Pre-pandemic live-attenuated influenza vaccine

DH He *, APY Chiu, JTK Wu, BJ Cowling

KEY MESSAGES

1. During the 2009 influenza pandemic in Hong Kong, matched vaccines for the pandemic strain were not available until 8 months after its start. We described the potential use of pre-pandemic seasonal vaccine to mitigate the next pandemic.
2. We used an age-structured epidemic model to identify the optimal timing and age-specific allocation strategies for administration of vaccinations.
3. With a stockpile of 200 000 doses, if we start vaccinating those aged 5 to 9 years and 15 to 19 years on day 1, the maximum peak time delayed is 17.4 days and the peak height reduction is 16.8%, compared with no vaccination.
4. If we start vaccinating on 98.8th day, the maximum reduction in death is 13.85% by vaccinating those aged 5 to 9 years and 15 to 19 years. The maximum reduction in hospitalisation is 15.00% by vaccinating those aged 5 to 19 years.
5. In future influenza pandemic with limited vaccine stockpile, vaccinating those aged 5 to 19 years one week before the major wave can minimise the number of hospitalisations and deaths. Vaccination campaign should be started early in order to delay the arrival of a major wave of infections and reduce its height.

Hong Kong Med J 2019;25(Suppl 9):S24-7
HMRF project number: 13121382

[1] DH He, [1] APY Chiu, [2] JTK Wu, [2] BJ Cowling

[1] *Department of Applied Mathematics, The Hong Kong Polytechnic University*
[2] *WHO Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong*

* Principal applicant and corresponding author: daihai.he@polyu.edu.hk

Introduction

During the 2009 influenza pandemic in Hong Kong, matched vaccines for the pandemic strain were not available until 8 months after its start. This study described the potential use of pre-pandemic seasonal vaccine to mitigate the next pandemic. A randomised trial of inactivated vaccine in Hong Kong suggested that seasonal influenza infection provides strong but possibly short-lived protection against pandemic influenza.[1] Children are protected against respiratory infections in general for the first few weeks after vaccination with live-attenuated influenza vaccine (LAIV). The strength and duration of this effect appears to be non-specific and may last a few weeks if associated with the innate immune response. This is known as temporary non-specific immunity (TNI).[2]

This study investigated strategies to use LAIV to mitigate a future influenza pandemic in Hong Kong. If LAIV is useful in mitigating a pandemic, this may support the idea of increasing seasonal coverage of LAIV. We expect that the TNI effect, the limited cross-protection post TNI, and the consequent interference (herd immunity, indirect benefit) at the population level may act together to slow the transmission and soften the impact to health services.

Assuming that LAIV can provide up to 2 weeks' protection against pandemic infection and limited cross-protection post TNI, what are the optimal vaccination administration strategy, optimal age-specific allocation plan, and optimal timing of vaccination? This study aimed (1) to maximise the peak height reduction of hospitalisation rates and peak time delayed in order to reduce peak demand for healthcare services, and (2) to minimise the total number of hospitalisations or deaths. We would vaccinate core transmitters and high-risk persons if the stockpile is large enough to hinder transmission. Assuming post TNI cross-protection is negligible, the optimal timing is to have the 2-week TNI to cover the period during which the force of infection is the highest.

Methods

In our age-structured epidemic model,[3] S denoted susceptible, E exposed, I infectious, R recovered, T those who have been given LAIV and have acquired TNI, P those who have lost TNI but have acquired limited immunity, H those who are hospitalised, and D deaths. Individuals aged 0 to 69 years were subdivided into fourteen 5-year groups plus an additional group of 70+ years (S_1 to S_{15}).

Without vaccination, a susceptible individual may go through: susceptible → exposed → infectious → (hospitalised) → recovered (or death). Stages with parentheses may be skipped. With vaccination, a susceptible individual may go through: susceptible →

TNI → (P: limited long-term immunity) → exposed → infectious → (hospitalised) → recovered (or death).

