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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.

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

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