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Simulation studies to assess the long-term effects of Japan's change from trivalent to quadrivalent influenza vaccination

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ABSTRACT

Background: Since 2013/2014, the WHO has been recommending quadrivalent influenza vaccines (QIV) to prevent seasonal influenza. In 2015, Japan replaced trivalent influenza vaccines (TIV) by QIV. We used computer simulations to calculate how this impacted the epidemiology and to assess its cost-effectiveness.

Methods: We simulated the seasonal transmission of the four influenza strains A(H1N1), A(H3N2), B/Yamagata and B/Victoria with the individual-based simulation tool 4Flu, using official demographic data and Japanese contact patterns. The model considered maternal protection, immunity boosting, new drift variants and different immunity durations for naturally acquired and vaccination-derived immunity. Starting with the 2015/16 season, simulations were evaluated for 20 years, using either TIV or QIV with the reported vaccination coverage. Costs and years of life saved (YOLSs) were calculated and discounted at 2%, using 2015 as base year.

Results: QIV annually prevents on average 548 influenza cases (4.7% of cases which occur when using TIV; 11.9% of influenza B), 1.62 hospitalizations and 0.078 deaths per 100,000 individuals. In Japan's population of 125.35 million, annually 91.51 YOLSs are gained by QIV and 10.75 million USD are saved (societal perspective). From payer perspective, the ICER is 3698 USD/YOLS.

Conclusions: QIV is cost-effective (payer perspective) or even cost-saving (societal perspective) in Japan.
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1. Background

The World Health Organization (WHO) has recommended vaccination as the most effective way of preventing infection and severe outcomes caused by influenza viruses [1]. Although the WHO's recommendation of Trivalent Influenza Vaccine (TIV) composition was regularly adjusted [2], years with vaccine mismatch for Influenza B strains (Victoria and Yamagata) frequently occurred because TIV included the wrong one of the two Influenza B lineages [3]. In 2012, WHO started recommending specific strains for both B lineages [4], paving the way for Quadrivalent Influenza Vaccines (QIV). QIV has been used in Japan since 2015/16, but the public health impact of this change has not yet been evaluated quantitatively. Several studies which use static models and a retrospective approach have estimated the epidemiologic impact of switching from TIV to QIV [5–8], but such models cannot appropriately consider effects of herd immunity. In this study, we take transmission dynamics into consideration by using computer simulations to estimate the current and future impact of replacing TIV by QIV at a national level in Japan.

2. Methods

2.1. Demography and contact network

We used the freely available simulation tool 4Flu (https://www.4flu.net), version 5.2 [9]. Simulations in 4Flu proceed in continuous time. The initial population size was chosen such that the simulated population consisted of exactly 100,000 individuals in 2015, i.e. at the beginning of our evaluation period. Each individual has his or her own birthday and its age is incremented when the simulation time reaches this birthday. Throughout the simulation, individuals are born, age and die; if needed, additional individuals of an older age are assumed to "immigrate" (i.e. are added) such

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that the demography of the simulated population can exactly reproduce the real Japanese age distribution in every year. For 2001 to 2015, we used observed national survey data for the age distribution; from 2016 onward, we used the official prediction data (Statistics Bureau, Ministry of International Affairs and Communications of Japan) [10]. The contact matrix which was used to construct a contact network for the simulated population describes the social contact patterns in Japan based on survey data of 4043 individuals in 2011 [11]. The process of translating demographic data and contact matrix into a dynamically changing contact network have been described elsewhere [12].

2.2. Initialization and evaluation period

To begin our simulations with a realistic age-distribution of immunity, seasonal influenza transmission was simulated for 14 years (from 2001/02 to 2014/15) before starting the comparison of TIV and QIV. During this initialization period, individuals in the simulations were vaccinated with TIV which contained the same sequence of B lineages as was used in Japan in these years. In the 20 years evaluation period (starting with 2015/16), an age-dependent percentage of individuals was vaccinated either with TIV or with QIV, whereby in both simulation branches, exactly the same individuals were vaccinated on exactly the same time points. As the future composition of TIV cannot be known in advance, a random B lineage was picked for each future simulation year. For the baseline parameter setting, 3000 pairs of simulations were run and averaged.

