3-18-2010

Optimizing Vaccine Allocation at Different Points in Time During an Epidemic

Laura Matrajt
University of Washington

Ira M. Longini Jr.
Fred Hutchinson Cancer Rsrch Ctr & Univ of Washington

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Laura Matrajt[1] and Ira M. Longini Jr.[2,3]

March 18, 2010

[1]Department of Applied Mathematics, University of Washington, Seattle, WA, USA
[2]Center for Statistics and Quantitative Infectious Diseases, Fred Hutchinson Cancer Research Center and the University of Washington, Seattle, WA, USA
[3]Department of Biostatistics, School of Public Health, University of Washington, Seattle, WA, USA.

Abstract

For current pandemic influenza H1N1, vaccine production started in the early summer, and vaccination started in the fall. In most countries, by the time vaccination started, the second wave of H1N1 was already under way. With limited supplies of vaccine, it might be a good strategy to vaccinate the high-transmission groups earlier in the epidemic, but it might be a better use of resources to protect instead the high-risk groups later on. We develop a deterministic epidemic model with two age-groups (children and adults) and further subdivide each age group in low and high risk. We compare optimal vaccination strategies started at various points in time in two different settings: a population in the United States (US) where children account for 24% of the population, and a population in Senegal, where children make up for the majority of the population, 55%. For each of these populations, we minimize mortality and we find an optimal vaccination vector that gives us the best vaccine allocation given a starting vaccination date and vaccine coverage level. We find that there is a switch in the optimal vaccination strategy at some time point just before the peak of the epidemic. For instance, with 25% vaccine coverage, it is better to protect the high-transmission groups before this point, but it is optimal to protect the most vulnerable groups afterward.

Introduction

For the current H1N1 influenza epidemic, vaccine production started in the early summer. Several countries immediately ordered vaccine [9, 27], with the hope that the first production batches would be ready in the early fall. This was not the case, however, and for most countries vaccine arrived much later than predicted. Meanwhile, WHO expected to supply 95 low- and middle-income countries with enough vaccine to cover 10% of their populations [30]. When vaccine supplies are limited, vaccinating the high-transmission groups, such as school children or young adults, has proven to be a good strategy for preventing the spread of the disease, and by doing so the groups at high risk will be indirectly protected [15, 11, 21, 24]. While this strategy makes sense earlier in the epidemic, this might not be the optimal use of vaccine once the epidemic has begun. Indeed, once there is a large proportion of the high-transmission groups infected and later on immune, vaccine would probably have little effect in these groups and could be more effectively used in the high-risk groups, giving them direct protection. Furthermore, the optimal use of vaccines depends on the structure of the population: countries or cities where school children or college students make up large proportions of the population will have different epidemic dynamics than a country where these younger people make up a smaller proportion of the population. We developed a deterministic model with two groups: children and adults, and we further divided each of these age groups into low and high risk. We compared optimal vaccination strategies in two different settings: a population in a developed country, United States (US), where the children make up for 24% of the population [26], and a population in a developing country, Senegal, where the children account for 55% of the population [23]. For each of these, we minimize mortality and we find an optimal vaccination vector that gives us the best vaccine allocation given a starting vaccination date and a given supply of vaccine.

Methods

Mathematical Model

Our model for influenza is based on the SIR model. We considered a closed population of size N. Since influenza has a very short time scale compared to immigration or demographics, none of these features are included. We divided the population into two subpopulations of children and adults of size N_1 and N_2, so that $N = N_1 + N_2$. Furthermore, within each sub-population, we divide members into high risk and low risk. Members in each group are either susceptible, infected asymptomatic, infected symptomatic or recovered and immune afterward. In addition, people can be either vaccinated or unvaccinated.

The susceptibles are denoted by S_{lij}, and S_{hij}; infectious asymptomatic by A_{lij} and A_{hij}; infectious symptomatic by I_{lij} and I_{hij}; recovered asymptomatic by RA_i, and recovered symptomatic by R_{li} and R_{hi} where $i = 1, 2$ denotes the age group (children and adults, respectively), j denotes the vaccination status ($j = 0$ for the unvaccinated and $j = 1$ for the vaccinated), l denotes the low risk group and h denotes the high risk group.

The following assumptions were made.

