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# Mechanisms of replacement of circulating viruses by seasonal and pandemic influenza A viruses

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SUMMARY

*Background:* Seasonal influenza causes annual epidemics by the accumulation of antigenic changes. Pandemic influenza occurs through a major antigenic change of the influenza A virus, which can originate from other hosts. Although new antigenic variants of the influenza A virus replace formerly circulating seasonal and pandemic viruses, replacement mechanisms remain poorly understood.
*Methods:* A stochastic individual-based SEIR (susceptible–exposed–infectious–recovered) model with two viral strains (formerly circulating old strain and newly emerged strain) was developed for simulations to elucidate the replacement mechanisms.
*Results:* Factors and conditions of virus and host populations affecting the replacement were identified. Replacement is more likely to occur in tropical regions than temperate regions. The magnitude of the ongoing epidemic by the old strain, herd immunity against the old strain, and timing of appearance of the new strain are not that important for replacement. It is probable that the frequency of replacement by a pandemic virus is higher than a seasonal virus because of the high initial susceptibility and high basic reproductive number of the pandemic virus.
*Conclusions:* The findings of this study on replacement mechanisms could lead to a better understanding of virus transmission dynamics and may possibly be helpful in establishing an effective strategy to mitigate the impact of seasonal and pandemic influenza.


## 1. Introduction

Infectious diseases are still of great concern for public health, particularly emerging and re-emerging infectious diseases such as pandemic influenza. Globalization has also increased the risk of the worldwide spread of infectious diseases. For example, after the 2009 detection of human infections with the novel swine-origin influenza A (H1N1) virus in North America, the virus spread worldwide within a few weeks and resulted in a pandemic.[1–3]

Pandemic influenza occurs through a major antigenic change (antigenic shift) of the influenza A virus, which can originate from other hosts, such as birds and swine.[4] Historically, pandemic influenza has replaced the previously circulating seasonal influenza virus.[5,6] In 1918, a novel H1N1 virus emerged (Spanish flu) that expelled the H3N8 virus that had been circulating among humans since the late 19th century. Similarly, a novel H2N2 virus (Asian flu) expelled the H1N1 virus in 1957, and a novel H3N2 virus (Hong Kong flu) expelled the H2N2 virus in 1968. However, the H1N1 virus, which re-emerged in 1977 (Russian flu), did not expel the H3N2 virus, and both H1N1 and H3N2 have been co-circulating since 1977.[7,8] The swine-origin H1N1 virus emerged and led to a pandemic in 2009. This virus was closely related to the virus that caused Spanish flu in 1918,[9] and some people, particularly the elderly, had some immunity to it.[10,11] After the emergence of the A(H1N1)pdm09 virus, the H3N2 virus (progeny of Hong Kong flu) did not disappear, whereas the former H1N1 virus disappeared; since then, both H1N1 and H3N2 viruses have continued to co-circulate in the human population.[12,13] The next influenza pandemic is an imminent threat to human health. Sporadic human infections with avian influenza viruses, such as H5N1 and H7N9, continue to occur, and these avian influenza viruses have the potential to cause a pandemic once they acquire the ability to efficiently transmit between humans.[14,15]

Seasonal influenza causes annual epidemics by the accumulation of antigenic changes (antigenic drift), which allows viruses to evade herd immunity.[4,16] It has been proposed that a new antigenic variant, generated by antigenic drift, first evolved in Southeast Asia and then spread to other parts of the world,

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replacing previously circulating viruses.[16–18] Therefore, genetically similar influenza viruses can cause global epidemics at almost the same time.[16,19] The influenza A virus epidemic shows a clear winter peak in temperate regions and year-round circulation with minor peaks in tropical regions.[20–22] Patterson Ross et al. showed that no strains persisted over the influenza season in temperate regions.[23] They suggested that an epidemic in temperate regions was caused by a strain imported from other areas, rather than strains lingering locally. Yet, little is known about the mechanisms through which a previously circulating strain is replaced by a new antigenic variant in temperate and tropical regions.

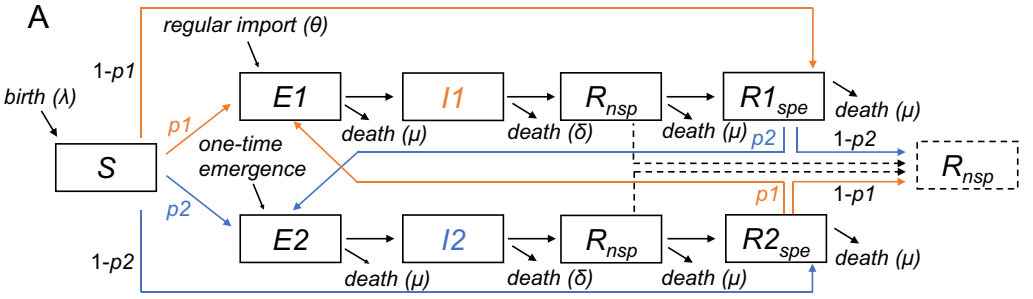
A mathematical model, specifically the compartment SIR (susceptible–infectious–recovered) model, is used widely to investigate the transmission dynamics of the influenza A virus. A simple compartment model has been used successfully to predict the behaviour of epidemics, which is consistent with that observed in 'real' epidemics.[24] In the compartment model, individuals in the population are assigned to different subgroups or compartments, each representing a specific stage of infection. The advancement of the compartment model can tell us the future of an ongoing pandemic,[1] effective control measures against a potential pandemic,[25] and the global dynamics of the virus.[26]

Although studies have shown that the host's immunity plays an important role in virus replacement by antigenic shift or drift,[27,28] we still have a limited understanding of the mechanisms of the replacement. Such information would lead to a better understanding of virus transmission dynamics. It could also possibly be helpful for establishing an effective avoidance strategy, such as vaccination and social distancing measures, to mitigate the impacts of seasonal and pandemic influenza. In this study, the compartment model was used to elucidate how a newly emerged influenza A virus (antigenic variant of seasonal influenza virus or pandemic influenza virus) is capable of replacing the currently circulating influenza A virus.

