

## A SIMPLE MATHEMATICAL APPROACH TO DECIDING THE DOSAGE OF VACCINE AGAINST PANDEMIC H1N1 INFLUENZA

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Results from early clinical trials have shown that a single dose of pandemic H1N1 influenza vaccine may generate sufficient antibody response, but the relevance of this fact to public health decision making has yet to be clarified. The present study compares the risk of clinical attack (i.e. clinical attack rate) between one- and two-dose vaccination schemes. If the efficacies do not greatly vary between one- and two-dose schemes, one-dose vaccination may well be supported. Nevertheless, two-dose vaccination is shown to result in less morbidity if the vaccine efficacies are greatly diminished by reducing the dose. As long as the detailed efficacy estimates rest on theoretical assumptions, single-dose vaccination may only be sufficiently justified in a specific setting where the number of vaccines is extremely limited.

### Introduction

As the world has experienced the global spread of the pandemic H1N1 influenza since April 2009, various pandemic vaccines have been manufactured around the world to reduce the incidence of the disease and to prevent severe illness and death. Since the number of vaccines that can be produced in parallel with a growing pandemic wave is limited, optimal timing of vaccination and prioritisation strategies have been sought to minimise the potential impact [1-3]. Results from early clinical trials have shown that a single dose of H1N1 vaccines probably generates antibody response at a sufficient level [4,5]. Following this early evidence, in United States it has been suggested that individuals aged  $\geq 10$  years receive a single dose [6]. However, although the early studies report immunogenicity (expressed as antibody titres) and safety of vaccination [4,5], their relevance to public health decision making has yet to be clarified. Taking into consideration that vaccines produced by various manufacturers differ in composition (e.g. adjuvanted and unadjuvanted vaccines), and optimal route of administration (i.e. intramuscular and subcutaneous injections), policymakers have faced the difficult choice whether to choose a one- or a two-dose regimen. The present study proposes a simple mathematical approach to deciding the optimal dosage of a pandemic vaccine by clarifying the population level implications of choosing either the one- or the two-dose vaccination scheme.

### Methods

#### Theoretical basis

The number of doses of vaccine to use against the pandemic H1N1 influenza has not been established to date. Given that the antibody response to single-dose vaccination is not significantly

different from that to a two-dose regimen (i.e. one dose on day 0 and another dose typically on day 21 or 28), the practical implication is that with one-dose alone we can vaccinate a population twice as large as that vaccinated with a two-dose regimen. In other words, given that the limited number of vaccines covers a proportion  $f$  of the population with a two-dose regimen, a one-dose regimen is expected to cover a proportion  $2f$  with the similar efficacy. Nevertheless, the expected risk of clinical attack (i.e. which is equivalent to the so-called clinical attack rate or illness attack rate) at the end of an epidemic is influenced by herd immunity (which is non-linear), and most importantly, the actual protective effects of vaccination are unknown for both one- and two-dose schemes. Accordingly, we formulated our study question as follows: "Which should we implement, one- or two-dose vaccination, to minimise the risk of contracting influenza?" Whereas the optimal dosing of a pandemic vaccine against H5N1, accounting for continuous dose-response phenomena [7,8] has been discussed, our approach is different from previous studies in that we solely focus on two discrete doses, i.e., one- or two-dose regimens alone, analysing a wide range of relative efficacies for the one-dose regimen compared to two-dose scheme specifically against the pandemic H1N1 influenza virus.

#### Epidemiological model

Our arguments rest on a type of Kermack and McKendrick epidemic model. For mathematical convenience, and to offer simple arguments which are not case-specific (i.e. arguments which are independent of the ongoing pandemic waves), we assume that vaccination takes place sufficiently in advance of a pandemic. The numbers of unvaccinated and vaccinated new cases at calendar time  $t$ ,  $j_u(t)$  and  $j_v(t)$ , respectively, are described by the following renewal equations [9]:

(1)

$$j_u(t) = R_{uu}(t) \int_0^\infty j_u(t-s)g(s)ds + R_{uv}(t) \int_0^\infty j_v(t-s)g(s)ds,$$

$$j_v(t) = R_{vu}(t) \int_0^\infty j_u(t-s)g(s)ds + R_{vv}(t) \int_0^\infty j_v(t-s)g(s)ds,$$

where  $R_{ij}(t)$  represents the average number of secondary cases in sub-population  $i$  generated by a single primary case in sub-population  $j$  at calendar time  $t$ , and  $g(s)$  is the density function of the generation time. Linearising the system (1) near the disease-free equilibrium, we get the next-generation matrix:

