Epidemics 13 (2015) 17–27

Contents lists available at ScienceDirect

Epidemics

journal homepage: www.elsevier.com/locate/epidemics

One versus two doses: What is the best use of vaccine in an influenza pandemic?

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ARTICLE INFO

Article history:
Received 17 December 2014
Received in revised form 22 May 2015
Accepted 1 June 2015
Available online 22 June 2015

Keywords:
Influenza
Influenza vaccine
Mathematical model
Infectious disease modeling

ABSTRACT

Avian influenza A (H7N9), emerged in China in April 2013, sparking fears of a new, highly pathogenic, influenza pandemic. In addition, avian influenza A (H5N1) continues to circulate and remains a threat. Currently, influenza H7N9 vaccines are being tested to be stockpiled along with H5N1 vaccines. These vaccines require two doses, 21 days apart, for maximal protection. We developed a mathematical model to evaluate two possible strategies for allocating limited vaccine supplies: a one-dose strategy, where a larger number of people are vaccinated with a single dose, or a two-dose strategy, where half as many people are vaccinated with two doses. We prove that there is a threshold in the level of protection obtained after the first dose, below which vaccinating with two doses results in a lower illness attack rate than with the one-dose strategy; but above the threshold, the one-dose strategy would be better. For reactive vaccination, we show that the optimal use of vaccine depends on several parameters, with the most important one being the level of protection obtained after the first dose. We describe how these vaccine dosing strategies can be integrated into effective pandemic control plans.

1. Introduction

On April 1st 2013, the first cases of human infection with influenza A (H7N9) were reported in China (WHO, 2013). As of November 17th, 2014, over 450 cases have been reported (CIDRAP, 2014a), with an estimated 30% mortality rate (CIDRAP, 2014b). Studies have shown that this strain may be better adapted to mammalian hosts than other avian strains (Xu et al., 2013; Chan et al., 2013), raising a global concern that influenza A (H7N9) could acquire the ability to transmit from person to person triggering a new influenza pandemic (Uyeki and Cox, 2013). In response to this threat, several candidate vaccines are currently being tested, with most of them requiring two doses: a prime and a boost three weeks later (CIDRAP, 2013; WHO, 2013). With new cases arising continuously (WHO, 2014), avian influenza A (H5N1) remains a threat (Linster et al., 2014). Vaccination remains the most effective intervention against pandemic influenza, but in the event of a pandemic, vaccine will likely be in short supply (Osterholm et al., 2013).

We developed a mathematical model to evaluate two possible strategies for allocating limited vaccine supplies: a *one-dose strategy*, where more people are vaccinated with a single dose of vaccine, or a *two-dose strategy*, where half as many people are vaccinated with the full, required, two doses. We considered both pre-pandemic vaccination and reactive vaccination. For pre-pandemic vaccination, we demonstrated that under certain conditions, there is a threshold in the primary response level (defined as the percentage of the full vaccine efficacy that will be reached after the first dose), below which the two-dose strategy is better, but above which vaccinating the most people with a single dose would yield lower attack rates. We analyzed different parameters affecting the course of an epidemic to determine which ones carry the most weight in favoring a one-dose versus a two-dose strategy: initiation of vaccination with respect to the start of the epidemic, primary response level, vaccination coverage, the kinetics of the vaccine efficacies post-vaccination as functions of time, and transmissibility of the virus, measured through the basic reproduction number, R_0 (defined as the expected number of secondary

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http://dx.doi.org/10.1016/j.epidem.2015.06.001

infections resulting from a single typical infectious person in a completely susceptible population).

For each parameter set, we found a threshold in the value of R_0, below which the strategy of fewer vaccinees with two doses results in a smaller final illness attack rate (defined as the percentage of the population who become infected and ill) than the strategy of more vaccines with one dose. Above this threshold, our model predicts that vaccinating more people with one dose is better. Though the threshold depends on all the parameters considered, the primary response level is the most important. Because a vaccine shortage is very likely to occur for pandemic influenza, our results could provide valuable insights for allocating limited resources.

2. Methods

We used a classic susceptible–infected–removed (SIR) differential equations model to simulate an influenza epidemic in a homogeneous population. Briefly, the population is partitioned into those who are susceptible unvaccinated or vaccinated, infectious unvaccinated or vaccinated, asymptomatic or symptomatic, and recovered. A fraction of those infected will develop symptoms, while the rest remain asymptomatic. Infected asymptomatic people are less infectious than those who are symptomatic. Fig. 1A shows a schematic diagram of the model.

Vaccine is assumed to be "leaky" (Halloran et al., 1989), that is, vaccine confers partial protection to all vaccinees. The effect of vaccination in an individual is modeled following Halloran et al. (1997) in which vaccine protection has three possible components: First, vaccinated individuals have a reduced probability of becoming infected (vaccine efficacy on susceptibility, VE_S). Then, once infected, a vaccinated individual has a reduction in his/her infectiousness (vaccine efficacy to reduce infectiousness given infection, VE_I), and a reduction in the probability of developing symptoms (vaccine efficacy to prevent or diminish symptoms VE_P).