## 2. Methods

A stochastic individual-based SEIR (susceptible–exposed–infectious–recovered) model was developed for simulations (Figure 1A). In a population of $N$, say that $S$ are susceptible, $E$ are exposed, $I$ are infectious, and $R$ are recovered. $I$ makes effective contact to transmit the infection during an infectious period randomly in the homogeneous mixing population. When effective contact occurs between $I$ and $S$ or $R$, one ($S$ or $R$) has a probability, $p$, of becoming either $E$ ($p$) or $R$ ($1-p$). An effective contact number ($c$) is generated for each $I$ by Poisson distribution ($R_0$); $R_0$ is a basic reproductive number. In addition, $R_0$ at time $t$ (day) can oscillate as seasonality. $R_0$ can also be a constant for the 'non-seasonality model' representing the year-round circulation of the virus in the tropics (Figure 1B).

An emerged strain (strain 2) appears in the model population at random. The intensity of the cross-immunity response is expressed




| | p1 | p2 |
|---|---|---|
| $S$ | 1 or $p_{pst}$ or $p1_{vac}$ | 1 or $p_{pst}$ or 'cross immunity from $p1_{vac}$' |
| $R_{nsp}$ | 0 | 0 |
| $R1_{spe}$ | 0 | 'cross immunity from $p1$' |
| $R2_{spe}$ | 'cross immunity from $p2$' | 0 |

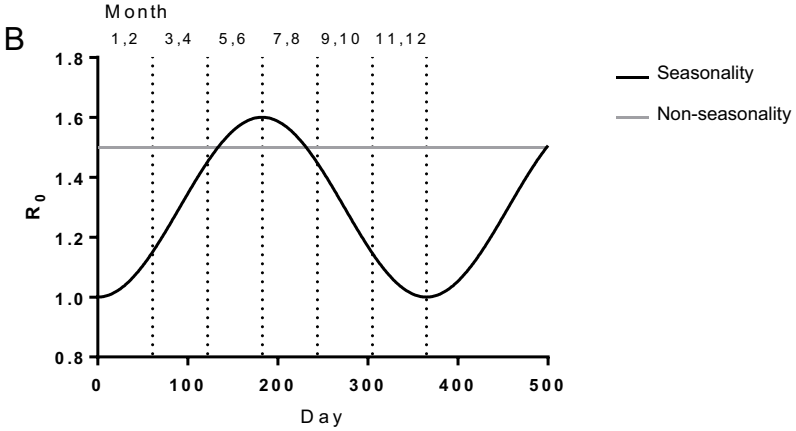



**Figure 1.** Simulation model. (A) Schematic diagram of the compartment model used in the present study ($S$, susceptible; $E$, exposed; $I$, infectious; $R$, recovered). Transitions made by effective contact with infectious individuals for strains 1 and 2 ($I1$ and $I2$) are coloured in orange and blue, respectively. When effective contact occurs between $I$ and $S$ or $R$, one ($S$ or $R$) has a probability, $p$, of becoming either $E$ ($p$) or $R$ ($1-p$). $p$ at each stage is listed in a table in the figure. The $R$ state can have strain-specific immunity ($R_{spe}$) or non-strain-specific immunity ($R_{nsp}$). Details of the model are described in the Methods. (B) Time courses of $R_0$ (basic reproductive number) for simulations in the 'seasonality model' and 'non-seasonality model' are shown; months are grouped as depicted.

by variable $\varphi$. The probability of becoming infected with strain 2 ($p_2$) for $R1_{spe}$ is described by the following equation:

$$p2 = 1-(1-p1)\times\varphi$$

and vice versa for $p1$. For details of the simulation modelling, please see the **Supplementary Material**. Parameters and references used for the simulation are also listed in the **Supplementary Material**. The Student $t$-test, Pearson's Chi-square test, Jonckheere's trend test, and the Mantel–Haenszel test were performed using SPSS version 18 software (SPSS Inc., Chicago, IL, USA). A $p$-value of less than 0.05 was considered statistically significant.

## 3. Results

### 3.1. Simulation with the SEIR model

A stochastic individual-based SEIR simulation model was developed with two different strains of influenza A virus (Figure 1A). In the simulation, $R_0$ (basic reproductive number) was set differently for the 'seasonality model' (oscillation) and 'non-seasonality model' (constant; Figure 1B). The results of the simulations with a single strain are shown in Figure 2. The epidemic curves show a clear single peak for the 'seasonality model' (simulating the temperate region) and a year-round circulation with occasional peak(s) for the 'non-seasonality model' (simulating the tropical region). The annual infection rate in the simulation was 14.9% (interquartile range 10.0–19.3%) for the 'seasonality model' (Figure 2C), which is compatible with many studies estimating the influenza infection rate by serological test.[29–31] Although there are limited studies on the epidemiology of influenza in the tropics, it is estimated that the disease burden of influenza is as significant as in temperate regions.[20,32] The simulations yielded an annual infection rate of 15.3% (interquartile range 12.8–17.4%) for the 'non-seasonality model'.

