91 million, respectively [264]. Although the disease burden during 2020 and 2021 in Japan was quite low compared to other countries, the results may be different if we include the burden in 2022.

Third, it would be better for us to estimate the disease burden due to COVID-19 in a “counterfactual” scenario. It is likely that NPIs such as the declaration of a state of emergency prevented a significant number of infections by reducing social contacts. By estimating the number of cases under the assumption of “no NPIs”, we can more accurately assess the effect of NPIs in Japan. As a result, we will be able to compare the impact of our NPIs on health indicators with their negative impact on the economy.

Last, the details of the information used in the current research project should be improved. For instance, we used vaccine efficacy for seasonal influenza derived from previous studies [126]. Obviously, it would be better to use empirical information specific to Japan. We tried to estimate the vaccine efficacy once, however, could not collect enough samples due to the change in prevalence caused by the emergence of COVID-19 [316]. We were not able to include information on the pressure on healthcare facilities when estimating the burden of COVID-19 and should try to quantify this burden in order to include it in the next time. We have other examples where there is room for quality improvement, and these will allow us to obtain more robust results if we succeed in updating these items.

10.4 Conclusion

The main objective of the thesis was to estimate the disease burden caused by COVID-19 and compare it with that of seasonal influenza. As a result, our findings revealed that the disease burden of COVID-19 in Japan during 2020 and 2021 was greater than that of seasonal influenza in the 2012/13 to 2014/15 seasons. In this context, it might be possible that strict NPIs implemented by the Japanese government such as declaration of an emergency state, had positive impact to mitigate the harm caused by this emerging infectious disease.

At the same time, we found that the disease burden due to COVID-19 in Japan appeared to be smaller than that in other countries, suggesting that Japanese countermeasures against COVID-19 could be considered a success, at least in terms of health outcomes.

Nevertheless, we have not sufficiently assessed the economic loss caused by these NPIs. Our results showed that Japanese contact behaviour changed after the emergence of COVID-19, and the frequency of social contact decreased drastically. This may indicate that we have suffered a great economic loss at the expense of reducing the disease burden. In this sense, the evaluation of our countermeasures against COVID-19 is not yet complete.

By addressing the future challenges left by our current researches, we will be able to evaluate our NPIs against COVID-19 more precisely, and this will contribute to make more appropriate health policy decision making in our society.

11. Summary

Disease burden provides a quantitative evaluation of “health”, that is necessary and useful for health policy decision making. Influenza-like illnesses (ILIs) are a source of substantial disease burden, then it is important for us to estimate their disease burden quantitatively to make more appropriate health policy decision making.

At present, COVID-19 seems one of the most important infectious diseases that we need to take action against. Therefore, we need to estimate the burden brought by COVID-19 precisely.

The aim of this thesis is to evaluate the disease burden caused by COVID-19 in Japan during the first two years of the pandemic (from the beginning of 2020 to the end of 2021) and compare it with that caused by seasonal influenza before the COVID-19 pandemic era. Through the process of assessing the disease burden due to seasonal influenza, we aim to evaluate the impact of societal factors specific to the Japanese society and the optimal vaccination policy for seasonal influenza that can best reduce the burden. We include the burden caused by isolation policy of COVID-19 and long-COVID in the estimation of the disease burden caused by COVID-19. Furthermore, we intend to quantify the behavioural change in social contact in this pandemic era for our future work.

Chapters 1 and 2 aimed to provide a quantitative assessment of the management of influenza-like illnesses (ILIs) in Japanese healthcare settings. 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 95.0% were treated with antivirals. The median quality-adjusted life-years (QALYs) 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). The influenza ILI group showed longer duration of absence from work (5 days, IQR 4–6 days) than the non-influenza ILI group (2 days, IQR 1–3days). 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.

In order to return to school after an influenza-related absence, most Japanese students are required to submit a recovery certificate. A cost analysis from a restricted societal perspective showed that the recovery certificate policy imposed an additional cost of 0.94 million USD per one million population, which was a substantial negative economic impact on the Japanese healthcare system and society from a restricted societal perspective.

In chapter 3, we assessed the total disease burden due to seasonal influenza and the optimal vaccination policy of seasonal influenza in Japan. We constructed a deterministic compartmental Susceptible-Exposed-Infectious-Recovered (SEIR) model with data from the 2012/13 to 2014/15 influenza seasons in Japan. Bayesian inference with Markov Chain Monte Carlo method was used for parameter estimation. Cost-effectiveness analyses were conducted from public health care payer's perspective. A scenario targeting children under 15 was expected to reduce the number of cases 6,382,345 compared to the current strategy. Totally, disease burden caused by seasonal influenza was estimated as 81,445.8 QALYs lost in total population of Japan (mean of 2012/13 - 14/15 season). Our model suggested that a vaccination programme which targets children under 15 is predicted to have much larger epidemiological impact than those targeting elderly.

In Chapters 4 to 7, we attempted to estimate the total disease burden due to COVID-19 during 2020 and 2021. In Chapter 4, we aimed to assess the differences between COVID-19 and other influenza like illnesses in the disease burden caused by isolation. Acute symptoms of outpatient COVID-19 and other ILIs lasted 17 (interquartile range [IQR] 9-32) and 7 (IQR 4-10) days, respectively. The length of isolation due to COVID-19 was 18 (IQR 10-33) days and that due to other ILIs was 7 (IQR 4-11) days, respectively. The monetary productivity loss of isolation due to COVID-19 was 1424.3 (IQR 825.6-2545.5) USD and that due to other ILIs was 606.1 (IQR 297.0-1090.9) USD, respectively. HRQoL at the time of the survey was lower in the COVID-19 group than in the "other ILIs" group (0.89 and 0.96, $p = 0.001$).

In chapter 5, we estimated the HRQoL of long-COVID. We conducted a cross sectional self-report questionnaire survey included 526 subjects. Among all, 349 participants reported no symptoms and 108 reported any symptoms at the time of the survey. The participants who reported any symptoms showed a lower average value on the EQ-VAS (69.9 vs 82.8, respectively) and on the EQ-5D-3L (0.85 vs 0.96, respectively) than those reporting no symptoms considering the average treatment effect of ongoing prolonged symptoms. Due to their long duration, long-COVID symptoms represent a substantial disease burden expressed in impact on health-related quality of life.