Infections can happen both within and between age-groups. We assume that transmissions happen from an infectious age-group i to a susceptible age-group j at a rate of $\beta_{ji}S_{ji}$. β_{ji} is called the transmission rate matrix. T and P individuals can also be infected but at reduced rates of $\eta\beta_{ji}S_jI_i$ and $\xi\beta jiSjIi$, respectively. Exposed individuals become infectious at a rate σ, and the mean latent period is $1/\sigma$. Infectious becomes recovered at a rate γ, and the mean infectious period is $1/\gamma$. T becomes P at a rate of κ, which is chosen such that the duration of TNI is about 2 weeks. Infectious is diagnosed and hospitalised at an age-specific rate h_i (from I_i to H_i). Hospitalised die at an age-specific rate d_i (from H_i to D_i). The model diagram without age structure is shown in Fig 1.

Fitting model to observed infection attack rate

We incorporated reasonable epidemiological parameter values and the age structure of the Hong Kong population into the model. For the contact matrix, we used the PolyMOD data of United Kingdom.[3] We re-scaled and altered part of the contact matrix, such that the yield age-profile of the attack rate may match the observed infection attack rate age-profile of the 2009 pandemic influenza in Hong Kong. We assumed that the prior immunity against the pandemic strain was linearly from 4% (age 0-4 years) to 39% (age ≥70 years).[4]

Infection peak time delayed and peak height reduced

We assumed that vaccine stockpile was sufficient for 200 000 individuals. For a targeted age class i, susceptible patients were vaccinated on a first-come first-serve basis until the stockpile ran out. The vaccination campaign was assumed to last for about 10 days. According to Centers for Disease Control and Prevention, the LAIV is only suitable for individuals aged 5 to 49 years. Each age-group was either vaccinated or not vaccinated. We had 512 different scenarios of target age-groups.

Results

Through simulations, a late start of the vaccination campaign only led to short or no delay in the peak of the influenza infections. We fixed the vaccination campaign on day 1 (beginning of the pandemic). We assumed the pandemic was ignited by n (2 to 20) infectious individuals in the each of the three age-groups (30-34, 35-39, and 40-45 years). We simulated each scenario 100 times (with a random number of seeds) and then averaged the outcomes. We considered 512 combinations of vaccination for various age-groups. For instance, scenario 1 was vaccination for those aged 5 to 49 years and scenario 512 was no vaccination. The maximum delay of the peak time of 17.4 days was achieved if those aged 5 to 10 and 15 to 19 years were vaccinated starting from day 1 of the pandemic, with a stockpile of 200000 (Fig 2). The second, third, and fourth optimal scenarios were vaccinating those aged 10 to 19, 5 to 14, and 5 to 19 years, respectively. Vaccinating all eligible ages (5-49 years) is less than ideal. The height of the peak was reduced by 16.78%, 15.86%, 15.76%, and 15% by vaccinating those aged 5 to 10 or 15 to 19, 10 to 19, 5 to 14, and 5 to 19 years, respectively. Fig 3 shows the effects of varying start dates of vaccination campaign on the numbers of hospitalisations and deaths secondary to the pandemic with a stockpile of 200 000 doses.