### 3.2. Replacement of seasonal influenza viruses

A model was then constructed with two strains to simulate the introduction of an emerged antigenic variant (strain 2) during the circulation of an existing strain (strain 1). It was simulated that the antigenic variant appeared in the population at random during the epidemic of an existing strain (see Methods for details). People who are currently infectious by infection with strain 1 are described as $I1$, and people who have immunity against strain 1 after recovery from the infection are described as $R1$. The same applies to strain 2; $I2$ and $R2$. The intensity of cross-immunity between the two strains is described by $\varphi$. Briefly, when $\varphi$ is 0, the emerged strain is completely different antigenically from the existing strain. When $\varphi$ is 1, the emerged strain is antigenically the same as the existing strain. Epidemiological parameters of the emerged strain were set to be same as the existing strain to simulate an epidemic by antigenic drift (**Supplementary Material**). Since the pre-immunity level ($1 - p_{pst}$; probability of escape from infection after exposure to the virus) for seasonal influenza

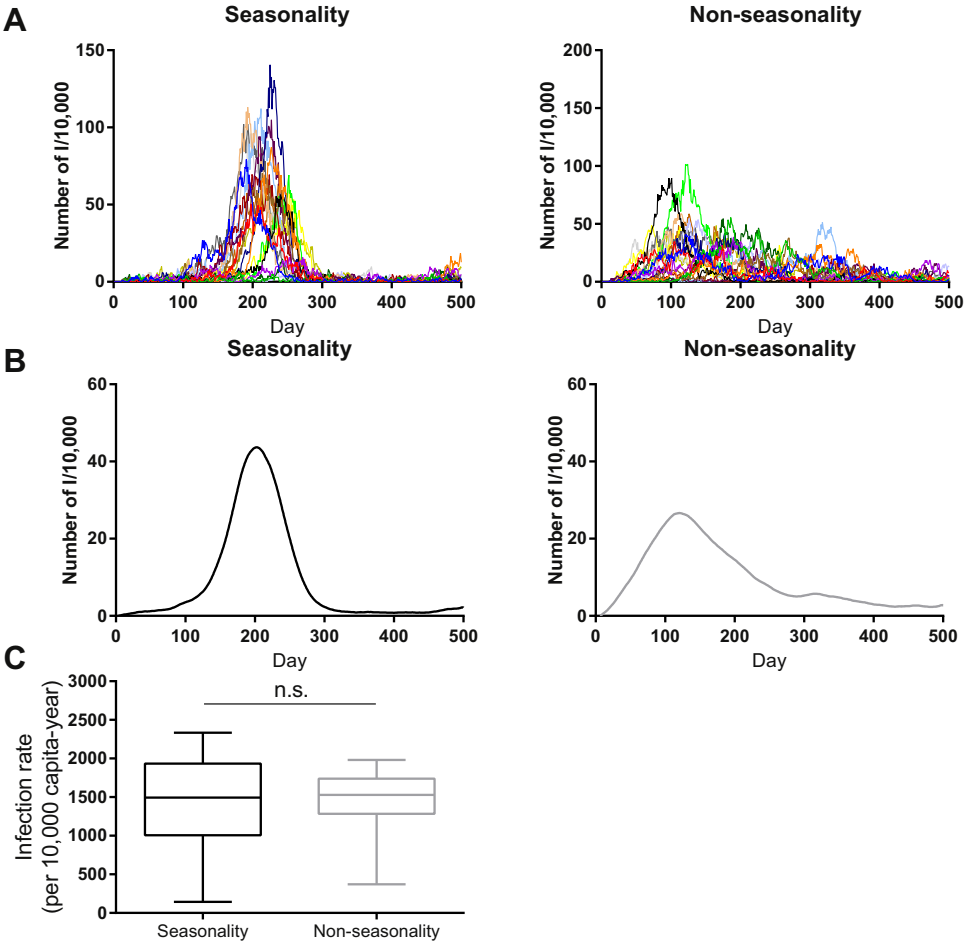



**Figure 2.** Simulation results with a single strain. (A) Epidemic curve (number of $I$) of 20 representative simulations (one colour represents one simulation). (B) Mean of the epidemic curve of 50 simulations. (C) Infection rates of the epidemic. Horizontal lines and boxes show median and interquartile ranges. $p$-Values were calculated using the two-tailed Student $t$-test. n.s., not significant ($p > 0.05$).

viruses (both existing and emerged strains) was set at 0.3, $\varphi$ was tested at 0.3 or above (**Supplementary Material**). 'Replacement' was defined by three criteria as follows: (1) surpassing ('number of *I2* is five or more per 10 000 per capita' and 'proportion of *I2* is 80% or more of the total number of *I1* and *I2*'), (2) suppressing ('number of *I1* is four or less per 10 000 per capita'), and (3) a decent duration of the condition (criteria 1 and 2) that lasts for at least 40 days.