In Chapter 6, we aimed to update social contact data in Japan. The main objectives of this study are to study mixing patterns in the context of the COVID-19 pandemic, and to compare the contact patterns during and after mass gathering events like the 2020 Olympic Games, which were held in 2021. The median number of contacts per day was 3 (interquartile range (IQR) = 1-6). The occurrence of the Olympic Games and the temporal source of the data (weekday or weekend) did not change the results substantially. The frequency of social contact in Japan did not change substantially during the Tokyo Olympic Games. However, the baseline frequency of social mixing declined versus those collected in 2011.

In Chapter 7, we estimated the total disease burden due to COVID-19 in Japan during 2020-2021. QALYs lost due to COVID-19 was estimated as 286,781.7 for two years, 114.0 QALYs per 100,000 population per year. 71.3% of them were explained by the burden derived from deaths.

The main objective of the thesis was to estimate the disease burden caused by COVID-19 and compare it with that of seasonal influenza. As a result, our findings revealed that the disease burden of COVID-19 in Japan during 2020 and 2021 was larger than that of seasonal influenza in the 2012/13 to 2014/15 seasons. In this context, we might say that strict NPIs implemented by the Japanese government such as declaration of an emergency state had positive impact to mitigate the harm caused by this emerging infectious disease.

At the same time, we found that the disease burden due to COVID-19 in Japan was obviously smaller than that in other countries. this suggested that Japanese countermeasures against COVID-19 could be regarded as a success, at least in terms of health outcome.

Nevertheless, we have not assessed the economic loss caused by these NPIs sufficiently. Our findings showed that Japanese contact behaviour changed after the emergence of COVID-19, and the frequency of social contact decreased drastically. This may indicate that we have suffered a great economic loss at the expense of reducing the disease burden. In this sense, the evaluation of our countermeasures against COVID-19 is not yet complete.

By addressing the future challenges our current research left, we will be able to evaluate our NPIs against COVID-19 more precisely, and this will contribute to make more appropriate health policy decision making in our society.

12. Samenvatting

Ziektelast biedt een kwantitatieve evaluatie van "gezondheid", die noodzakelijk en nuttig is voor de besluitvorming inzake gezondheidsbeleid. Influenza-achtige ziekten (ILI's) zijn een bron van aanzienlijke ziektelast, en daarom is het belangrijk dat wij de ziektelast ervan kwantitatief ramen om tot een adequatere besluitvorming inzake het gezondheidsbeleid te komen.

Momenteel lijkt COVID-19 een van de belangrijkste infectieziekten waartegen we moeten optreden. Daarom moeten wij de door COVID-19 veroorzaakte last nauwkeurig schatten.

Het doel van dit proefschrift is het evalueren van de ziektelast veroorzaakt door COVID-19 in Japan tijdens de eerste twee jaar van de pandemie (van begin 2020 tot eind 2021) en deze te vergelijken met de ziektelast veroorzaakt door seizoensinfluenza vóór het tijdperk van de COVID-19 pandemie.

Door de ziektelast als gevolg van seizoensinfluenza te beoordelen, willen wij de impact evalueren van maatschappelijke factoren die specifiek zijn voor de Japanse samenleving en het optimale vaccinatiebeleid voor seizoensinfluenza waarmee de last het best kan worden verminderd. Bij de schatting van de ziektelast ten gevolge van COVID-19 en lang-COVID nemen wij de door het isolatiebeleid veroorzaakte last mee. Voorts zijn wij van plan de gedragsverandering in sociale contacten in dit pandemische tijdperk te kwantificeren voor ons toekomstige werk.

De hoofdstukken 1 en 2 waren gericht op een kwantitatieve beoordeling van het beheer van influenza-achtige ziekten (ILI's) in Japanse zorginstellingen. In totaal hadden 261 van de 600 (43,5%) deelnemers ten minste één episode van influenza-achtige ziekte in januari 2019. Hiervan bezochten 194 (75,5%) zorginstellingen, 167 (86,1%) binnen 2 dagen na het begin van de symptomen. In totaal kregen 169 van de 191 (88,5%) een snelle influenzadiagnosetest en 101 werden gediagnosticeerd met influenza, waarvan 95,0% werd behandeld met antivirale middelen. Het mediane aantal verloren kwaliteitsgecorrigeerde levensjaren (QALY's) bedroeg 0,0055 (interkwartielbereik, IQR 0,0040-0,0072) en het mediane arbeidsverzuim voor één episode van influenza-achtige ziekte bedroeg 2 dagen (IQR 1-5 dagen). De influenza ILI-groep vertoonde een langere verzuimduur (5 dagen, IQR 4-6 dagen) dan de niet-influenza ILI-groep (2 dagen, IQR 1-3 dagen). In Japan bezoeken de meeste mensen met een griepachtige ziekte snel na het optreden van de symptomen de gezondheidszorg en krijgen een diagnostische test. Degenen met influenza worden gewoonlijk behandeld met antivirale middelen. Het ziekteverzuim was bij influenza langer dan bij andere soortgelijke ziekten.Om na een griepgerelateerde afwezigheid weer naar school te kunnen gaan, moeten de meeste Japanse studenten een herstelcertificaat overleggen. Uit een kostenanalyse vanuit een beperkt maatschappelijk perspectief bleek dat het beleid inzake het herstelcertificaat een extra kostenpost van 0,94 miljoen USD per miljoen inwoners met zich meebracht, wat vanuit een beperkt maatschappelijk perspectief een aanzienlijke negatieve economische impact op de Japanse gezondheidszorg en de samenleving betekende.

In hoofdstuk 3 evalueerden we de totale ziektelast als gevolg van seizoensinfluenza en het optimale vaccinatiebeleid voor seizoensinfluenza in Japan. We construeerden een deterministisch compartimentaal Susceptible-Exposed-Infectious-Recovered (SEIR) model met gegevens van de griepseizoenen 2012/13 tot 2014/15 in Japan. Bayesiaanse inferentie met Markov Chain Monte Carlo-methode werd gebruikt voor parameterschatting. Kosteneffectiviteitsanalyses werden uitgevoerd vanuit het perspectief van de publieke gezondheidszorgbetaler. Een scenario gericht op kinderen jonger dan 15 jaar zou naar verwachting het aantal gevallen met 6.382.345 verminderen in vergelijking met de huidige strategie. De totale ziektelast als gevolg van seizoensinfluenza werd geschat op 81.445,8 verloren QALY's voor de totale bevolking van Japan (gemiddelde van het seizoen 2012/13 - 14/15). Ons model suggereerde dat een vaccinatieprogramma dat gericht is op kinderen onder de 15 jaar naar verwachting een veel grotere epidemiologische impact zal hebben dan programma's die gericht zijn op ouderen.