- A fraction ρ of the infected people will never develop symptoms but will still transmit the infection to others. Asymptomatic infected people have their infectiousness reduced by a factor m compared to symptomatic infected people, where $m \in [0, 1]$.
- c_{ij} represents the number of contacts per day between people in age group i and people in age group j, where $i, j = 1, 2$.
- p is the probability of infection given contact. It will be used here as a parameter to vary the severity of the infection.
- People are infectious as soon as they get infected, and they will stay infectious for an average of $1/\gamma$ time units, where γ is the recovery rate.
- Following the ideas in [10], we consider that vaccination has three major effects:

  (i) $\mathsf{VE_S}$, the vaccine efficacy for susceptibility, is the ability of the vaccine to prevent infection.

  (ii) $\mathsf{VE_I}$, the vaccine efficacy for infectiousness, is the effect of the vaccine in reducing infectiousness and transmission to others.

  (iii) $\mathsf{VE_P}$, the vaccine efficacy for pathogenicity, accounts for the effect of the vaccine in reducing the symptoms given infection.

- The effect of each of the efficacies builds monotonically in time according to expontial-like functions. Based on previous immunogenicity studies ([17, 18, 22, 20] for example), we assumed that on average, the vaccine would reach its full potential 14 days after it was administered and would remain constant afterward for the period being modeled.

This gives rise to the following system:

Equations for susceptibles

Unvaccinated

$$\frac{dS_{l10}}{dt} = -\lambda_1 S_{l10}$$
$$\frac{dS_{h10}}{dt} = -\lambda_1 S_{h10}$$
$$\frac{dS_{l20}}{dt} = -\lambda_2 S_{l20}$$
$$\frac{dS_{h20}}{dt} = -\lambda_2 S_{l20}$$

Vaccinated

$$\frac{dS_{l11}}{dt} = -\lambda_1 \theta S_{l11} \quad (1)$$
$$\frac{dS_{h11}}{dt} = -\lambda_1 \theta S_{h11} \quad (2)$$
$$\frac{dS_{l21}}{dt} = -\lambda_2 \theta S_{l21} \quad (3)$$
$$\frac{dS_{h21}}{dt} = -\lambda_2 \theta S_{l21} \quad (4)$$

Equations for infected asymptomatics

Unvaccinated

$$\frac{dA_{l10}}{dt} = \lambda_1(1-\rho)S_{l10} - \gamma A_{l10}$$
$$\frac{dA_{h10}}{dt} = \lambda_1(1-\rho)S_{h10} - \gamma A_{h10}$$
$$\frac{dA_{l20}}{dt} = \lambda_2(1-\rho)S_{l20} - \gamma A_{l20}$$
$$\frac{dA_{h20}}{dt} = \lambda_2(1-\rho)S_{h20} - \gamma A_{h20}$$

Vaccinated

$$\frac{dA_{l11}}{dt} = \lambda_1(1-\rho\psi)\theta S_{l11} - \gamma A_{l11} \quad (5)$$
$$\frac{dA_{h11}}{dt} = \lambda_1(1-\rho\psi)\theta S_{h11} - \gamma A_{h11} \quad (6)$$
$$\frac{dA_{l21}}{dt} = -\lambda_2(1-\rho\psi)\theta S_{l21} - \gamma A_{l21} \quad (7)$$
$$\frac{dA_{h21}}{dt} = \lambda_2(1-\rho\psi)\theta S_{h21} - \gamma A_{h21} \quad (8)$$

Equations for infected symptomatics

Unvaccinated

$$\frac{dI_{l10}}{dt} = \lambda_1 \rho S_{l10} - \gamma I_{l10}$$
$$\frac{dI_{h10}}{dt} = \lambda_1 \rho S_{h10} - \gamma I_{h10}$$
$$\frac{dI_{l20}}{dt} = \lambda_2 \rho S_{l20} - \gamma I_{l20}$$
$$\frac{dI_{h20}}{dt} = \lambda_2 \rho S_{h20} - \gamma I_{h20}$$

Vaccinated

$$\frac{dI_{l11}}{dt} = \lambda_1 \rho\psi\theta S_{l11} - \gamma I_{l11} \quad (9)$$
$$\frac{dI_{h11}}{dt} = \lambda_1 \rho\psi\theta S_{h11} - \gamma I_{h11} \quad (10)$$
$$\frac{dI_{l21}}{dt} = \lambda_2 \rho\psi\theta S_{l21} - \gamma I_{l21} \quad (11)$$
$$\frac{dI_{h21}}{dt} = \lambda_2 \rho\psi\theta S_{h21} - \gamma I_{h21} \quad (12)$$