Figure 3A shows the results of a representative simulation without a replacement (example 1: $\varphi = 0.3$, 'non-seasonality model') and with a replacement (example 2: $\varphi = 0.3$, 'non-seasonality model'). The frequency of replacements was calculated in 2000 simulations. The simulations found that the frequencies of replacements in the 'non-seasonality model' were significantly higher than those in the 'seasonality model' (Figure 3B). Furthermore, the frequency increased with a decrease in intensity of cross-immunity between the two strains ($\varphi$). The frequency of replacement reached 0.03 in the 'seasonality model' and 0.13 in the 'non-seasonality model'. Replacement hardly occurs (frequency is less than 0.01) when cross-immunity is high (i.e., large $\varphi$). If an emerged strain has a high cross-immunity, which means that there is not much of an antigenic difference between existing and emerged strains, an emerged strain cannot replace an existing one because the emerged strain has no advantage.

While replacement of the emerged strain occurred soon after its emergence in some simulations (Figure 3A, example 2), there was a long time lag between emergence and replacement in other simulations (example 3). It was then checked whether the time lag for replacement was different between the 'seasonality model' and 'non-seasonality model'. As shown in Figure 3C, there was no significant difference in the time lag from emergence to replacement between the 'seasonality' and 'non-seasonality' models.

### 3.3. Possible factors and conditions affecting replacement

Next, whether any specific conditions can increase the frequency of replacement in addition to low cross-immunity was explored. As the emerged strain (strain 2) appears at random in the simulations, it was checked whether the epidemic characteristics of the existing strain (strain 1) at the advent of the emerged strain would affect the occurrence of replacement (Figure 4). The 'number of *I1*' represents the magnitude of the ongoing epidemic by the existing strain, and 'number of *R1*' reflects herd immunity against the existing strain. In the 'seasonality model' with high cross-immunity, both *I1* and *R1* at the emergence of strain 2 were significantly smaller in simulations in which replacement occurred compared with simulations without replacement. Besides, the time lag between emergence and replacement of strain 2 in such a situation (large $\varphi$ in the 'seasonality model') was short (Figure 3C). Taken together, these findings imply that replacement takes place only when an emerged strain appears at the initial stage of an epidemic and has become predominant (Figure 3A; example 4: $\varphi = 1.0$, 'seasonality model'). Furthermore, an analysis of timing when the emerged strain appears also proves that replacement is more likely to occur when the emerged strain appears before the peak of $R_0$ in the 'seasonality model' (Figure 1B and Figure 4C). However, in this situation where cross-immunity was high ($\varphi > 0.6$) with 'seasonality', replacement was fairly rare (frequency of approximately 0.005; Figure 3B).

The numbers of *I1* and *R1* at the appearance of the emerged strain are not so different between simulations with and without replacement in the 'non-seasonality model' (Figure 4A and Figure 4B). Further, the frequency of replacement does not differ at any stage of the epidemic when the emerged strain appears (Figure 4C). The timing of appearance of the emerged strain is not that important for replacement in the 'non-seasonality model'.

Yet, an exception was found in which the number of *R1* in simulations with replacement was slightly but significantly higher than simulations without replacement when $\varphi$ is 0.3 (Figure 4B). If herd immunity (number of *R1*) does affect the frequency of replacement, vaccination might be able to increase the probability of replacement. Therefore, vaccination was introduced into the simulation. Vaccine efficiency (VE) to prevent infection with