2.3. Natural history and seasonality of infectivity

An infected individual can pass on the virus to all the contact persons in his or her network at a given daily probability. This transmission probability per contact per day was assumed to be subject to seasonal fluctuations. Using a similar approach as Vynnycky et al. [13], we used the seasonality function cos((t-136)/365) for the transmission probability to obtain realistic seasonal waves [14]. As we start the simulation year on 1 September, the transmissibility peaks in the middle of January (on day 136) and reaches a minimum of zero in the middle of July. We assume that the latent period lasts for 2 days and that the infectious period lasts for 4 days in children below 18 years and for 2 days in older individuals (Table 1) [15]. A percentage of 66.9% of all influenza infections were assumed to result in clinical disease [16].

2.4. Dynamics of natural immunity

We assumed that infected individuals acquire temporary immunity after recovery which lasts on average for six years. When individuals lose their immunity, they become susceptible again. The duration of immunity can be boosted and, thus, prolonged by getting into contact with infectious individuals or by being vaccinated (infection of already immune individuals does not render the individual contagious, but only extends their existing immunity). We assumed 60% cross-immunity between the two B lineages as was done by Eichner et al. [9], but we did not assume any cross-immunity among A strains or between A and B. This means that individuals who are infected with one influenza B lineage have a 60% probability to additionally acquire (or booster) immunity against the other B lineage. Neonates are protected by maternal antibodies against strains to which their mothers are immune. The effect of maternal antibodies was assumed to last for two to four months (Table 1) [17–19].

Table 1
List of parameters and baseline values.

Parameter	Baseline value	References
Day of maximum seasonal transmission	15th January	
Duration of the latent period	2 days	[15]
Duration of the infectious period		[15]
- Children (age 0–17 years)	4 days	
- Adults (age 18 years and above)	2 days	
Duration of maternal protection	2–4 months	[17–19]
Immunity loss rate after infection	1/9.13 years	[9]
Cross protection after infection	60%	[9]
Cross protection after vaccination	60%	[9]
Vaccination coverage		[26]
0.5–4 years of age	39.8%	
5–14 years of age	55.7%	
15–24 years of age	41.7%	
25–34 years of age	45.5%	
35–54 years of age	50.9%	
55–64 years of age	45.3%	
65 years of age or older	49.3%	
Vaccine efficacy (well-matched vaccine) (with 95% confidence intervals)		
0–2 years of age	49.8 (41.8–56.8)	[20]
3–8 years of age	55.4 (39.1–67.3)	[21]
9–15 years of age	69.0 (62.0–77.0)	[22]
16–64 years of age	63.0 (49.0–80.0)	[23]
65 years of age or older	58.0 (34.0–73.0)	[24]
Revaccination preference factor	4.25	[25]
Percentage of cases developing clinical symptoms	66.9%	[16]
Number of hospital admissions (per 1000 cases)		[27]
0–4 years of age	1.91	
5–9 years of age	1.35	
10–14 years of age	0.53	
15–19 years of age	0.20	
20–29 years of age	0.20	
30–39 years of age	0.26	
40–49 years of age	0.41	
50–59 years of age	1.03	
60–69 years of age	2.78	
70 years of age and older	5.21	
Number of deaths (per 10,000 cases)		[27]
0–4 years of age	0.07	
5–9 years of age	0.03	
10–14 years of age	0.01	
15–19 years of age	0.01	
20–29 years of age	0.05	
30–39 years of age	0.09	
40–49 years of age	0.31	
50–59 years of age	0.66	
60–69 years of age	1.47	
70 years of age and older	2.82	

2.5. Vaccination

An age-specific percentage of individuals are vaccinated annually from October to November. The age-specific vaccine efficacy (VE) [20–24] was regarded as an all-or-noting process: successfully vaccinated individuals become immune, the others remain susceptible. After the occurrence of a new drift strain, a vaccine design mismatch can occur, which was modeled by multiplying the "matched" VE (which was used otherwise) by a reduction factor (Table 1). Only TIV was used in the initialization period (until 2014). For the evaluation period (starting with 2015), we assumed the same coverage and efficacy for TIV and QIV. Although one of the two Influenza B lineages is missing in TIV, it is assumed to be able to protect vaccinees against the missing lineage, yet at a reduced vaccine efficacy (the age-dependent "matched" vaccine efficacy is multiplied by factor 0.6). Successful vaccination results in an immunity which lasts throughout the transmission season

until the end of the simulation year; it can also boost and extend the remaining duration of preexisting naturally acquired immunity or it can be boosted by infections. To reflect personal preferences for vaccination, we assumed that previously vaccinated individuals are 4.25 times as likely to be revaccinated in the next year [25].