(2)

$$K = \begin{pmatrix} R_{uu}(0) & R_{uv}(0) \\ R_{vu}(0) & R_{vv}(0) \end{pmatrix}$$

Let  $p_i$  be the vaccination coverage under an  $i$ -dose vaccination scheme ( $i = 1$  or  $2$ ),  $p_1 = 2p_2$  for  $p_2 \leq 0.5$ . There are two different types of efficacy which directly influence the transmission dynamics; i.e., reductions in susceptibility and in infectiousness, denoted by  $\alpha_s$  and  $\alpha_i$ , respectively. We assess the risk of a clinical attack in a homogeneously mixing population in which the next-generation matrix is simplified as

(3)

$$K = R \begin{pmatrix} (1-p_2) & (1-p_2)(1-\alpha_i) \\ p_2(1-\alpha_s) & p_2(1-\alpha_s)(1-\alpha_i) \end{pmatrix}$$

for a two-dose regimen, and

(4)

$$K = R \begin{pmatrix} (1-p_1) & (1-p_1)(1-k_i\alpha_i) \\ p_1(1-k_s\alpha_s) & p_1(1-k_s\alpha_s)(1-k_i\alpha_i) \end{pmatrix}$$

for one-dose regimen where  $R$  is referred to as the reproduction number, i.e., the average number of secondary cases generated by a typical infected individual at the initial growth phase of an epidemic. It should be noted that we do not use more widely known notation, the basic reproduction number,  $R_0$  in light of the potential presence of immune adults before the pandemic.  $k_s$  and  $k_i$ , respectively, represent the relative efficacies of  $\alpha_s$  and  $\alpha_i$  for a one-dose regimen compared to a two-dose scheme ( $k_s, k_i \leq 1$ ). The reproduction number under vaccination  $R_v$  is expressed as  $R\{1-p_2+p_2(1-\alpha_s)(1-\alpha_i)\}$  for a two-dose scheme and  $R\{1-p_1+p_1(1-k_s\alpha_s)(1-k_i\alpha_i)\}$  for a one-dose scheme.

Assuming that everyone without vaccination is susceptible before the epidemic, the proportions of those who have experienced infection by the end of the epidemic (i.e. final sizes) among unvaccinated and vaccinated individuals,  $z_u$  and  $z_v$ , are given by [10]:

(5)

$$z_u = 1 - \exp[-(R_{uu}(0)z_u + R_{uv}(0)z_v)],$$

$$z_v = 1 - \exp[-(R_{vu}(0)z_u + R_{vv}(0)z_v)].$$

Let  $b$  be the conditional probability of symptomatic disease given infection. The expected risk of clinical attack is expressed as  $b[(1-p_u)z_u + p_i(1-\alpha_p)z_v]$  where  $\alpha_p$  is the efficacy of reducing the probability of symptomatic disease, assumed to be independent of the transmission dynamics. We examine the sensitivity of the expected risk of clinical attack for different values of  $\alpha_s$ ,  $\alpha_i$  and  $\alpha_p$  by iteratively solving  $z_u$  and  $z_v$  in equations (5), where  $R_{ij}(0)$  are dependent on the reproduction number ( $R$ ), susceptibility effect ( $\alpha_s$ ), vaccine-induced reduction in infectiousness ( $\alpha_i$ ) and vaccination coverage ( $p_i$ ).

#### Vaccine efficacy and other parameter values

The Table summarises parameter values that we extracted from literature. Although the reproduction number may vary across

time and place as the subpopulations involved tend to vary greatly [11-17], we assume  $R = 1.5$  as a common estimate in different settings [1,11,12]. The conditional probability,  $b$ , of developing symptomatic disease (given infection) has been suggested to be 66.7% [18]. Since vaccine efficacy estimates for the pandemic H1N1 influenza have yet to be reported, we adopt the estimates for seasonal influenza vaccines from an epidemiological analysis of metadata [19]. Conservatively, we assume that  $\alpha_i$  and  $\alpha_p$  following