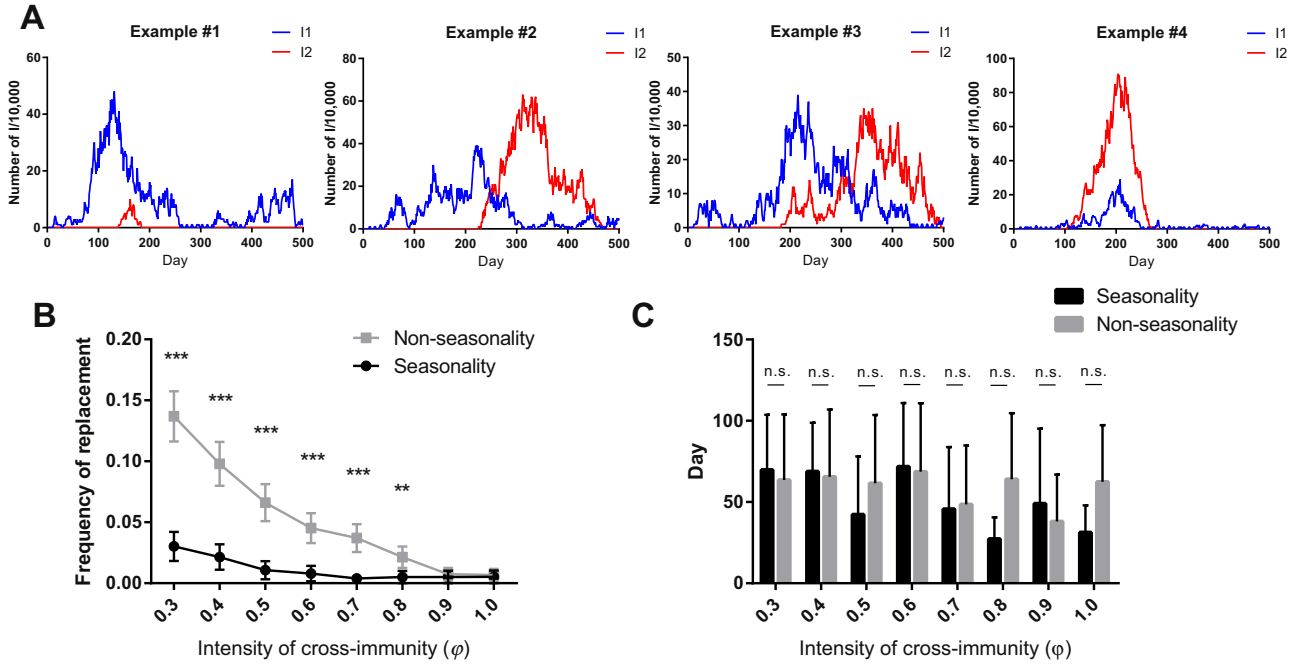



**Figure 3.** Replacement by the emerged strain in the epidemic model. (A) Epidemic curves of representative simulations. Examples 1–3: $\varphi = 0.3$, 'non-seasonality model'. Example 4: $\varphi = 1.0$, 'seasonality model'. (B) The frequency of replacement was calculated by 2000 simulations for each parameter setting the 'seasonality model' and 'non-seasonality model'. Error bars show 95% confidence intervals. (C) Time lag between the emergence and replacement of strain 2 in the 'seasonality model' and 'non-seasonality model' in simulations in which replacement happened. Error bars show standard deviations. *p*-Values were calculated using the two-tailed Pearson Chi-square test for (B) and Student *t*-test for (C). $^{***}p < 0.001$, $^{**}p < 0.01$, n.s., not significant ($p > 0.05$).

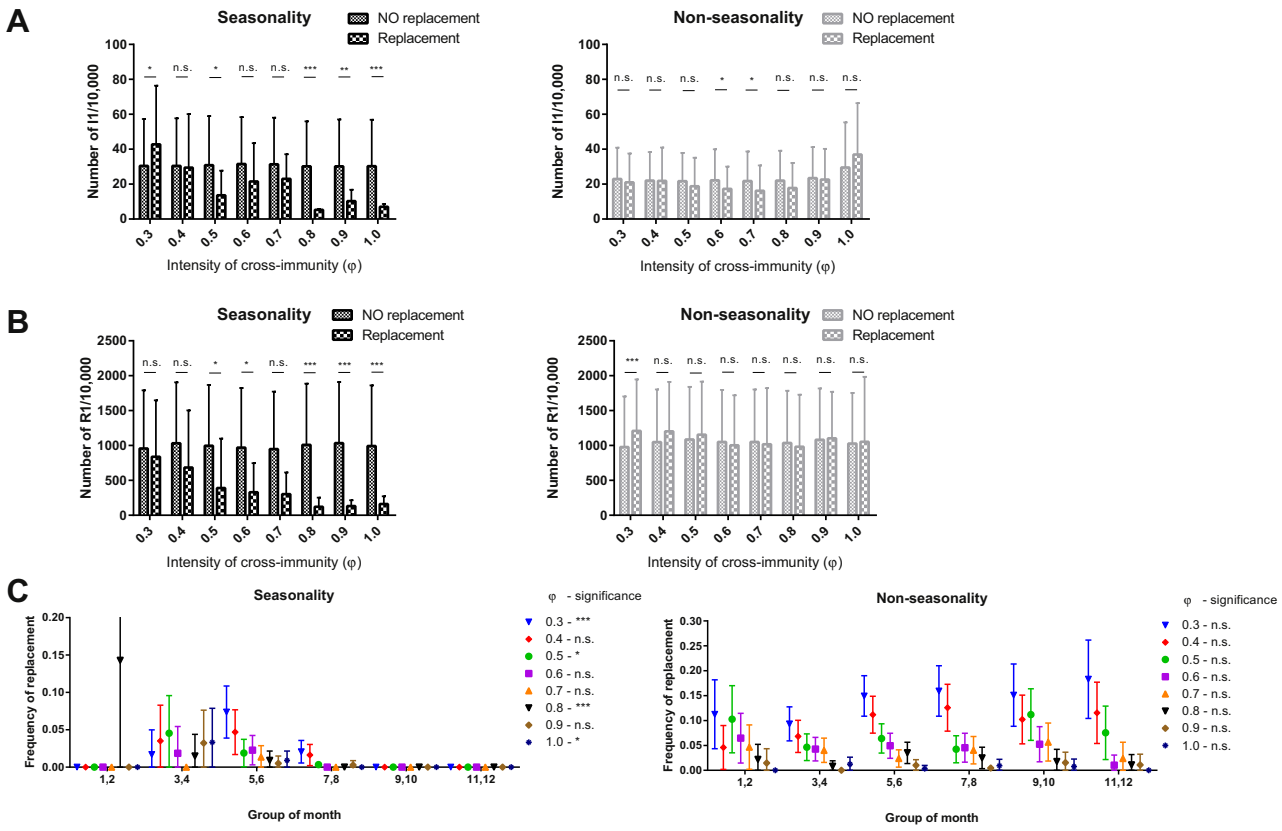



**Figure 4.** Situation of epidemic timing and strain emergence. Numbers of *I1* (A) and *R1* (B) when the strain emerged in simulations in which replacement did and did not take place. Error bars show standard deviations of 2000 simulations. (C) Frequency of replacement by month group in which the emerged strain appeared, as described in Figure 1B. Error bars show 95% confidence intervals. *p*-Values were calculated using the two-tailed Student *t*-test for (A) and (B), and the Pearson Chi-square test for (C). $^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$, n.s., not significant ($p > 0.05$).

influenza is considered to range between 40% and 90%.[33,34] Vaccination has both direct effects (reduction of individual susceptibility) and indirect effects (herd immunity). VE was set to decrease infection by 50% at the population level with a vaccination coverage of 100% (Figure 5A; **Supplementary Material**). As a result, the introduction of vaccination did not change the frequency of replacement, except for conditions where $\varphi$ was 0.4 and 0.7 in the 'non-seasonality model' (Figure 5B). Even under exceptional conditions, the effects of vaccination in augmenting the frequency of replacement were small.