2.6. Model calibration

During our model calibration, we varied the infection probability, and ran more than 1000 simulations for each proposed value until we obtained simulation results with a median incidence of symptomatic cases of 11.7% (i.e. of individuals who visited a health facility with respiratory symptoms and were diagnosed as influenza mainly by rapid tests) as was observed in Japan in three consecutive years [26]. This calibration goal was met when using an infection probability of 1.3% per day per contact.

2.7. Epidemiologic impact

To assess the epidemiologic impact of QIV vs. TIV, we separately calculated for each simulation, how many patients visited healthcare facilities, how many were hospitalized, and how many died (age-specific parameter values are shown in Table 1) [27].

2.8. Cost-Effectiveness analyses

We conducted cost-effectiveness analyses for the 20 years evaluation period to assess the economic impact of QIV introduction. We used the years of life saved (YOLSs) as health outcome instead of quality adjusted life years (QALYs), because the duration of influenza illness is short and we do not consider any complication or sequelae. The discounted YOLSs were calculated by multiplying the discounted remaining life expectancy of each age with the number of averted deaths, as follows:

$$YOLS = \sum_{y=2015}^{2034}\left(\sum_{a=0}^{100} D(\mathrm{y},\mathrm{a}) \times E(a) \times \left(\frac{1}{1+\mathrm{d}}\right)^{y-2015}\right)$$

whereby D(y, a) is the average number of deaths which were averted in simulation year y in age group a, and d is the discount rate (default value: 2%). E(a) is the discounted value of the remaining life expectancy L(a) of individuals at age a: $E(a) = \sum_{i=1}^{L(a)}\left(\frac{1}{1+d}\right)^{i}$; (the values of L (a) are rounded to full years). The age-dependent remaining life expectancy L(a) obtained from [10] was used for all simulation years (although it may slightly increase in the years to come).

If QIV strategy was not dominant against TIV strategy, incremental cost-effectiveness ratios (ICERs) were calculated as follows:

$$ICER = \frac{discounted\ additional\ cost\ of\ QIV\ strategy}{discounted\ YOLS}$$

We set the willingness to pay (WTP) threshold to 50,000 USD/YOLS. As for payer perspective, we considered the difference of the vaccine prices, outpatient and inpatient costs, and costs of death after hospitalization (Table 2). Because the difference of the two scenarios was only caused by the type of vaccine used, we did not consider transportation or immunization costs. In the baseline scenario, we assumed the difference of vaccine price between TIV and QIV to be 2.4 United States Dollars (USD), based on average prices in 2014 and 2015 [28]. Other medical costs are estimated from a previous study [29]. All values were calculated with USD converted from Japanese Yen (JPY) with the rate of 1 USD = 110 JPY.

The societal perspective additionally included costs due to productivity loss. In the base case, productivity losses were calculated according to the human capital approach and losses for caregivers caring for sick children were also included. We assumed that the working age ranged from 20 to 65 years and we used average monthly wages from 2015 as reported by the Ministry of Health, Labour and Welfare Japan [30]. As for hospitalization, we assumed eight days of admission for all age groups [31,32] (30.0% of a monthly wage). As for outpatients, we assumed two days of productivity loss for adult patients [31,32] (7.14% of a monthly wage), and six days of absence for school age children, using Japan's legal regulation for school absenteeism due to influenza infection [33] (21.4% of monthly wage of caregivers).

Table 2
Parameters for the cost-effectiveness analysis.