In de hoofdstukken 4 tot en met 7 hebben wij getracht de totale ziektelast ten gevolge van COVID-19 in 2020 en 2021 te schatten. In hoofdstuk 4 hebben wij getracht de verschillen tussen COVID-19 en andere griepachtige ziekten in de ziektelast door isolatie te beoordelen. De acute symptomen van poliklinische COVID-19 en andere ILI's duurden respectievelijk 17 (interkwartielbereik [IQR] 9-

32) en 7 (IQR 4-10) dagen. De duur van de isolatie als gevolg van COVID-19 was respectievelijk 18 (IQR 10-33) dagen en die als gevolg van andere ILI's 7 (IQR 4-11) dagen. Het monetaire productiviteitsverlies van isolatie als gevolg van COVID-19 was respectievelijk 1424,3 (IQR 825,6-2545,5) USD en dat als gevolg van andere ILI's 606,1 (IQR 297,0-1090,9) USD. De HRQoL ten tijde van de enquête was lager in de COVID-19-groep dan in de "andere ILI's"-groep (0,89 en 0,96, p = 0,001).

In hoofdstuk 5 schatten we de HRQoL van lange-COVID. Wij voerden een cross-sectioneel zelfrapportagevragenlijstonderzoek uit waaraan 526 proefpersonen deelnamen. Van alle deelnemers meldden 349 geen symptomen en 108 enige symptomen ten tijde van het onderzoek. De deelnemers die symptomen meldden, vertoonden een lagere gemiddelde waarde op de EQ-VAS (respectievelijk 69,9 vs 82,8) en op de EQ-5D-3L (respectievelijk 0,85 vs 0,96) dan degenen die geen symptomen meldden, rekening houdend met het gemiddelde behandelingseffect van aanhoudende langdurige symptomen. Wegens hun lange duur vertegenwoordigen langdurige COVID-symptomen een aanzienlijke ziektelast, uitgedrukt in impact op de gezondheidsgerelateerde levenskwaliteit.In hoofdstuk 6 hebben wij de gegevens over sociale contacten in Japan geactualiseerd. De belangrijkste doelstellingen van deze studie zijn het bestuderen van mengpatronen in de context van de COVID-19 pandemie, en het vergelijken van de contactpatronen tijdens en na massabijeenkomsten zoals de Olympische Spelen van 2020, die in 2021 werden gehouden. Het mediane aantal contacten per dag was 3 (interkwartielbereik (IQR) =

1-6). Het plaatsvinden van de Olympische Spelen en de temporele bron van de gegevens (weekdag of weekend) veranderden de resultaten niet wezenlijk. De frequentie van sociale contacten in Japan veranderde niet wezenlijk tijdens de Olympische Spelen in Tokio. De basisfrequentie van sociale vermenging daalde echter ten opzichte van de in 2011 verzamelde gegevens.

In hoofdstuk 7 schatten we de totale ziektelast als gevolg van COVID-19 in Japan in 2020-2021. Het verlies aan QALY's ten gevolge van COVID-19 werd geschat op 286.781,7 voor twee jaar, 114,0 QALY's per 100.000 inwoners per jaar. 71,3% daarvan werd verklaard door de last als gevolg van sterfgevallen. Het hoofddoel van het proefschrift was de ziektelast veroorzaakt door COVID-19 te schatten en te vergelijken met die van seizoensgriep. Uit onze bevindingen bleek dat de ziektelast van COVID-19 in Japan in 2020 en 2021 groter was dan die van seizoensinfluenza in de seizoenen 2012/13 tot 2014/15. In dit verband kunnen we stellen dat de strenge NPI's die door de Japanse regering worden toegepast, zoals het uitroepen van een noodtoestand, een positief effect hebben gehad om de schade door deze opkomende infectieziekte te beperken.

Tegelijkertijd vonden wij dat de ziektelast als gevolg van COVID-19 in Japan duidelijk kleiner was dan in andere landen. Dit suggereerde dat de Japanse tegenmaatregelen tegen COVID-19 als een succes kunnen worden beschouwd, althans wat de gezondheidsresultaten betreft.

Niettemin hebben wij het economische verlies als gevolg van deze NPI's onvoldoende geëvalueerd. Uit onze bevindingen bleek dat het Japanse contactgedrag na het verschijnen van COVID-19 veranderde en dat de frequentie van sociale contacten drastisch afnam. Dit kan erop wijzen dat wij een groot economisch verlies hebben geleden ten koste van de vermindering van de ziektelast. In die zin is de evaluatie van onze tegenmaatregelen tegen COVID-19 nog niet voltooid.

Door de toekomstige uitdagingen aan te gaan die ons huidige onderzoek nog laat, zullen wij onze NPI's tegen COVID-19 nauwkeuriger kunnen evalueren, en dit zal bijdragen tot een adequatere besluitvorming inzake het gezondheidsbeleid in onze samenleving.

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14. Curriculum Vitae

Shinya Tsuzuki is a researcher at National Center for Global Health and Medicine, Japan. He completed his medical training at Hokkaido University and after worked as a clinical paediatrician, obtained his Master degree at London School of Economics and Political Science (MSc Health, Population and Society).
He was dispatched to Public Health England from 2016 to 2017 as a liaison officer of Ministry of Health, Labour and Welfare Japan and took up the current position in 2019.
At present he leads several research projects related to infectious disease epidemiology, such as COVID-19 epidemics, quantitative evaluation of vaccination policy in Japan, disease burden of antimicrobial resistance, and so forth. He has published a large number of articles in peer reviewed journals and is currently working as an academic editor of *Infectious Diseases and Therapy*, *PLOS ONE,* and *PeerJ*.
He initiated his PhD programme in January 2019, under supervision of Professor Philippe Beutels.

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15. List of scientific outputs related to the thesis

Peer-reviewed articles

1. **<u>Tsuzuki S</u>***, Asai Y, Ibuka Y, Nakaya T, Ohmagari N, Hens N, Beutels P. Social contact patterns in Japan in the COVID-19 pandemic during and after the Tokyo Olympic Games *J Glob Health*. 2022 Sep.
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Conference presentations

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Appendix

Chapter 3

Supplementary information 1: Tables

Table S3-1. Basic characteristics of people registered with NEO MARKETING INC.