Equations for the recovered

$$\frac{dRA_1}{dt} = \gamma(A_{l10} + A_{l11} + A_{h10} + A_{h11}) \tag{13}$$
$$\frac{dRA_2}{dt} = \gamma(A_{l20} + A_{l21} + A_{h20} + A_{h21}) \tag{14}$$
$$\frac{dRI_{l1}}{dt} = \gamma(I_{l10} + I_{l11}) \tag{15}$$
$$\frac{dRI_{h1}}{dt} = \gamma(I_{h10} + I_{h11}) \tag{16}$$
$$\frac{dRI_{l2}}{dt} = \gamma(I_{l20} + I_{l21}) \tag{17}$$
$$\frac{dRI_{h2}}{dt} = \gamma(I_{h20} + I_{h21}) \tag{18}$$

with forces of infection given by

$$\lambda_1 = \frac{pc_{11}}{N_1}\Big(m(A_{l10} + A_{h10}) + m\phi(A_{l11} + A_{h11}) + I_{l10} + I_{h10} + \phi(I_{l11} + I_{h11})\Big) + \frac{pc_{12}}{N_2}\Big(m(A_{l20} + A_{h20}) + m\phi(A_{l21} + A_{h21}) + I_{l20} + I_{h20} + \phi(I_{l21} + I_{h21})\Big),$$

and

$$\lambda_2 = \frac{pc_{21}}{N_1}\Big(m(A_{l10} + A_{h10}) + m\phi(A_{l11} + A_{h11}) + I_{l10} + I_{h10} + \phi(I_{l11} + I_{h11})\Big) + \frac{pc_{22}}{N_2}\Big(m(A_{l20} + A_{h20}) + m\phi(A_{l21} + A_{h21}) + I_{l20} + I_{h20} + \phi(I_{l21} + I_{h21})\Big).$$

We calibrated this model to the current H1N1 epidemic using the numbers given in table 1 to obtain the final illness attack rates (defined as the percentage of the population that became ill) shown in table 2. Based on current estimates, [8, 31, 1], we considered the basic reproduction number R_0 in the range $[1.2, 1.8]$. The basic reproduction numbers were computed following the the approach given in [6] and [28, 4]. For the optimization, the basic reproduction number was set to 1.6.

The different vaccination coverages considered were 2%, 15% and 25% of the population. Vaccination could start on days one, 20, 40, 60, 80, and 100 days after the beginning of infection transmission. For simplicity, we assumed that all the vaccine is delivered at once, however, vaccinated people acquire their protection gradually as the vaccine efficacies build up over time.

Our objective function $g(f_{l1}, f_{h1}, f_{l2}, f_{h2})$ was defined as follows

$$g(f_{l1}, f_{h1}, f_{l2}, f_{h2}) = 0.000031 \cdot RI_{l1} + 0.000416 \cdot RI_{h1} + 0.000101 \cdot RI_{l1} + 0.000821 \cdot RI_{h2} \quad (19)$$

(the dependence in the vaccination fractions in each group is not apparent since it is embedded in the initial conditions of the system 1-18). This function represents the expected number of deaths in each subgroup (children low and high risk, adults low and high risk) and was computed as a weighted average with weights defined in table 1. Thus, we obtained the optimization problem

$$\min_{(f_{l1}, f_{h1}, f_{l2}, f_{h2})} g(f_{l1}, f_{h1}, f_{l2}, f_{h2})$$

subject to the constraints

$$0 \leq f_{l1}, f_{h1}, f_{l2}, f_{h2} \leq 1$$
$$f_{l1}(1 - 0.089)N_1 + f_{h1}0.089N_1 + f_{l2}(1 - 0.212)N_2 + f_{h2}0.212N_2 = T$$

where T denotes the total number of doses available.

No influenza mortality or high risk data is available for Senegal, so we assumed that both the proportions of people at high risk and the mortality rates for influenza A(H1N1) for each group in Senegal were the same as the ones in the US. For each of the dates above, and for each of the coverages given, we used an optimization package to determine a vector $(f_{l1}, f_{h1}, f_{l2}, f_{h2})$ which corresponds to the optimal vaccine distribution for minimizing the total number of deaths. Thus, the vector $(f_{l1}, f_{h1}, f_{l2}, f_{h2})$ gives us the fractions f_{l1} and f_{h1} of children at low and high risk, and the fractions f_{l2} and f_{h2} of adults at low and high risk respectively that would minimize mortality during the entire epidemic.