Parameter	Value	References
Difference of vaccine prices QIV-TIV	2.40 USD	[28]
Costs per outpatient	135.00 USD	[29]
Costs per hospitalization	2,428.00 USD	[29]
Costs per death	9,180.00 USD	[29]
Monthly wage (average)	2,763.60 USD	[29]
Discount rate	2.0%	Assumed

2.9. Univariate and probabilistic sensitivity analyses

We ran univariate sensitivity analyses to explore the robustness of our cost-effectiveness results by increasing or decreasing key parameter values. For the discount rate, we used 0% and 4%, respectively. For difference of vaccine prices, we used 0.00 and 4.80 USD, respectively. For the loss rate of naturally acquired immunity, we used half and twice the baseline value. When varying the vaccine efficacy, we ran one set of simulations in which we used all the lower bound of the corresponding 95% confidence intervals and one set where we used all the upper bounds (cf. Table 1). To study the influence of B lineage cross protection, we ran a series of simulations where neither infection nor vaccination resulted in cross protection. For each set of parameters, we ran and evaluated 1000 pairs of simulations.

We additionally performed a probabilistic sensitivity analysis (PSA) by randomly and independently sampling model parameter values from probabilistic distributions (see Table A1 in the Online Supporting Material for details). In order to have the results primarily reflect the variability which comes from the sampling of parameter values (rather than from the stochastic nature of our simulations), we ran and averaged 100 simulations for each combination of parameter values.

When determining the range of each parameter, we referred to the Japanese guidelines for cost-effectiveness analyses [34] as well as to the ISPOR and ISPOR SMDM guidelines [35,36]. 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%) [29] as reasonable and used normal or uniform distribution. As for discount rate, we set a range from 0% to 4.0% according to Japanese guideline [34]. Details of all parameter ranges and their sampling distributions are presented in the Supplementary material Table A1.

3. Results

3.1. Epidemiologic impact

On average, 11,773 symptomatic influenza cases occur annually in a population of 100,000 inhabitants if TIV is used and 11,225 if QIV is used. Thus, QIV additionally prevents 548 symptomatic cases per 100,000 per year (95% CI: 536.5–559.1), representing

Table 3
Univariate sensitivity analyses for the mean annual incremental costs of QIV introduction (time span: 20 years; averages of 1000 simulations with 100,000 individuals; negative costs denote cost savings).

	Range	Payer perspective[a] (USD)	Societal perspective[b] (USD)
Difference of vaccine prices	Upper value (USD 4.80)	1,631,825.35	−200,415.73
	Lower value (USD 0.00)	−1,638,785.41	−3,471,026.48
Costs per outpatient	Upper value (+30%)	−475,275.73	−2,307,516.81
	Lower value (−30%)	468,315.67	−1,363925.41
Costs per hospitalization	Upper value (+30%)	−20,250.22	−1,852,491.30
	Lower value (−30%)	13,290.16	−1,818,950.90
Costs per death	Upper value (+30%)	−6549.76	−1,838,790.80
	Lower value (−30%)	−410.29	−1,832,651.40
Monthly wage	Upper value (+30%)	Not applicable	−2,385393.40
	Lower value (−30%)	Not applicable	−1,286,048.80
Discount rate	Upper value (4%)	−2,406.32	−873,824.81
	Lower value (0%)	−5069.74	−3,923,062.80
B lineage Cross Protection	Upper value (60%; baseline)	53,992.09	−1,715,520.19
	Lower value (no cross protection)	−2,393,278.68	−6,824,210.35
Duration of natural immunity	Upper value (immunity loss rate = half of baseline)	377,150.15	−1,110,322.75
	Lower value (immunity loss rate = double of baseline)	−821,216.92	−3,384,923.27
Vaccine efficacy	Upper values of all 95% CIs	−255,493.31	−2,391,204.84
	Lower values of all 95% CIs	481,314.68	−828,242.28

[a] Includes vaccine prices and healthcare costs.
[b] Includes vaccine prices, healthcare costs and productivity loss.

4.7% of all influenza cases which still occur with TIV, and 11.9% of influenza B cases. When translating the simulated population to the Japanese population size of 125.35 million inhabitants in 2015, QIV reduces the annual number of influenza cases from about 14,800,000 to 14,100,000.