Table S3-2. Number of missing values in the original data

Table S3-3. Difference in outcomes between the two groups after propensity score matching with complete data only

Table S3-4. Difference in outcomes between the two groups after inverse probability-weighted propensity score analysis

Table S3-1. Basic characteristics of people registered with NEO MARKETING INC.

Variable	Number (Percentage) or median (IQR)	
Male	52.9%	
Age (year)	<30	9.2%
	30s	17.4%
	40s	26.2%
	50s	25.0%
	60s	16.0%
	>70	6.2%
Marital status	Married	51.4%
	Unmarried	43.3%
	Widowed	5.3%
Having children	41.7%	
Income level of household	< 50,000 USD/year	56.7%
	50,000 USD/year < < 100,000 USD/year	25.4%
	> 100,000 USD/year	10.5%
	Unknown	7.4%

USD: US dollars, 1 USD = 110 Japanese Yen

Table S3-2. Number of missing values in the original data

Variable	Number of missing values (%)
Number of household members	**0**
Sex	**3 (1.5%)**
Age	**0**
High-risk group	**0**
Smoker	**0**
Day of healthcare facility visit (days from symptom onset)	**5 (2.5%)**
Patients examined by RIDT	**8 (4.0%)**
Treated by antivirals	**86 (43.0%)**
Vaccinated for seasonal influenza	**7 (3.5%)**
Income level	**22 (11.0%)**
Education level of householder	**0**
Duration of symptoms (days)	**0**
QOL during symptomatic period	**0**
QALYs lost per episode	**0**
Duration of absenteeism (days)	**0**

QOL: quality of life, QALYs: quality-adjusted life-years, RIDT: rapid influenza diagnostic test

Table S3-3. Difference in outcomes between the two groups after propensity score matching with complete data only

Outcome	Estimate	SE	*p*-value
QOL score			
Intercept	0.666	0.0346	< 0.001
Influenza group	0.0443	0.0489	0.374
QALYs lost			
Intercept	0.00567	0.00127	< 0.001
Influenza group	0.000419	0.00179	0.817
Duration of symptoms			
Intercept	2.731	0.548	< 0.001
Influenza group	-0.192	0.774	0.806
Duration of absenteeism			
Intercept	2.692	0.502	< 0.001
Influenza group	2.077	0.710	0.00739

QOL: quality of life, QALYs: quality-adjusted life-years, SE: standard error

Table S3-4. Differences in outcomes between the two groups after inverse probability-weighted propensity score analysis

Outcome	Estimate	SE	*p*-value
QOL score			
Intercept	**0.688**	**0.0134**	**< 0.001**
Influenza group	**-0.0108**	**0.0192**	**0.574**
QALYs lost			
Intercept	**0.00392**	**0.000360**	**< 0.001**
Influenza group	**0.00123**	**0.000493**	**0.0140**
Duration of symptoms			
Intercept	**2.156**	**0.196**	**< 0.001**
Influenza group	**0.600**	**0.263**	**0.0248**
Duration of absenteeism			
Intercept	**2.112**	**0.197**	**< 0.001**
Influenza group	**2.382**	**0.339**	**< 0.001**

QOL: quality of life, QALYs: quality-adjusted life-ears, SE: standard error

Supplementary information 2: English translation of the questionnaire

This is a translation of the original Japanese questionnaire used for the survey. Responders answer all questions through an online system.

- Please answer your sex
- Please answer your age
- Please answer prefecture you live in
- How many people does your family have?
- Please answer the relationship between you and each your family member.
- Within a month, did you or your family member(s) have symptoms such as fever >38°C and cough? Please specify the family member(s) who had the symptoms.
- Please answer the age of your family member(s).
- Does the person who had fever and cough have any past history shown below?
  - Asthma
  - Allergic rhinitis
  - Atopic dermatitis
  - Neurologic disease (Developmental retardation, cerebral paralysis, etc.)

- Chronic lung diseases (COPD, etc.)
- Cardiac diseases (congenital heart diseases, heart failure, myocardial infarction, angina, etc.)
- Diabetes
- Renal diseases (diabetic nephropathy, chronic glomerulonephritis, etc.)
- Liver diseases (chronic hepatitis, etc.)
- Metabolic diseases (Phenylketonuria, methylmalonic acidemia, etc.)
- Immunodeficiency (HIV/AIDS, malignant tumour [cancer], etc.)
- Pregnancy (when you had fever and cough)
- Other diseases

- Please answer the person who smokes in your family (if there is).
- How long did your and/or your family member's symptoms continue?
- How do you think about the source of infection which caused your and/or your family member's symptoms?
    - Someone in school
    - Someone in workplace
    - Someone in family
    - Public place where people gather (parks, event sites, etc.)
    - Others
    - Do not know
- When you and/or your family member(s) had fever and symptoms, do you

and/or your family member(s) visit any healthcare facility?

- If no, do you and/or your family member(s) use any drug during having symptoms?
- If you and/or your family member(s) use any drug, please answer the name of the drug.
- If you and/or your family member(s) visited a health facility, what kind of facility?
  - Primary care physician
  - Public general hospital
  - Private general hospital
  - University hospital or national center hospital
  - Do not know
- What was the diagnosis of you and/or your family member(s)?
  - Common cold
  - Bronchitis
  - Pneumonia
  - Otitis media
  - Influenza A
  - Influenza B
  - RS virus infection
  - Adenovirus infection

- Group A streptococcus infection
- Mycoplasma infection
- Pertussis
- Others (please specify)

- Please answer the name of drug prescribed when you and/or your family member(s) visited a healthcare facility.
- When did you and/or your family member(s) visited a healthcare facility after symptoms occurred?
- When you and/or your family member(s) visited a healthcare facility, were you and/or your family member(s) examined by influenza diagnostic test?
- Did you and/or your family member(s) admit due to these symptoms?
- How long did you and/or your family member(s) stay in the hospital? What was the diagnosis?
- When visited a healthcare facility, how much was the transportation cost?
- When visited a healthcare facility, how much did you and/or your family member(s) pay to the facility?
- When visited a healthcare facility, how much did you and/or your family member(s) pay to the pharmacy?
- How many days did you and/or your family member(s) take sick leave due to the symptoms?
- How many days did you and/or your family member(s) take nursing care leave

due to other family member's symptoms?