### 3.4. Replacement by pandemic influenza virus

Finally, an investigation was performed to determine how a pandemic influenza virus with antigenic shift expels a seasonal influenza virus. Replacement of a previously circulating seasonal virus with a pandemic virus has been observed historically.[5,6] Further, experimental and epidemiological studies have shown that there is non-strain-specific viral interference following influenza virus infection.[35,36] Therefore, there must be an interaction between seasonal and pandemic viruses.[37] In the model, it was assumed that there is a non-strain-specific (strain-independent) immunity state ($R_{nsp}$), regulated by innate immunity such as interferon, soon after recovery. The $R_{nsp}$ is followed by a strain-specific (antibody-mediated) immunity state ($R_{spe}$; see Methods and Figure 1A). Different parameters were used for simulations in the pandemic model from the seasonal influenza model: namely, no cross-immunity between existing and emerged strains ($\varphi$ was 0), a high initial susceptibility (0.7–1.0 for $p_{pst}$), a high $R_0$ (1.0–1.5 times higher $R_0$ than the seasonal virus), and a strong immune response (long period of non-strain-specific immunity, 7–28 days) for the emerged strain with antigenic shift (strain 2, pandemic virus; see **Supplementary Material**).

The frequency of replacement by the pandemic virus ranged between 0.02 and 0.63 (Figure 6). It should be noted that these frequencies were calculated by a single introduction of the emerged strain. Multiple introductions from other areas could occur after a widespread pandemic outbreak. If the probability of replacement is 0.4 by a single introduction, it increases to 0.92 by five introductions and to 0.99 by 10 introductions. The frequencies were higher in the 'non-seasonality model' compared to the 'seasonality model', which were the same as simulations for the seasonal influenza model (Figure 3B and Figure 6).

Even when $R_0$ of the pandemic virus does not differ from that of the seasonal influenza virus, low pre-immunity (i.e., high initial susceptibility) is enough to dramatically increase the frequency of replacement (Figure 6). When assuming that pre-immunity for a pandemic virus was 0.3, which is as high as the seasonal influenza virus (i.e., initial susceptibility, $p_{pst}$, is as low as 0.7), a higher $R_0$ of a pandemic virus also leads to a higher frequency of replacement. It has been reported that the immune response to a pandemic virus is somehow different from that to a seasonal influenza virus.[38–41] A strong immune response (long period of non-strain-specific immunity) to a pandemic virus increases the frequency of replacement. However, it contributes only marginally to the frequency of replacement compared to the effects of low pre-immunity or high $R_0$ of the pandemic virus (Figure 6).

## 4. Discussion

In the present study, the possible mechanisms of replacement of a previously circulating strain of the influenza A virus by an