Considering the age-specific probabilities of hospitalization and influenza-related deaths as shown in Table 1, QIV annually prevents 1.62 hospital admissions (95% CI: 1.58–1.65) and 0.078 deaths per 100,000 (95% CI: 0.077–0.080). On average, 2,030.67 hospitalizations (95% CI: 1,980.53–2,068.28) and 97.77 deaths (95% CI: 96.52–100.28) are annually prevented in Japan by QIV.

3.2. Cost-effectiveness analysis

On average, 0.73 YOLSs per 100,000 inhabitants are gained annually by QIV (95% CI: 0.72–0.75). QIV reduces yearly healthcare costs by 85,776 USD (95% CI: 82,411–89,141) per 100,000 inhabitants from a societal perspective. In the total population of Japan, annually 91.51 YOLSs are gained by QIV and 10.75 million USD are saved. From a payer perspective, QIV strategy additionally costs 2700 USD per 100,000 inhabitants per year, leading to 3698 USD/YOLS. When considering a time span of 20 years, 14.65 YOLSs per 100,000 inhabitants are gained and 1.72 million USD per 100,000 inhabitants are saved from a societal perspective; from a payer perspective, the additional costs of the QIV strategy are 53,992.09 USD per 100,000 inhabitants.

3.3. Univariate sensitivity analyses

Univariate sensitivity analyses were conducted on the duration of naturally acquired immunity, on the degree of B lineage cross protection (after infection and after vaccination), on the vaccine efficacy, on the difference in vaccine prices, on healthcare costs (for outpatient, hospitalization, and death, respectively), on wages, and on the discount rate. Lower and upper values of each variable and results are shown in Table 3. Fig. 1a and b show tornado plots of these sensitivity analyses for payer and societal perspective, respectively. As the number of hospitalizations and deaths are simply derived from the number of cases by multiplication, the economic results for hospitalizations and deaths can either be interpreted as (a) these events occur at a lower or higher frequency (±30%) or (b) that the costs per event are lower or higher (±30%).

From a payer perspective, the difference of the vaccine prices is most important, followed by the degree of B lineage cross protection and the duration of naturally acquired immunity (Fig. 1a). Although QIV causes further costs from the payer perspective, it is cost-effective due to low ICERs (Table 3). From societal perspective, the degree of B lineage cross protection is most important, followed by the difference in vaccine prices, the discount rate and the duration of naturally acquired immunity, yet for all parameter values examined, QIV is a dominant strategy against TIV (Fig. 1b and Table 3).