- Did you and/or your family member(s) who had the symptoms take influenza vaccine within six months?
- If your family member(s) is/are under 13 years old, did he/she take second dose of influenza vaccine?
- How much did the vaccine cost?
- When did you and/or your family member(s) take vaccine?

[Next, the questionnaire included SF-12v2 Standard, Japanese questionnaire (SF-12v2® Health Survey © 1994, 2002, 2009 Quality Metric Incorporated, Medical Outcomes Trust and Shunichi Fukuhara. All rights reserved). Permission is required to access the original version]

- Please answer your household income.
- Please answer your and your partner's profession.
- Please answer your education level.
- Please answer your postcode.

Chapter 5

Supplementary information

Table S5-1. The estimated total number of medically attended influenza in each season

Table S5-2. The details of vaccination coverage for each age group, each scenario in 2012/13 season

Table S5-3. Parameters for the cost-effectiveness analysis

Table S5-4. Vaccine efficacy for sensitivity analysis

Table S5-5. Details of model parameters

Table S5-6. Susceptibility of each age group population to each influenza strain

Table S5-7. Assumed vaccine efficacy and probability of severe outcome, proportion of high-risk population

Table S5-8. Estimated values of each strain's R_0 in each year

Table S5-1. The estimated total number of medically attended influenza in each season

Age group	2012/13	2013/14	2014/15
<5	1,436,400	1,879,800	1,447,000
5-9	1,795,500	3,470,400	2,459,900
10-14	1,316,700	2,169,000	2,170,500
15-19	837,900	723,000	868,200
20-29	1,197,000	1,012,200	1,447,000
30-39	1,556,100	1,735,200	1,591,700
40-49	1,316,700	1,446,000	1,591,700
50-59	957,600	867,600	1,012,900
60-69	718,200	578,400	723,500
70+	837,900	578,400	1,157,600
Total	11,970,000	14,460,000	14,470,000

Table S5-2. The details of vaccination coverage for each age group, each scenario in 2012/13 season

Age group	<5	5-9	10-14	15-19	20-29	30-39	40-49	50-59	60-69	70+
Real Coverage*	42.2%	66.8%	56.6%	48.2%	49.3%	56.1%	55.4%	48.8%	38.7%	56.3%
Scenario 1 (0-4)	90%	66.8%	56.6%	48.2%	49.3%	56.1%	55.4%	48.8%	38.7%	56.3%
Scenario 2 (0-9)	90%	90%	56.6%	48.2%	49.3%	56.1%	55.4%	48.4%	38.7%	56.3%
Scenario 3 (0-14)	90%	90%	90%	48.2%	49.3%	56.1%	55.4%	48.8%	38.7%	56.3%
Scenario 4 (50+)	42.2%	66.8%	56.6%	48.2%	49.3%	56.1%	55.4%	90%	90%	90%
Scenario 5 (60+)	42.2%	66.8%	56.6%	48.2%	49.3%	56.1%	55.4%	48.8%	90%	90%
Scenario 6 (70+)	42.2%	66.8%	56.6%	48.2%	49.3%	56.1%	55.4%	48.8%	38.7%	90%

Table S5-3. Parameters for the cost-effectiveness analysis

Parameter	Value	SD*	Form of distribution	Reference
Cost for vaccination	**38.0 USD**	**3.8**	**Gamma**	[159]
Cost per outpatient	**135.0 USD**	**13.5**	**Gamma**	[159]
Cost per hospitalization	**2,428.0 USD**	**242.8**	**Gamma**	[159]
Cost per death	**9,180.0 USD**	**918.0**	**Gamma**	[159]
Discount rate	**0.02**	**0.03**	**Normal**	[159]
QALYs lost by outpatient influenza case (low risk)	**0.0043**	**0.00043**	**Gamma**	[96]
QALYs lost by outpatient influenza case	**0.0075**	**0.00075**	**Gamma**	[96]
QALYs lost by inpatient influenza case	**0.008**	**0.0008**	**Gamma**	[96]

***SD: standard deviation**

Table S5-4. Vaccine efficacy for sensitivity analysis [161]

Year	Age group	Vaccine efficacy
2012/13	**0-59**	**0.4**
	60+	**0.49**
2013/14	**0-59**	**0.37**
	60+	**0.46**
2014/15	**0-59**	**0.15**
	60+	**0.18**

Table S5-5. Details of model parameters

Posterior distribution of parameter value (Median, 95%CI*)			
	2012	2013	2014
initial number of infected in H1N1 (10 to the Nth power)	2.482 (2.414, 2.551)	-5.941 (-6.141, -5.766)	1.919 (1.807, 2.013)
transmissibility in H1N1	0.0244 (0.0236, 0.0254)	0.0502 (0.0492, 0.0516)	0.0342 (0.0334, 0.0349)
initial number of infected in H3N2 (10 to the Nth power)	-3.942 (-4.032, -3.862)	0.518 (0.415, 0.627)	-0.625 (-0.658, -0.592)
transmissibility in H3N2	0.0476 (0.0466, 0.0491)	0.0351 (0.0346, 0.0360)	0.0618 (0.0612, 0.0624)
initial number of infected in BV (10 to the Nth power)	-2.359 (-2.721, -2.021)	-1.525 (-1.716, -1.328)	-0.838 (-1.157, -0.516)
transmissibility in BV	0.0597 (0.0544, 0.0630)	0.0443 (0.0412, 0.0464)	0.0487 (0.0439, 0.0526)
initial number of infected in BY (10 to the Nth power)	-3.403 (-3.710, -3.109)	-3.450 (-3.617, -3.291)	-2.313 (-2.731, -1.940)
transmissibility in BY	0.0545 (0.0497, 0.0575)	0.0456 (0.0431, 0.0476)	0.0607 (0.0547, 0.0655)
rate of medical attendance in age 0-4	0.248 (0.242, 0.254)	0.178 (0.175, 0.181)	0.387 (0.379, 0.396)
rate of medical attendance in age 5-19	0.664 (0.648, 0.669)	0.664 (0.650, 0.669)	0.669 (0.667, 0.669)
rate of medical attendance in age 20-59	0.348 (0.336, 0.361)	0.198 (0.191, 0.205)	0.212 (0.209, 0.215)
rate of medical attendance in age 60+	0.270 (0.0250, 0.0286)	0.115 (0.107, 0.121)	0.113 (0.109, 0.117)
latent period of A strains (days)	1.986 (1.927, 2.0)	1.871 (1.741, 1.985)	1.997 (1.984, 2.0)

infectious period of A strains (days)	**4.000 (3.849, 4.095)**	**4.070 (3.958, 4.099)**	**4.095 (4.075, 4.10)**
latent period of B strains (days)	**1.055 (0.889, 1.216)**	**1.961 (1.828, 2.087)**	**1.250 (0.994, 1.464)**
infectious period of B strains (days)	**1.903 (1.804, 2.087)**	**3.092 (2.942, 3.280)**	**1.953 (1.809, 2.165)**