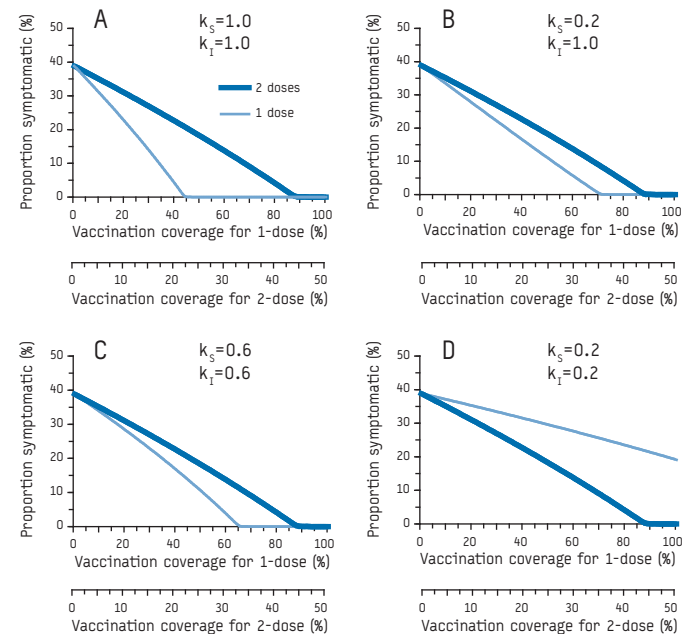
TABLE

#### Parameter values used for comparative risk assessment of vaccination against pandemic H1N1 influenza

Parameter	Value	References
Reproduction number ( $R$ )	1.5	[1,11,12]
Conditional probability of symptomatic disease given infection ( $b$ )	66.7 %	[18]
Reduction in susceptibility ( $\alpha_s$ )	40.0%, 60.0%, 80.0%	Assumption and [19]
Reduction in infectiousness ( $\alpha_i$ )	40.0 %	[19]
Reduction in the risk of contracting clinical disease ( $\alpha_p$ )	67.0%	[19]

FIGURE 1

#### The expected risk of clinical attack as a function of vaccination coverage



Panels A-D compare the expected risks of contracting clinical disease between one- and two-dose vaccination schemes with different dose-related protective effects. The vaccination coverage (horizontal axis) for a one-dose regimen is twice as large as that for a two-dose scheme.  $k_s$  represents the relative efficacy (of one dose as compared to two doses) for reducing susceptibility, while  $k_i$  represents the relative efficacy of reducing infectiousness by the same dose reduction. The relative reduction in reducing the conditional probability of symptomatic disease (given infection) is assumed to be equal to that of infectiousness. The baseline parameters for a two-dose vaccination scheme are shown in Table, and the reduction in susceptibility  $\alpha_s$  is assumed to be 0.6 for two-dose regimen.

a two-dose regimen are the same as those reported in [19] for inactivated vaccine (the estimates in literature are based on a one-dose regimen). We allowed  $\alpha_s$  following two-dose vaccination to vary from 40% to 80% where the lower bound is equivalent to an estimate of meta-analysis based on one-dose scheme [19]. For a one-dose scheme, we assume that the susceptibility effect is reduced to  $k_s\alpha_s$  where  $k_s \leq 1$ . Similarly, the reduction in infectiousness and the conditional probability of clinical disease given infection are reduced to  $k_i\alpha_i$  and  $k_i\alpha_p$  where  $k_i \leq 1$ ; for simplicity we use the identical reduction factor for these two different types of efficacy.

### Results

Figure 1A shows the baseline results of the risk of clinical attack as a function of vaccination coverage, assuming that the efficacies are identical between one- and two-dose vaccinations. In the absence of vaccination, 38.9% of the population is expected to experience clinical attack. If the efficacy estimates were identical, a one-dose vaccination could limit the impact using only half of the vaccine doses which are required for a two-dose scheme.

The superiority of a one-dose regimen is maintained even when  $k_s$  is reduced to 0.2 (with  $k_i = 1.0$ ; Figure 1B), though the vaccination coverage needs to be higher to achieve the similar reduction of the risk of clinical attacks to that in Figure 1A. Even when both  $k_s$  and  $k_i$  are reduced (Figure 1C), this relationship (i.e.

one-dose being superior) is still maintained. Nevertheless, when both  $k_s$  and  $k_i$  are greatly reduced (to 0.2; Figure 1D), a two-dose scheme becomes more efficient.