Results

Results for United States

The baseline epidemic curves for both US (blue) and Senegal (red) are plotted in figure 1 for a basic reproduction number of 1.6. Both countries have similar epidemic curves in that there is no substantial spread before day 60, and the exponential phase of the epidemic starts around day 45. The peak for Senegal occurs slightly earlier than for the US.

Figures 2 - 4 summarize the results for the US population. For each vaccination coverage, the figures show the optimal vaccine allocation if vaccination were to start one, 20,

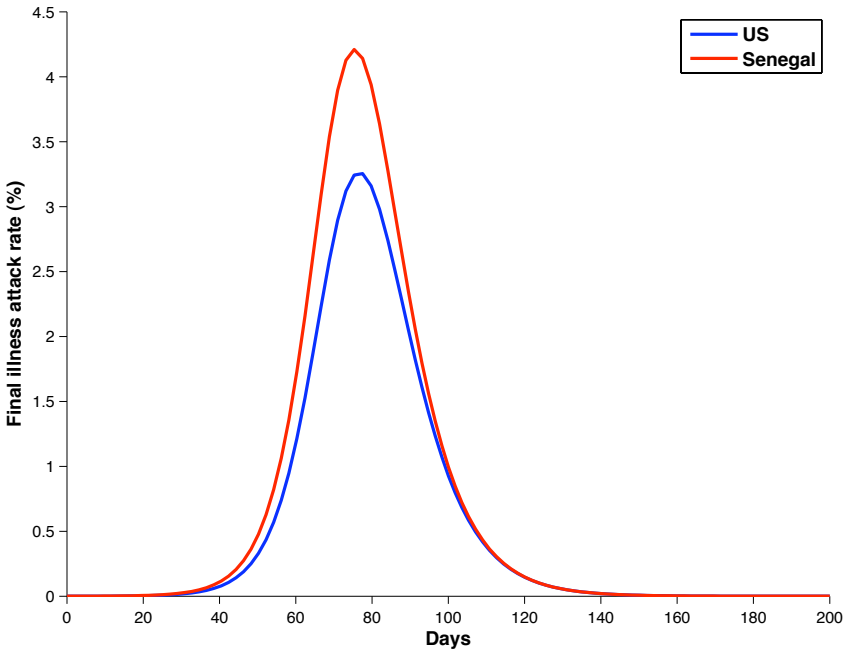

Figure 1: Baseline epidemic curves for the US and Senegal for a basic reproduction number of 1.6

Parameter	Description	Value	Reference
γ	recovery rate	0.25	[12]
ρ	fraction of symptomatic	2/3	[12]
m	reduction of infectiousness for asymptomatics	0.5	[12]
$c_{11}, c_{12}, c_{21}, c_{22}$	contact rates	1,0.2, 0.2, 0.4	calculated[a]
$\mathsf{VE_S}, \mathsf{VE_I}, \mathsf{VE_P}$	vaccine efficacies for susceptibility, infectiousness and pathogenicity	0.4, 0.45, 0.75	[3]
N	total population	200 000	assumption
	initially infected fraction of the population	$1/N$	assumption
	percentage of children under 18 (US)	24.16	[26]
	percentage of children under 19 (Senegal)	55	[23]
	percentage of children at high risk	8.9	[19]
	percentage of adults at high risk	21.2	[19]
	mortality in low risk children	0.000031	[5][b]
	mortality in high risk children	0.000416	[5]
	mortality in low risk adults	0.000101	[5]
	mortality in high risk adults	0.000821	[5]

Table 1: Parameter values.

[a]The contact rates were calculated to obtain the final illness attack rates shown in table 2.

[b]The mortality rates in the last four rows were computed by weighting the estimates of deaths given in [5] by the percentages of people in each subgroup given in [19].

40, 60, 80, or 100 days after the beginning of transmission. When there is enough vaccine to cover only two percent of the US population, the best strategy is to allocate all the vaccine to the high-risk children (93% coverage) regardless of when vaccination begins (see figure 2).