***Credible interval**

Table S5-6. Susceptibility of each age group population to each influenza strain [127]

year	2012			
age group	**H1N1**	**H3N2**	**B Victoria**	**B Yamagata**
0-4	**0.88**	**0.81**	**0.83**	**0.92**
5-19	**0.38**	**0.53**	**0.61**	**0.71**
20-69	**0.69**	**0.71**	**0.63**	**0.77**
70+	**0.69**	**0.73**	**0.73**	**0.85**
year	**2013**			
age group	**H1N1**	**H3N2**	**B Victoria**	**B Yamagata**
0-4	**0.95**	**0.81**	**0.83**	**0.87**
5-19	**0.40**	**0.38**	**0.65**	**0.79**
20-69	**0.71**	**0.70**	**0.66**	**0.7**
70+	**0.83**	**0.67**	**1.0**	**0.58**
year	**2014**			
age group	**H1N1**	**H3N2**	**B Victoria**	**B Yamagata**
0-4	**0.83**	**0.93**	**0.88**	**0.87**
5-19	**0.35**	**0.26**	**0.64**	**0.58**
20-69	**0.58**	**0.58**	**0.71**	**0.53**
70+	**0.65**	**0.50**	**0.75**	**0.75**

Table S5-7. Assumed vaccine efficacy and probability of severe outcome, proportion of high-risk population

Age group	Vaccine efficacy (95% CI*) [86,317,318]	Number of hospital admission [160]**	Number of Death [160]***	Proportion of high-risk group [141]
0-4	0.45 (0.41-0.49)	1.91 (1.72)	0.07 (2.70)	0.060
5-9	0.45 (0.41-0.49)	1.35 (7.70)	0.03 (1.16)	0.060
10-14	0.45 (0.41-0.49)	0.53 (3.02)	0.01 (0.39)	0.060
15-20	0.61 (0.313-0.778)	0.20 (0.98)	0.01 (0.07)	0.142
20-29	0.61 (0.313-0.778)	0.20 (0.98)	0.05 (0.33)	0.142
30-39	0.61 (0.313-0.778)	0.26 (1.27)	0.09 (0.59)	0.142
40-49	0.61 (0.313-0.778)	0.41 (1.85)	0.31 (2.05)	0.142
50-59	0.2 (0-0.427)	1.03 (4.64)	0.66 (4.36)	0.142
60-69	0.2 (0-0.427)	2.78 (5.00)	1.47 (3.38)	0.471
70+	0.2 (0-0.427)	5.21 (9.38)	2.82 (6.49)	0.471

***Confidence Interval**

**** per 1,000 cases, values in brackets represent that of high-risk population** [135].

***** per 10,000 cases, values in brackets represent that of high-risk population** [135].

Table S5-8. Estimated values of each strain's R_0 in each year

Year/strain	H1N1	H3N2	B Victoria	B Yamagata
2012	1.767 (1.761-1.774)	3.455 (3.442-3.470)	2.061 (2.056-2.068)	1.882 (1.876-1.888)
2013	3.70 (3.679-3.725)	2.592 (2.581-2.603)	2.486 (2.471-2.499)	2.557 (2.543-2.572)
2014	2.543 (2.530-2.557)	4.589 (4.572-4.609)	1.726 (1.721-1.731)	2.153 (2.146-2.159)

***These numbers in the table represent the median value of 1,000 simulations and numbers in the brackets represent 1st quartile and 3rd quartile.**

Chapter 8

Supplementary information 1: English version of the questionnaire

As a preliminary step, you will be asked to view the page on explanation and consent for the study, and only monitors who click on the "I agree" button will be able to reach the original questionnaire.

First, let me ask you about yourself.

1. Please tell us your age.

2. Please tell us your gender.

3-a. Please indicate your current prefecture of residence.

3-b. Please indicate your current municipality of residence.

4. Do you currently have a job that pays an income?

(a) Yes (full-time)

(b) Yes (part-time)

(c) No (looking for a job)

(d) No (currently in school, retired, full-time housewife/husband, etc.)

5. If you answered "Yes (full-time)" or "Yes (part-time)" to the previous question

Please select one main item regarding the contents of your job (occupation).

(a) Management (company director, manager, etc.)

(b) Professional/technical (doctor, technician, teacher, etc.)

(c) Administrative (clerks, receptionists, etc.)

(d) Sales (salespersons, sales clerks, etc.)

(e) Service (beauticians, cooks, nursing staff, etc.)

(f) Security (police officers, security guards, etc.)

(k) Agriculture, forestry and fishery (agriculture, forestry, fishery workers, etc.)

(k) Production, construction, transportation (assembly workers, drivers, cleaners, etc.)

(k) Unclassifiable/other than the above

6. Please indicate the school you last graduated from.

(a) Junior high school

(b) High school, special training school

(c) Junior college, vocational school, university/graduate school (science, engineering, medicine, dentistry, agriculture, biology)

(d) Junior colleges, vocational schools, universities and graduate schools (faculties other than the above)

(e) Other

7-a. Please indicate the number of family members living with you.

7-b. Please indicate the age of your family members living with you.

8-a. In your profession, do you routinely converse with an unspecified number of people?

8-b. On average, how many people (customers, patients, students, etc.) do you talk to in a day (from 0:00 to 24:00) in the course of your work?

9. Approximately which of the following age groups do the people you converse with on the job belong to?

a. 0-4

b. 5-9

c. 10-14

d. 15-19

e. 20-29

f. 30-39

g. 40-49

h. 50-59

i. 60-69

j. 70-79

k. 80-89

l. 90 and over

10. We would like to ask you about people with whom you had conversations outside of work yesterday.

First, which of the following dates is 'yesterday' for you?