During the first two weeks after the first dose, the vaccine efficacies increase until they reach their *primary response level*, r_1, defined as the percentage of the overall maximum efficacy obtained after the full recommended two doses. For example, a *primary response level* of 50% corresponds to obtaining half of the protection after one dose, and full protection after two doses.

We further assumed that it would take only one week for the second dose to reach its full efficacy, and that the vaccine efficacy components would remain constant during the third week before the second dose.

Little is known about the pharmacodynamics of influenza vaccines and their interplay with the immune response. Since we were interested in investigating the impact of the shape and the speed of the vaccine efficacy kinetics on the population-level attack rates of the *one-* and *two-dose strategies*, we modeled vaccine efficacy building up over time and constructed, for each vaccine efficacy component, a family of functions that allows us to change these features. A concave shape corresponds to a vaccine in which protection is acquired mostly during the first few days after vaccination and then levels off. A convex shape corresponds to a vaccine efficacy in which protection takes a few days to kick in, then grows exponentially, finally leveling off during the last few days (Fig. 1B). The full description of the model, its equations, and the parameters values used here are presented in the Appendix. In the text below, the values of VE_S, VE_I, and VE_P always refer to the vaccine efficacy values obtained after the second dose of vaccine.

We analyzed vaccination under two different settings: prepandemic vaccination in which vaccination occurs well before the epidemic starts, and reactive vaccination in which vaccination occurs after the epidemic has started. We considered vaccinating 50% of the population with a single dose of vaccine or 25% of the population with two doses. A sensitivity analysis showed that our conclusions do not depend on the population coverage (Supplemental material).

3. Results

3.1. Prepandemic vaccination

In this section we assume that vaccination occurred before the beginning of the epidemic, so that vaccinated people have acquired all the protection given by a vaccine before the epidemic starts. This scenario allows us to mathematically analyze the model in full detail.

Here, we considered a variety of vaccines with different characteristics. First, assume a vaccine reducing susceptibility only (so that $VE_S > 0$ but $VE_I = 0 = VE_P$). This is the most common perception of how a vaccine works. We analytically demonstrated that for this model, there is a threshold in the primary response level, $r_1^* > 0.5$, that depends on the other parameters, at which the two strategies are equivalent. If $r_1 < r_1^*$, then the *two dose strategy* is always better, but, if $r_1 > r_1^*$ vaccinating twice as many people with one dose would result in lower attack rates (Fig. 2A and Theorem 1, Appendix).

Then, suppose that we have a vaccine that reduces either infectiousness only (so that $VE_I > 0$ but $VE_S = 0 = VE_P$) or pathogenicity only (so that $VE_P > 0$ but $VE_I = 0 = VE_S$). In both cases, we analytically proved that the threshold r_1^* in the primary response level is exactly 50%, and that this threshold is independent of all the other parameters of the model (Fig. 2B and C, and Theorems 2 and 3, Appendix).

Finally, using numerical simulations, we studied prepandemic vaccination when the three vaccine efficacy components can take any non-negative value. We considered four different vaccines: a low-efficacy vaccine ($VE_S = 15\%$, $VE_I = 0\%$, and $VE_P = 24\%$), a medium-efficacy vaccine ($VE_S = 40\%$, $VE_I = 22.5\%$, and $VE_P = 62\%$), a vaccine as efficacious as a seasonal vaccine ($VE_S = 40\%$, $VE_I = 45\%$, and $VE_P = 75\%$), and a high-efficacy vaccine ($VE_S = 66\%$, $VE_I = 45\%$, and $VE_P = 100\%$). These values were taken from *Basta et al.*, where the authors used challenge and community-based study data to estimate seasonal influenza vaccine efficacy (Basta et al., 2008). When $r_1 = 30\%$, for all the vaccines considered, the *two-dose strategy* was better with a maximum absolute difference of 6% in the attack rate (for $R_0 = 1.4$ and the medium-efficacy vaccine, Fig. 3A). For $r_1 = 50\%$ and $r_1 = 70\%$ and for all these vaccines, our simulations suggested that vaccinating with a single dose would be better than vaccinating half as many people with two doses. This difference was accentuated with more efficacious vaccines, with the highest difference seen for the high-efficacy vaccine when $R_0 = 1.5$ and $r_1 = 50\%$ (10% difference in the attack rate, Fig. 3B); and for $R_0 = 1.6$ for $r_1 = 70\%$ (16% difference in the attack rate), Fig. 3C.

3.2. Reactive vaccination

Next, we considered the situation in which vaccination is provided after the epidemic has started by solving the differential equations numerically. We assumed that the three components of vaccine efficacy are non-negative, and that they all reach the same primary response level after a single dose of vaccine. We considered vaccination taking place 45, 60, 75, or 90 days after the epidemic has started (Fig. S1). We also considered a model in which vaccination campaigns are stretched over 10, 20 or 30 days, and showed that our results are robust to this change (Sensitivity Analysis, Figs. S2–S6).

Our results suggested that there is a threshold R^*, in the basic reproduction number, above which priming a large number of