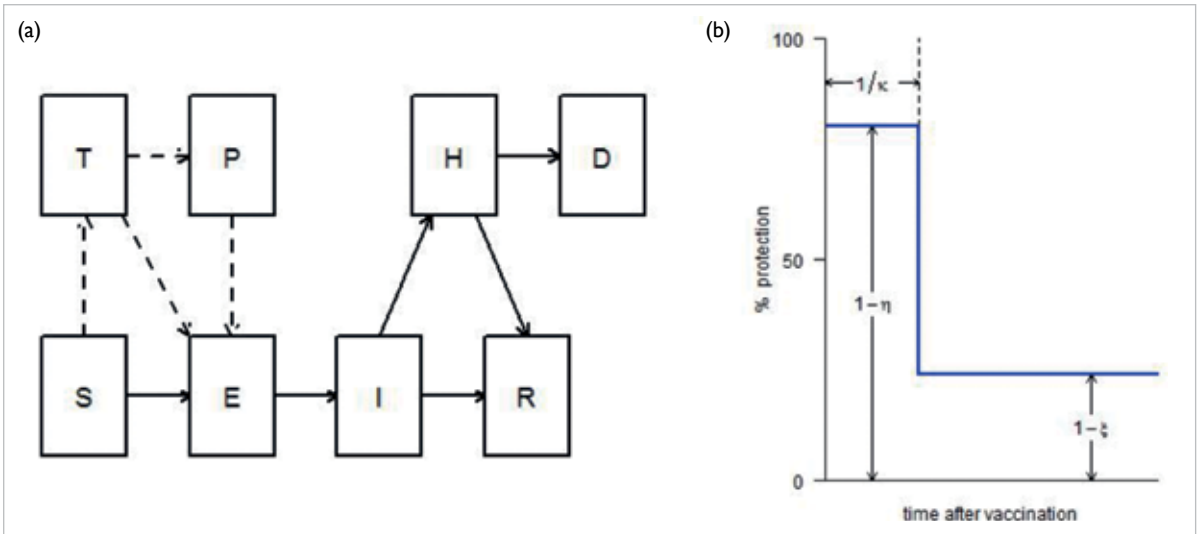

FIG 1. (a) Model structure without specifying age structure; (b) schematic diagram of cross-protection provided by temporary non-specific immunity.

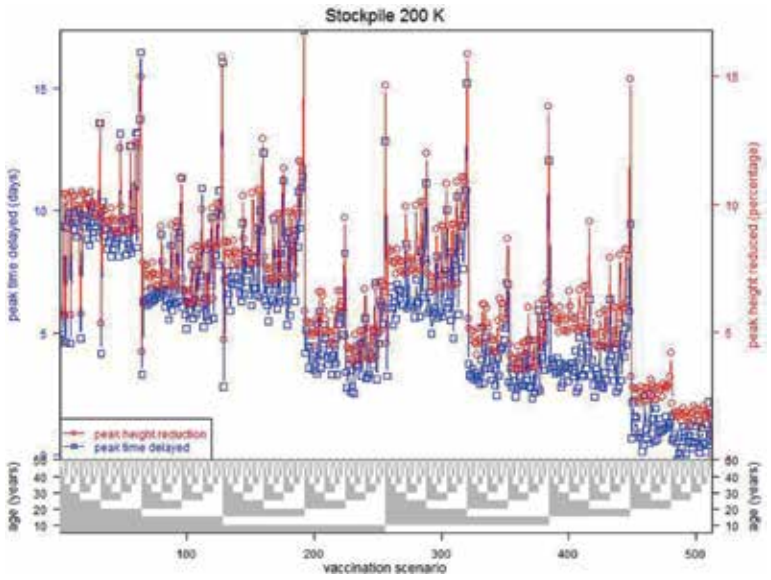

FIG 2. The impacts of temporary non-specific immunity on the infection peak time delayed and peak height reduction under different vaccination scenarios, with a stockpile of 200 000 doses and the campaign starting on day 1. The optimal strategy is to start vaccinating for those aged 5-10 and 15-19 years. The maximum peak time delayed is 17.4 days and the maximum peak height reduction is 16.78%.