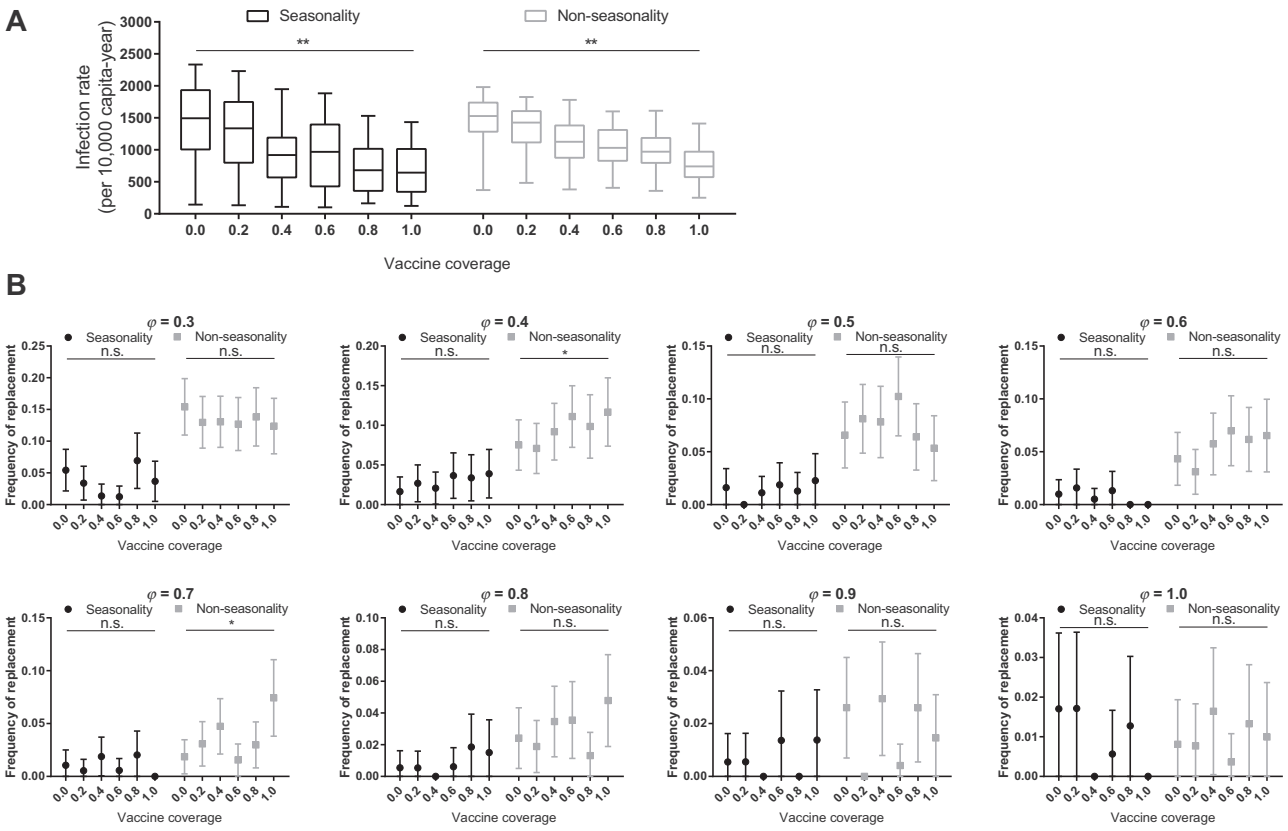



**Figure 5.** Vaccination and replacement. (A) Infection rate of the epidemic with a single strain and various levels of vaccination coverage, calculated by 50 simulations. Horizontal lines and boxes show median and interquartile ranges. (B) Frequency of replacement with various levels of vaccination coverage. Five hundred simulations with two stains were run for each parameter setting. Error bars show 95% confidence intervals. *p*-Values for the trend were calculated using Jonckheere's trend test for (A) and the Mantel–Haenszel test for (B). $^{**}p < 0.01$, $^{*}p < 0.05$, n.s., not significant ($p > 0.05$).

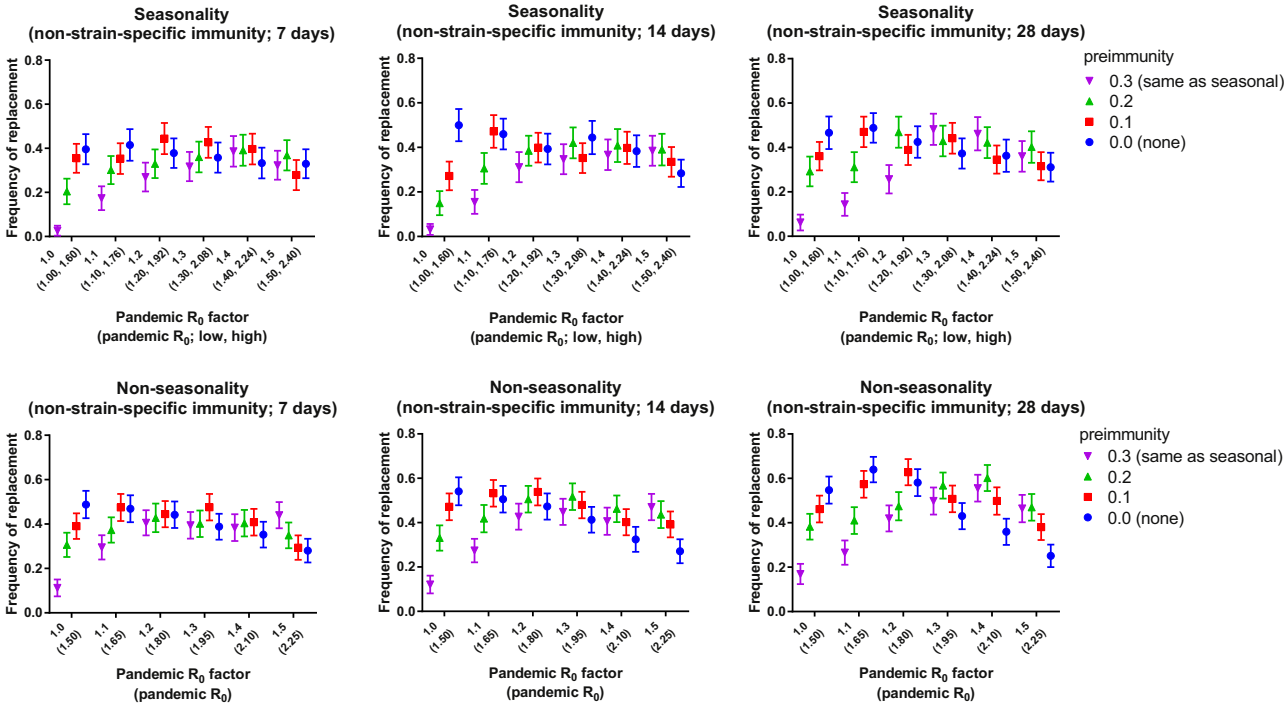



**Figure 6.** Replacement by the emerged strain in the pandemic model. Frequency of replacement calculated by 500 simulations for each parameter setting. Pre-immunity ($1 - p_{pst}$), $R_0$, and non-strain-specific immunity period of the pandemic virus are the parameter variables. Error bars show 95% confidence intervals.

antigenic variant was analysed for both seasonal and pandemic influenza by simulation modelling. A recent study by Bedford et al. showed the global dynamics of the influenza virus by analysing how the virus can be disseminated among different countries (i.e., among populations).[26] On the other hand, the present study investigated the local dynamics of the virus within a population. The virus causing a seasonal epidemic in temperate regions is probably imported from the tropics where year-round circulation of the virus is ongoing.[16–18,23] In addition to the significance of the tropical region as a virus reservoir during an inter-epidemic period in the temperate region, this study found that the tropical region could play an important role as a place for replacement.