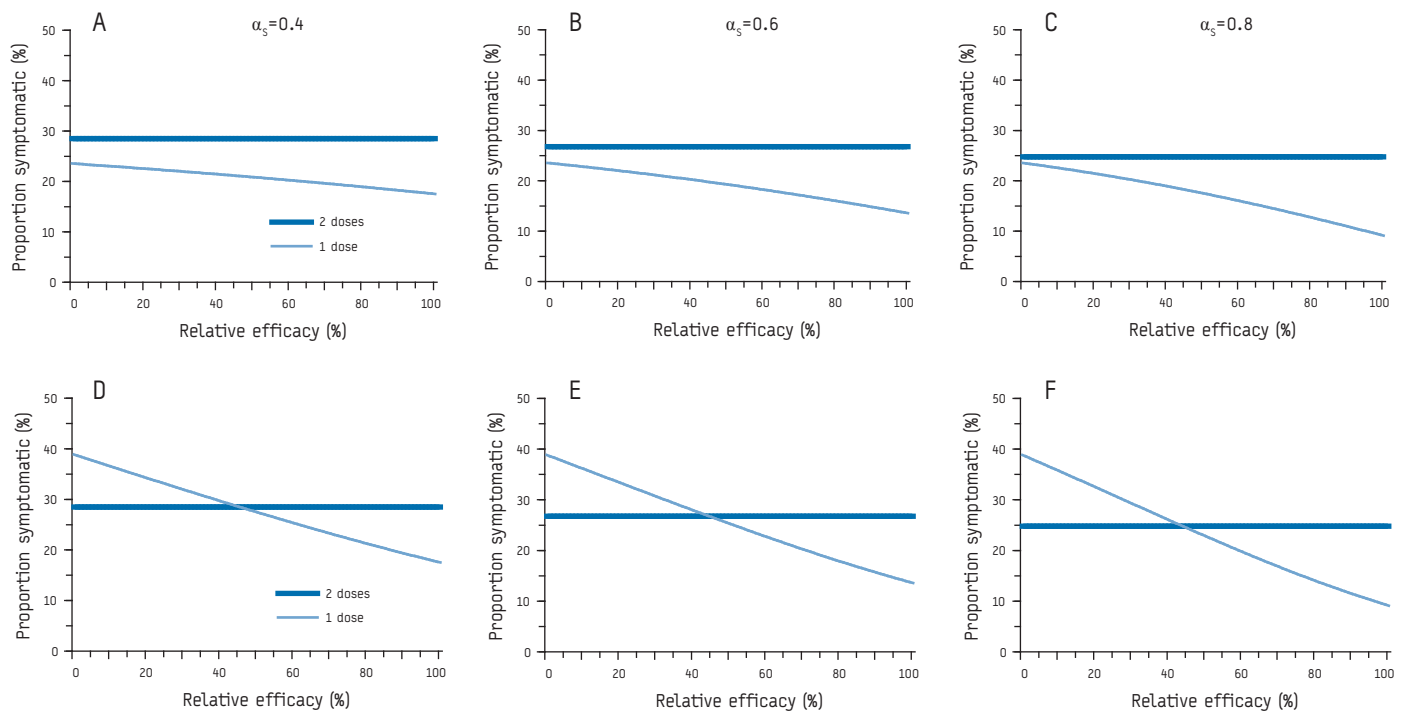
Figure 2 examines the sensitivity of the expected risk of clinical attack to different relative efficacy estimates (i.e.  $k_s$  and  $k_i$ ) due to dose-reductions with fixed vaccination coverage under a one-dose scheme (30%). Figures 2A-2C compare the risk between one- and two-dose vaccinations, assuming that  $k_s$  alone varies with dose and  $k_i$  is fixed at 1.0. The expected risk with a one-dose scheme is more sensitive to  $k_s$  with a higher  $\alpha_s$  estimate, but in general the superiority of a one-dose scheme is commonly seen. Figures 2D-2F compare the risks, varying both  $k_s$  and  $k_i$  simultaneously. If the dose-related relative reduction in efficacy is > 50%, a two-dose scheme yields a smaller risk of clinical attacks than a one-dose regimen. In addition, even when we discard the herd immunity effect (so that  $\alpha_s$  and  $\alpha_p$  alone would directly inform the frequency of clinical attack by  $1-(1-\alpha_s)(1-\alpha_p)$ ), a two-dose scheme yields smaller risk than that of a one-dose scheme for the large dose-related relative reduction in efficacy. For instance, if  $\alpha_s = 0.400$  and  $\alpha_p = 0.667$ , making  $k_i < 0.42$  shows the two-dose regimen to be superior to the one-dose scheme.