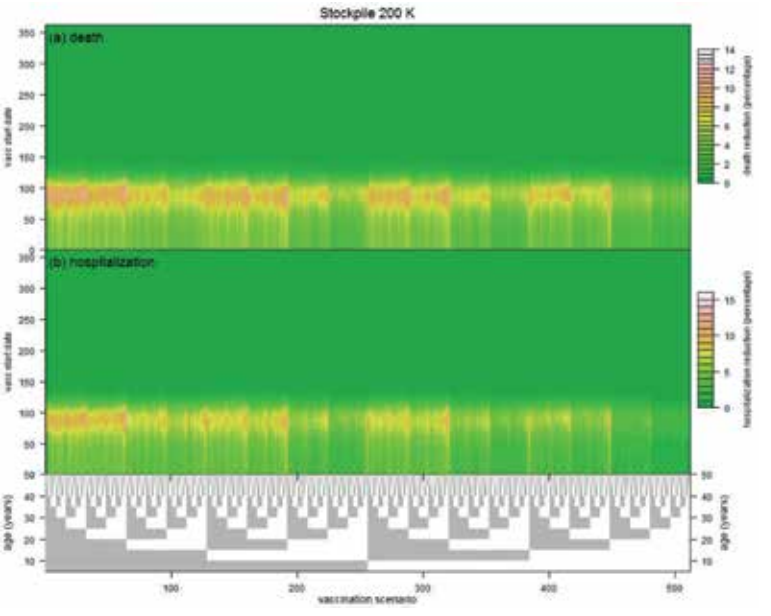

FIG 3. Effects of varying start dates of vaccination campaign on reduction of (a) death and (b) hospitalisation (in percentage) with a stockpile of 200 000 doses. The largest reduction is achieved on the 98.8th day for death when vaccinating those aged 5-9 and 15-19 years and for hospitalisation when vaccinating those aged 5-19 years, and maximum reduction is 13.85% for death and 15% for hospitalisation.

Discussion

Assuming a stockpile of 200 000 LAIV doses, if the goal is to reduce hospitalisations and deaths as much as possible, vaccination should not be started until the arrival of the major wave (a week before the peak time) to maximise the effect of TNI. The target age-group should be those aged 5 to 19 years. If the goal is to delay the arrival time of the major wave of infections and to reduce its height, the vaccination campaign should be started as early as possible, because the initial development stage plays a crucial role on the arrival time of the major wave.

Our models are calibrated to the observed infection attack rates in a Hong Kong study by Wu et al.[5] We have considered several plausible scenarios to make our model more applicable for policymakers' decision making. Previous studies on optimal strategies for mitigating an influenza pandemic showed that school-age children should be the priority groups for vaccination because they have higher contact rates and higher secondary attack rate of household transmission.

Our study has limitations. We made simplifying assumptions about several epidemiological features the pandemic influenza: we did not consider (1) the possibility of multiple waves of pandemic influenza, (2) the impact of co-circulation of seasonal influenza during a pandemic, and (3) cross-subtype immunity and age-variations of vaccine efficacy. In addition, we did not consider the impacts of multifaceted intervention strategies in our mathematical model. During an influenza pandemic, both non-pharmaceutical and pharmaceutical intervention strategies are likely to be applied. Furthermore, the age-structured epidemic model did not consider other risk groups such as people with chronic respiratory disease, those aged ≥65 years, and healthcare workers.

Conclusion

An age-specific compartmental model is useful for studying pandemic influenza transmission and determining the optimal mitigation strategies. We highlight the use of seasonal LAIV and an age-specific allocation process.

Acknowledgement

This study was supported by the Health and Medical Research Fund, Food and Health Bureau, Hong Kong SAR Government (#13121382).

Results from this study have been published in:

(1) He D, Chiu APY, Lin QY, Cowling BJ. Differences in the seasonality of MERS-CoV and influenza in the Middle East. Int J Infect Dis 2015;40:15-16.

(2) He D, Lui R, Wang L, Tse CK, Yang L, Stone L. Global spatio-temporal patterns of influenza in the post-pandemic era. Sci Rep 2015;5:11013.

(3) Yang L, Chan KH, Suen LK, et al. Impact of the 2009 H1N1 pandemic on age-specific epidemic

curves of other respiratory viruses: a comparison of pre-pandemic, pandemic and post-pandemic periods in a subtropical City. PLoS One 2015;10:e0125447.

References

1. Cowling BJ, Ng S, Ma ES, et al. Protective efficacy of seasonal influenza vaccination against seasonal and pandemic influenza virus infection during 2009 in Hong Kong. Clin Infect Dis 2010;51:1370-9.
2. Kelly H, Barry S, Laurie K, Mercer G. Seasonal influenza vaccination and the risk of infection with pandemic influenza: a possible illustration of non-specific temporary immunity following infection. Euro Surveill 2010;15:pii:19722.
3. Wallinga J, Teunis P, Kretzschmar M. Using data on social contacts to estimate age-specific transmission parameters for respiratory-spread infectious agents. Am J Epidemiol 2006;164:936-44.
4. Dorigatti I, Cauchemez S, Ferguson NM. Increased transmissibility explains the third wave of infection by the 2009 H1N1 pandemic virus in England. Proc Natl Acad Sci U S A 2013;110:13422-7.
5. Wu JT, Leung K, Perera RA, et al. Inferring influenza infection attack rate from seroprevalence data. PLoS Pathog 2014;10:e1004054.