(You can choose one of between 3^{rd} to 23^{rd} August)

11. How many people did you have face-to-face conversations with between midnight and midnight yesterday?

12. Approximately which of the following age groups do the people you converse with outside the job belong to? Please answer for each person.

a. 0-4

b. 5-9

c. 10-14

d. 15-19

e. 20-29

f. 30-39

g. 40-49

h. 50-59

i. 60-69

j. 70-79

k. 80-89

l. 90 and over

13. Was yesterday a telework or online meeting, study or lecture day?

14. Yesterday, did you watch the Tokyo Olympic Games at your venue?

15. Yesterday, did you watch the Tokyo Olympic Games in a sports bar or other place where an unspecified number of people gathered (other than a venue where you could watch the games)?

16. Before the outbreak of COVID-19, how many times a month did you have the opportunity to meet or drink with others?

17. After the outbreak of COVID-19, how many times a month did you have the opportunity to meet or drink with others?

18. Do you currently commute to work or school?

19. How often do you currently telework, hold online meetings, study/lectures, etc.?

Please indicate how many days per week.

20. Now we would like to ask you about your minor child (or youngest child if you have more than one) who live with you.

Please indicate the sex and age of your child

21. Does your child use group childcare such as nursery school or kindergarten?

22. Please indicate the approximate number of children in the class of your child.

23. Does your child attend school?

24. Please indicate the approximate number of children in the class of your child.

25. How many people did your child have face-to-face conversations with between midnight and midnight yesterday?

26. Approximately which of the following age groups do the people your child converse with belong to? Please answer for each person.

a. 0-4

b. 5-9

c. 10-14

d. 15-19

e. 20-29

f. 30-39

g. 40-49

h. 50-59

i. 60-69

j. 70-79

k. 80-89

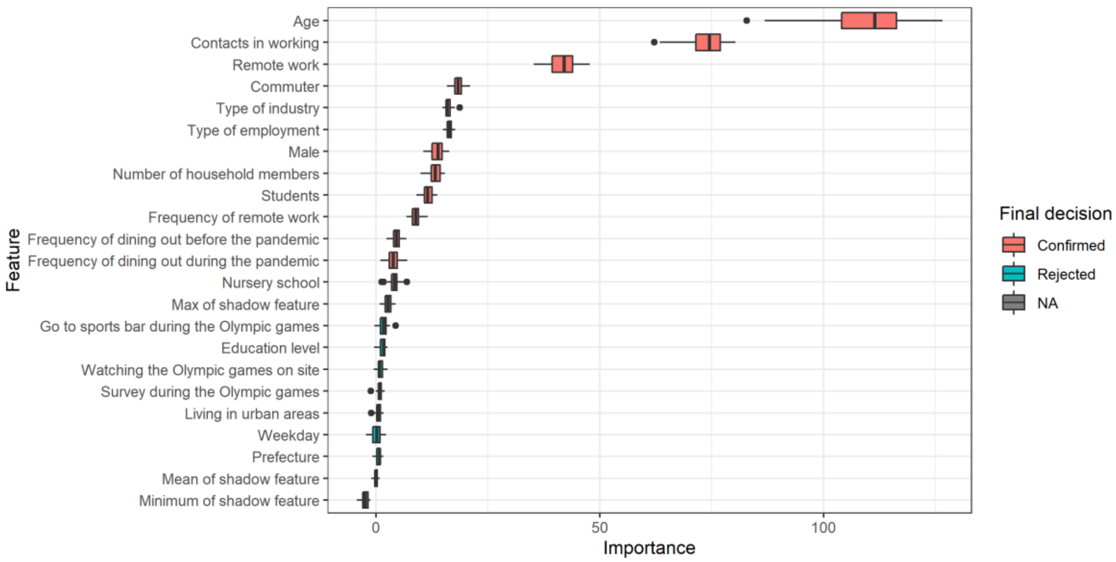
l. 90 and over

Supplementary information 2: methodological details

The Boruta algorithm consists of following steps [252];

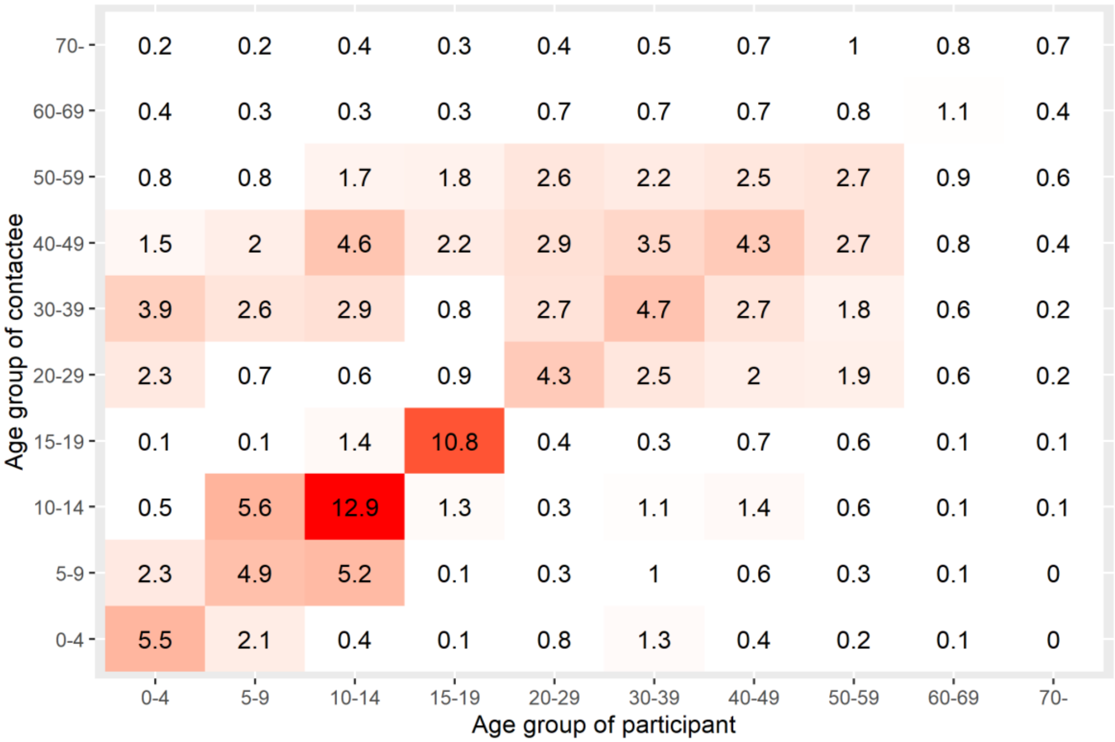
1. Extend the information system by adding copies of all variables (the information system is always extended by at least 5 shadow attributes, even if the number of attributes in the original set is lower than 5).
2. Shuffle the added attributes to remove their correlations with the response.
3. Run a random forest prediction on the extended information system and gather the Z scores computed.
4. Find the maximum Z score among shadow attributes (MZSA), and then assign a hit to every attribute that scored better than MZSA.
5. For each attribute with undetermined importance perform a two-sided test of equality with the MZSA.
6. Deem the attributes which have importance significantly lower than MZSA as ‘unimportant’ and permanently remove them from the information system.
7. Deem the attributes which have importance significantly higher than MZSA as ‘important’.
8. Remove all shadow attributes.
9. Repeat the procedure until the importance is assigned for all the attributes, or the algorithm has reached the previously set limit of the random forest runs.