Even if a new strain emerges in the temperate region, it might be difficult to detect the emerged strain because of a low level of circulation. Usually only a small fraction of circulating strains can be detected and characterized in influenza surveillance. Yet, once such an emerged strain appears in the tropical region or appears in the temperate region and is then imported into the tropical region, the strain is more likely to be detected because of a high probability of replacement in the tropical region. Interestingly, the present findings suggest that timing (stage of epidemic and herd immunity for the existing strain) barely affects replacement in the tropical region (Figure 4). While a new antigenic variant is thought to have emerged in Southeast Asia and then spread to other parts of the world,[16–18] this is still controversial.[42] This study proposes another possibility – that such an antigenic variant can emerge anywhere worldwide. Once such a virus is introduced into the tropical region, it can become dominant by replacement, since replacement is more likely to occur where there is no or little seasonality of influenza. This could be why new antigenic variants tend to be found first in Southeast Asia.[16,17] Furthermore, there are a few reports on the shift of antigenic variants during one epidemic season,[43] although the majority of such a shift was observed in two influenza seasons in the temperate region.[44,45] That can also be explained by replacement (shift of antigenic variants) in the tropical regions. The infection rate in the tropical regions, which is constant and adequate but lower than that in the high season of temperate regions, is responsible for a high chance of replacement there in the model presented herein. It is still not known whether the epidemiological characteristics there are only the result of climate factors or a combination of climate and environmental factors such as poor hygiene and infection control in developing countries in the tropical regions.[20,46]

The pandemic influenza virus had a much higher frequency of replacement compared to the seasonal influenza virus in the present simulations (Figure 3B and Figure 6). In addition, the frequency of replacement was higher in the 'non-seasonality model' than in the 'seasonality model'. Southeast Asia can be a source of novel influenza A virus strains with a pandemic potential because of close interactions between poultry, swine, and humans, with a high human population density.[47] Not only is there a high probability of the advent of a novel influenza A virus from different host species in such a situation, but there is also a high probability of replacement by the emerged virus in an area at high risk of a pandemic. Historically, most pandemic viruses have expelled former seasonal viruses; the former seasonal viruses disappeared after the emergence of a pandemic virus.[5,6] Mechanisms for their replacement by a pandemic virus have barely been discussed and remain largely unknown. The present findings along with those reported in a recent paper by Asaduzzaman et al. using a different model, suggest that either or both a high initial susceptibility and high $R_0$ of a pandemic virus is required to cause the replacement.[27]

The H1N1 virus that re-emerged in 1977 (Russian flu) was genetically and antigenically close to H1N1 viruses isolated in the 1950s.[48] There must have been substantial herd immunity against the virus among those in the population aged over 25 years,[49,50] resulting in the co-circulation of two viruses without replacement. Similarly, the H3N2 virus did not disappear after the emergence of the A(H1N1)pdm09 virus, although the antigenically closer H1N1 virus – a descendant of the Russian flu virus – disappeared.[12,13] It has been reported that pre-immunity against the pandemic virus A(H1N1)pdm09 existed in the population, particularly in the elderly.[10,11] An epidemiological study showed that the initial susceptibility of the pandemic virus was just a little greater than the seasonal virus (75–76% vs. 64–71%).[31] Besides, the same study indicated that the estimated $R_0$ of the pandemic was as low as seasonal influenza.[31] These characteristics of the 2009 pandemic might be the reasons for no replacement of the H3N2 virus.

There are a couple of limitations to the present study. Firstly, age-specific parameters were not used in the model, in order to make the model simple. The contact rate, infection rate, and immunity must be different among age groups.[51,52] The individual-based stochastic model set different infection rates and immunity for each person. This could have reproduced heterogeneous populations to some extent. Still, the homogeneous mixing population in the model cannot reproduce age-specific social contacts and mixing patterns.[53] Secondly, epidemiological parameters used in the model were acquired from studies of different populations in different time periods (**Supplementary Material**). Since few epidemiological studies have focused on epidemiological characteristics of antigenic variants of influenza A virus, it was not possible to fit parameters in the model to observed data. It was simply assumed that those parameters are stationary in different populations over time.

The present study reports new aspects on the ecology of the influenza A virus. Replacement of an existing strain by an emerged strain takes place through the composite effects of viral evolution (antigenic change), host immunity, infectivity ($R_0$), and seasonality, although these factors are all intricately linked. Today, seasonal influenza vaccine strains are updated every few years to match the strains circulating in the coming season. Since replacement by a new antigenic variant is likely to take place in the tropical region, it is necessary to strengthen surveillance there in order to detect antigenic variants in a timely manner.[54] Such an effort could avoid a mismatch between circulating and vaccine strains.[55,56] Also, knowing whether a pandemic virus has replaced a former (seasonal) virus would be useful when considering which subtypes of the virus should be included in the vaccine. A universal vaccine that is effective for any subtypes of the influenza A virus by targeting the stalk region of hemagglutinin (HA) or conserved proteins like M2 is under development.[57,58] This study could also be a springboard for discussions on how such universal vaccines would affect the ecological dynamics of the viruses, including the replacement of strains.

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*Conflict of interest:* The authors declare no conflict of interest.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijid.2016.08.012.

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