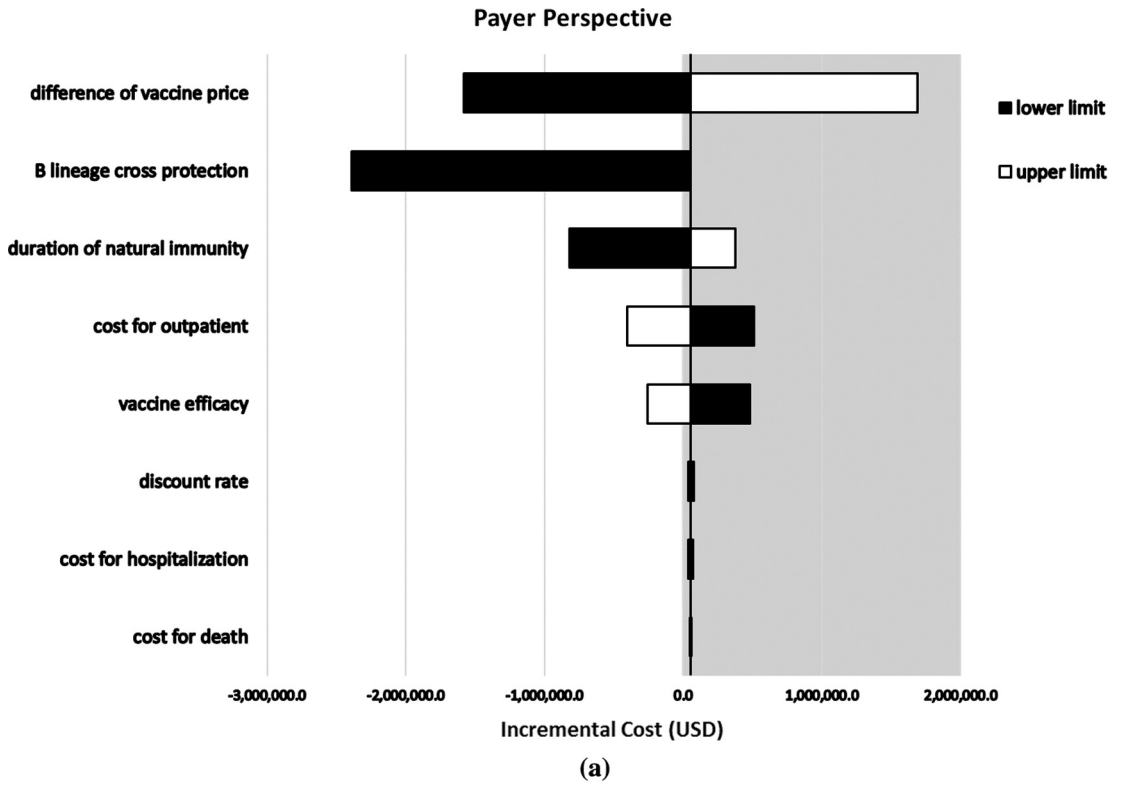
3.4. Probabilistic sensitivity analyses

Probabilistic sensitivity analyses (PSA) were conducted both from payer and societal perspective. We randomly sampled 1100 sets of parameter values (see Table A1 in the Online Supporting Material for details) and for each of them, we ran and averaged 100 simulations. From a payer perspective, 69.0% of these 1100 averaged simulation bundles showed that the additional cost of the QIV strategy was lower than the willingness to pay (WTP) threshold of USD 50,000 per YOLS; 94.2% were below the WTP threshold from societal perspective. Fig. 2A and B shows the scatter plots of these PSA results and Fig. 3 shows the cost-effectiveness acceptability curve derived from the same results.

4. Discussion

Our simulations indicate that annually about 700,000 influenza cases (representing 11.9% of all influenza B cases) are prevented in Japan without increasing the vaccination coverage by switching from TIV to QIV. QIV also prevents about 2000 hospital admissions and 100 deaths annually. Our cost-effectiveness analyses demonstrate that QIV is a dominant strategy against TIV from a societal perspective and a cost effective strategy from a payer perspective. These results suggest that Japan's decision to switch from TIV to QIV was an appropriate choice, and it confirms the results of previous studies from other countries [5–8,37,38].

As there is little evidence about vaccination policy of seasonal influenza and its cost-effectiveness [29,39] and as there are no analyses about the impact of QIV, our research is an important contribution to evaluating the introduction of QIV to Japan. We used a dynamic transmission model which is more appropriate than static