Figure S8-1. Feature importance of variables included in the random forest model



Feature importance was evaluated by mean squared error.

Figure S8-2. Contact matrix derived from the previous study about social mixing pattern in Japan



Average number of contacts per day between age groups. Red colour indicates higher contact numbers compared to white cells, with darker colour signifying higher number of contacts.

Chapter 9

Supplementary information

Table S9-1. Additional results with adjusted Life Years Lost by the age-specific population norm for quality of life [319,320]

	QALYs lost			
Two years total	**260,426.2**			
Per 100,000 population per year	**103.5**			
Each clinical status:				
Fatal cases	**171,804.8**			
Outpatient cases	**57,031.5**			
Severe cases	**422.5**			
	Age group			
Each epidemic wave:	**Under 40**	**40-69**	**70 and over**	**Total**
Wave 1	**529.7**	**2995.1**	**5591.9**	**9109.0**
Wave 2	**2083.8**	**3999.0**	**5914.2**	**11958.9**
Wave 3	**8173.0**	**20423.7**	**43646.3**	**72207.6**
Wave 4	**9511.1**	**16675.6**	**27995.2**	**51398.1**
Wave 5	**34176.3**	**52716.9**	**35991.4**	**109784.5**

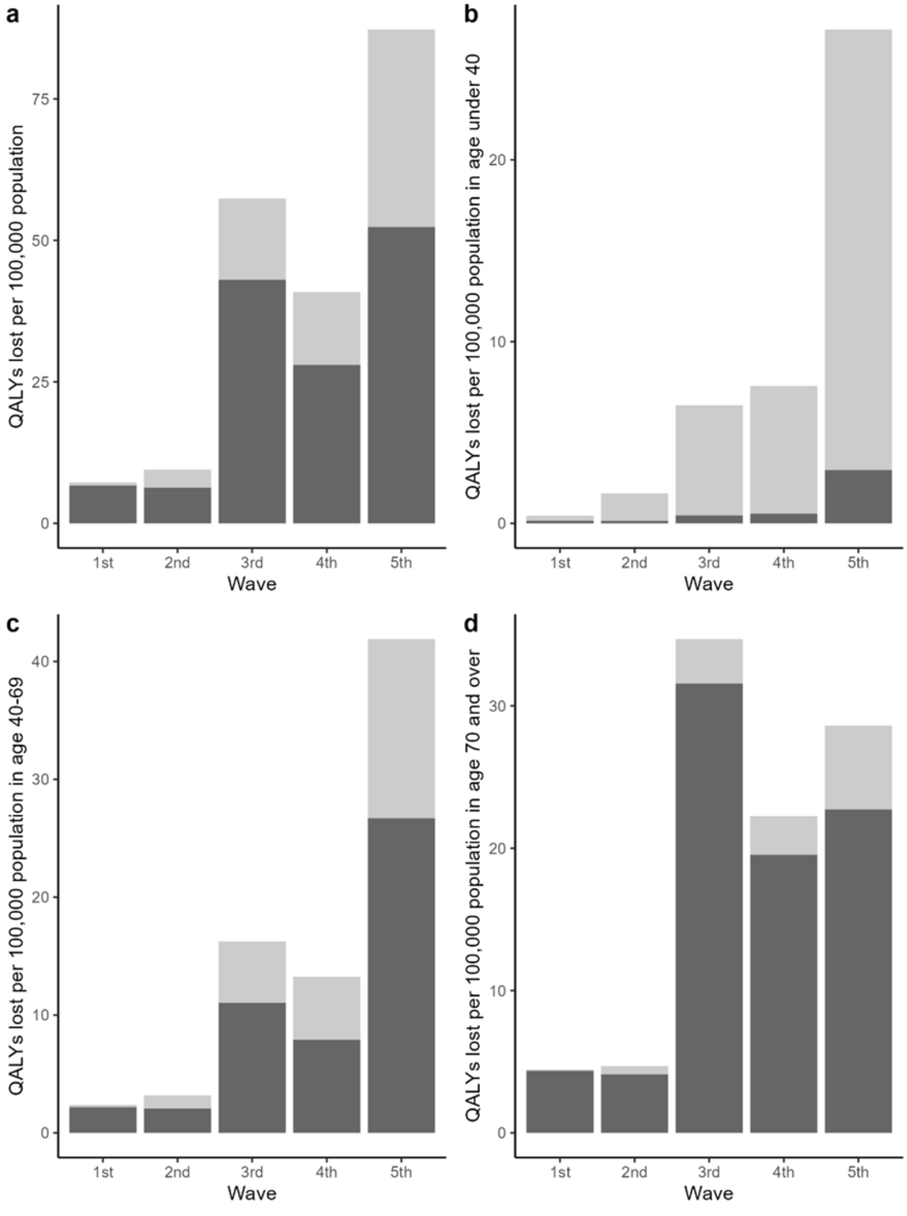


Figure S1. Wave-specific disease burden with Life Years Lost adjusted by the age-specific population norm for quality of life

Light grey bars represent QALYs lost due to morbidity and dark grey bars represent QALYs lost due to mortality.

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