### Discussion

The present study compared the risk of clinical attack in pandemic H1N1 influenza under one- and two-dose vaccination

**FIGURE 2**

**The expected risk of clinical attack as a function of the relative efficacy of vaccination as a result of a reduction in vaccine dosage**



All panels compare the expected risks of contracting clinical disease between one- and two-dose vaccination schemes. In panels A-C, we assume that only the reduction in susceptibility is altered by reduction in the dosage of the vaccine. In panels D-F, all the efficacies (i.e. reductions in susceptibility, infectiousness and probability of symptomatic disease) are assumed to be equally reduced due to reduction in the vaccine dose. The baseline parameters for a two-dose vaccination scheme are shown in Table, and the reduction in susceptibility  $\alpha_s$  is assumed to be 0.4 (A and D), 0.6 (B and E) and 0.8 (C and F) under a two-dose regimen. The vaccination coverage is fixed at 30% for one dose and 15% for two doses.

regimens, with an intention to assist relevant public health decision making. Instead of studying the impact of vaccination on reducing the probability of death among high risk groups (e.g. reducing the risk of death among those with underlying medical conditions), we employed a simple transmission model to find the optimal vaccination strategy which reduces the transmission itself. A single dose enables us to vaccinate twice as many people as a two-dose scheme can cover. Under the circumstances of an extremely limited number of vaccines, one-dose vaccination may well be supported if the efficacies do not greatly vary between one- and two-dose schemes. Although the dose-reduction for such a purpose (i.e. decrease doses to increase vaccination coverage) has not been recommended in the present pandemic because the number of vaccines is expected to increase over time [20], similar suggestions were given prior to the emergence of the H1N1 pandemic [7,8]. Moreover, exploring a wide range of relative efficacies for a one-dose regimen, the present study has also shown that a two-dose scheme may result in less morbidity if the vaccine efficacies are greatly diminished by reducing the dose.

An important technical message from the present study is that the relevant decision cannot be made by measuring antibody titres alone. Interpreting antibody titre usually forces us to adopt a well-known criterion, i.e. the haemagglutination inhibition titre > 1/40, as a correlate for individual protection [21], but this criterion itself has yet to be validated for the pandemic H1N1 influenza virus. Moreover, even if we can gain some practical insights into actual protection from the antibody titre, the validity of individual protection does not directly extend to the validity of herd immunity, which is more pertinent in respect to population level protection from infection. To understand the population level implications it is necessary to study in more detail the multidimensional protective effects of vaccination based on epidemiological studies [7,22], because an assessment of any infectious disease risks at the population level requires vaccine efficacy estimates which influence the transmission dynamics. Such efficacies include reductions in susceptibility, infectiousness and probability of symptomatic disease, as described in the present study.

The most difficult aspect of the ongoing pandemic H1N1 influenza is that we do not have an opportunity to analyse the abovementioned estimates in advance of vaccination practice. Moreover, the decision making for vaccination in the ongoing pandemic has to be done during the course of the pandemic waves [12]. In particular, one may prefer a one-dose to a two-dose scheme near the peak incidence of any pandemic wave to immunise as many susceptible individuals as possible. Nevertheless, as a practical implication of the present study, and as long as the detailed efficacy estimates rest on theoretical assumptions, one may consider that single-dose vaccination may be sufficiently justified only in a specific setting where the number of vaccines is extremely limited. At the same time, any observation of dose-related reduction in any biological action of vaccine efficacy (i.e. dose-related effects of reducing susceptibility and infectiousness) needs to be reported as soon as such an insight is gained during the course of the pandemic.

It should be noted that there are several limitations in the arguments we make here. First, parameter values in Table rest on theoretical assumptions, as the empirical estimates for H1N1 vaccines have yet to be clarified. Second, potential heterogeneity in vaccine efficacy must be noted as relevant. Efficacy estimates

may differ between age- and risk- groups, as is the case for antibody responses [6,20], and this in turn may greatly influence decisions related to dosage for different age- and risk-groups. Third, we ignored heterogeneous patterns of transmission. In a heterogeneously mixing population, a one-dose regimen may not yield as large community benefit as presented in the present study, because the residual number of vaccines which were generated by reducing dosage from two-dose to one-dose may well be distributed to those with small risks of secondary transmission and severe manifestations.

There are several different pandemic vaccines (including those adjuvanted and unadjuvanted) with different routes of administration [23], and the efficacies of these are likely to be different. Thus, the decision on dosage cannot be made in a uniform theoretical fashion. Nevertheless, we believe that our simple approach satisfies the need to offer a basic insight into the question of vaccine dosage based on firm theoretical understanding.

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