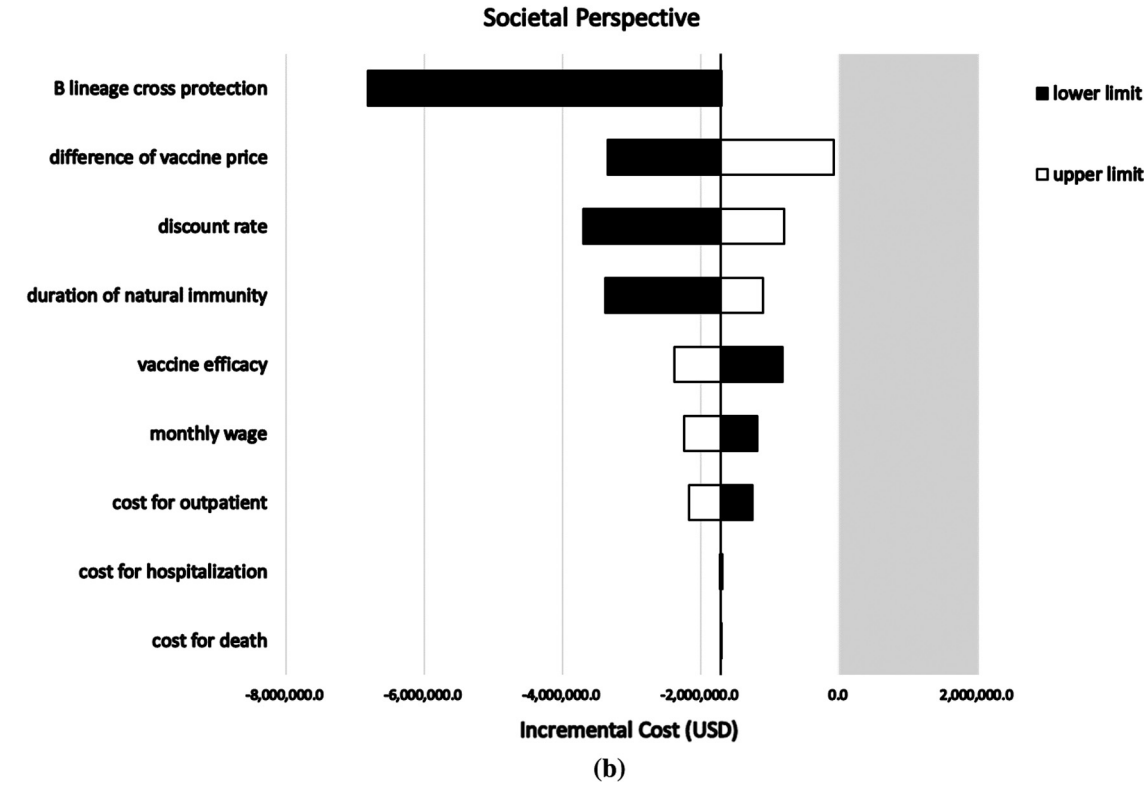


Fig. 1. (a) Tornado plot of sensitivity analyses from payer perspective; negative values denote cost savings (US$ per 100,000 individuals per year), positive values denote additional costs. If the lower limit of a bar is below 0, this signifies that QIV is a dominant strategy against TIV. Parameter variation: (1) the loss rate of naturally acquired immunity was set to half or twice of the baseline value; (2) B lineage cross protection (conveyed by infection or vaccination) was set to 0% or 60% (baseline value); (3) for vaccine efficacy, either the upper or the lower values of the 95% confidence intervals were used simultaneously in all age groups; (4) the difference of vaccine prices was set to USD 0.00 or USD 4.80; (5) for wages and healthcare costs (for outpatients, hospitalizations, and deaths), the baseline values were decreased or increased by 30%; (6) for the discount rate, 0% and 4% were used; further details are given in Table 3. (b) Tornado chart of sensitivity analyses for societal perspective; negative values denote cost savings (US$ per 100,000 individuals per year), positive values denote additional costs. If the lower limit of a bar is below 0, this signifies that QIV is a dominant strategy against TIV. Parameter values and further details are given in Fig. 1a and Table 3.

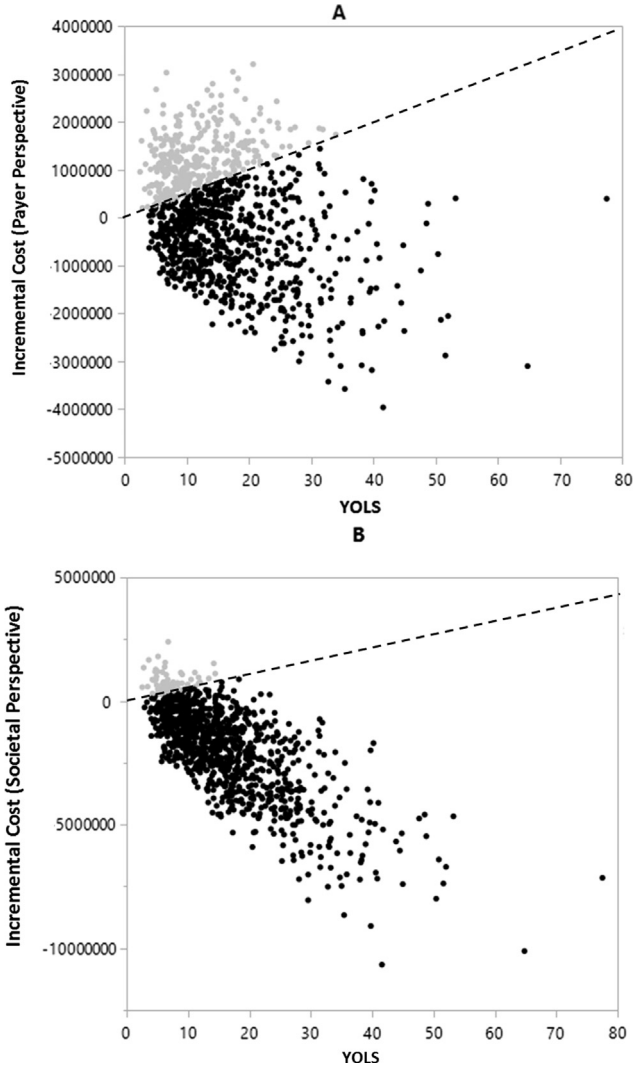


Fig. 2. Scatter plot of incremental costs and years of life saved (YOLS) for the probabilistic sensitivity analysis. Dotted lines denote the willingness to pay (WTP) threshold (50,000 USD/YOLS). (A). Payer perspective. Number of dots below the WTP threshold/total number of dots = 759/1100 = 69.0%. (B) Societal perspective. Number of dots below the WTP threshold/total number of dots = 1036/1100 = 94.2%.

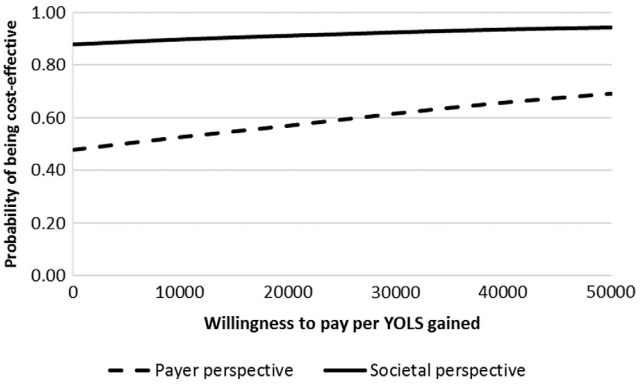


Fig. 3. Cost-effectiveness acceptability curve.

models [40], because for influenza transmission, herd immunity effects are crucial [25,41,42]. Our model includes a long-term projection which takes demographic changes into consideration.

Regarding cost-effectiveness, the QIV strategy is less costly and more effective than the TIV strategy from a societal perspective. From a payer perspective, QIV is cost-effective because its ICER is lower than the WTP threshold. Univariate and probabilistic sensitivity analyses also support this. Our results on varying cost parameters confirm the observation of other studies [37] that the impact of seasonal influenza is mainly due to productivity loss, and that applying an appropriate vaccination policy can reduce it.

Several limitations must be noted. We had no specific data about hospital admission rates and case fatality risks for the different influenza strains, but only for H1N1pdm09 (these rates had to be applied to all strains); according to a report from Hong Kong [43], mortality of influenza is not largely different by strain. As Japan has no syndromic surveillance system for influenza like illness, we had to estimate the total number of flu patients from sentinel surveillance data. As for vaccination coverage, data were not available on a national level, and we had to use estimates from voluntary participants. These weaknesses of the Japanese surveillance system may have impaired the reliability of our results. Furthermore, we assumed that every case had the same age-dependent risk of hospitalization and death, yet some people are at higher risk of severe influenza (their proportion and age-distribution are not known for Japan). This may have resulted in a general underestimation of the severity of disease which would have led to an underestimation of the benefits of QIV (which still was revealed as the dominant strategy). We assumed the same costs of out/inpatient medical care and fatal cases for all age groups, although there must be some differences in medical costs among different age groups due to complications, severity, and so forth. More detailed information would be necessary to obtain more precise economic estimates.

5. Conclusion

The present study examined the new vaccination policy for seasonal influenza which has been in place since the 2015/16 season in Japan. Employing a dynamic transmission model which reproduced the observed patterns of annual incidence, QIV was shown to be at payer perspective a cost-effective and at societal perspective even a dominant strategy against TIV.

Conflict of interest

ST has nothing to disclose. MS is shareholder of ExploSYS GmbH, which has received payments from Epimos GmbH for developing the simulation tool 4Flu. ME is shareholder of Epimos GmbH, which has received research support from the GlaxoSmithKline group of companies and from AstraZeneca.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2017.12.058.

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