When supplies are large enough to vaccinate 15% of the population (figure 3), the optimal strategy is to vaccinate all of the high-risk children and then to concentrate the remainder of the vaccine in low-risk children, provided that vaccination occurs before the peak. However, after the peak, it is optimal to cover all high-risk children and to switch the remaining vaccine to high-risk adults (this accounts for 80% coverage in this group). For instance, if vaccination were to start 20 days after the beginning of transmission, it would be optimal to give vaccine to all the children at high risk (100% coverage in this group) and to allocate the rest in the children at low risk (58% coverage in this group), but if vaccination were to start 80 days after the beginning of transmission, then it would be optimal to still vaccinate all the high-risk children and to vaccinate a fraction of the adults

R_0	Overall illness attack rate	Illness attack rate in children	Illness attack rate in adults
1	0	0	0
1.2	8.1	11.6	3.9
1.3	19.9	27.4	10.6
1.4	26.7	35.9	15.5
1.5	31	40.8	19
1.6	34.6	44.8	22.1
1.7	37.9	48.3	25.3
1.8	40.6	50.9	28

Table 2: Final illness attack rates for the range of basic reproduction numbers considered.

high-risk (80% coverage in this group).

Figure 4 presents the results for the US when enough vaccine is available to cover 25% of the population. Assuming that vaccination occurred before the exponential phase of the epidemic, vaccinating all of the high-risk children and then concentrating the remainder of the vaccine in low-risk children (90% coverage in this group) is the optimal solution, but this time a small amount of vaccine can be given to high-risk adults (19% coverage in high risk adults). In contrast, if vaccination takes place during or after the exponential phase, then it is optimal to favor first all of the high-risk children and all high-risk adults, and then to concentrate the remainder of supplies in low-risk children (30% coverage in low-risk children).

In general, with limited supplies of vaccine, it is always optimal to concentrate vaccine in high-risk children to provide them with direct protection, as they are part of the high-transmission chain and they are among the most vulnerable. As vaccine supplies increases, it becomes optimal to allocate the resources in the high-transmission group; in our model, children at low-risk. This makes sense since by protecting the high-transmission group, we stop the chain of transmission and indirectly protect the high risk groups. However, this policy is optimal only up to a certain time during or after the exponential rise phase, when too many high-transmission people have already been infected and have acquired natural immunity. After this point in time, it is optimal to concentrate vaccine in high-risk groups protecting them directly.

Results for Senegal

Figures 5 - 7 give the analogous results for Senegal as to those in the US. In this scenario, children make up a much larger proportion (55%) than they do in the US (24%). Here, if coverage is very low, (two percent of the population) and vaccination were to occur before exponential phase, it is optimal to concentrate all the available vaccine in high-risk children (41% coverage); whereas if vaccination were to occur during or after the exponential phase, it is optimal to shift vaccine coverage to high-risk adults (21% coverage), see figure 5.

When there is enough vaccine for 15% of the population, then, regardless of the phase of the epidemic, it is optimal to protect both the high-risk groups, children and adults, and to allocate the remainder of supplies in low-risk children (1% coverage in this group), see figure 6. This is due to the fact that with this coverage, we would not be able to block transmission by protecting the high-transmission groups, so it is better to directly protect all the members of the most vulnerable groups, and by doing so the number of deaths are greatly diminish.

Interestingly, this policy is no longer optimal with 25% coverage. In this situation, there is again a shift in the optimal policy depending on the time of vaccination relative to the peak: if vaccination occurs before the exponential phase, it is optimal to concentrate it in children (100% of the high-risk children and 40% of the low-risk). But when vaccination occurs later on, the optimal strategy shifts to the high-risk groups, (100% coverage of both children and adults at high-risk) with allocation of the remainder of the vaccine to low-risk children (21% coverage in this group). This makes sense, because according to our model, by allocating this much vaccine in children earlier on in the epidemic, we would be able to block transmission and mitigate the disease, but if vaccination took place later on in the epidemic, there are too many people already infected and this strategy is no longer useful (see figure 8).

In this scenario, the optimal solution is to concentrate vaccine in the high-risk groups. Indeed, for low supplies of vaccine, it is optimal to concentrate vaccine in high-risk children before the peak and in high risk adults after the peak. As more vaccine becomes available, it is optimal to allocate it to the high risk groups until there is enough vaccine to fully cover this groups. However, once we have supplies to cover a significant fraction (around 40%) of the high-transmission group, then it is optimal to vaccinate this group before the peak of the epidemic as this will greatly reduce transmission.

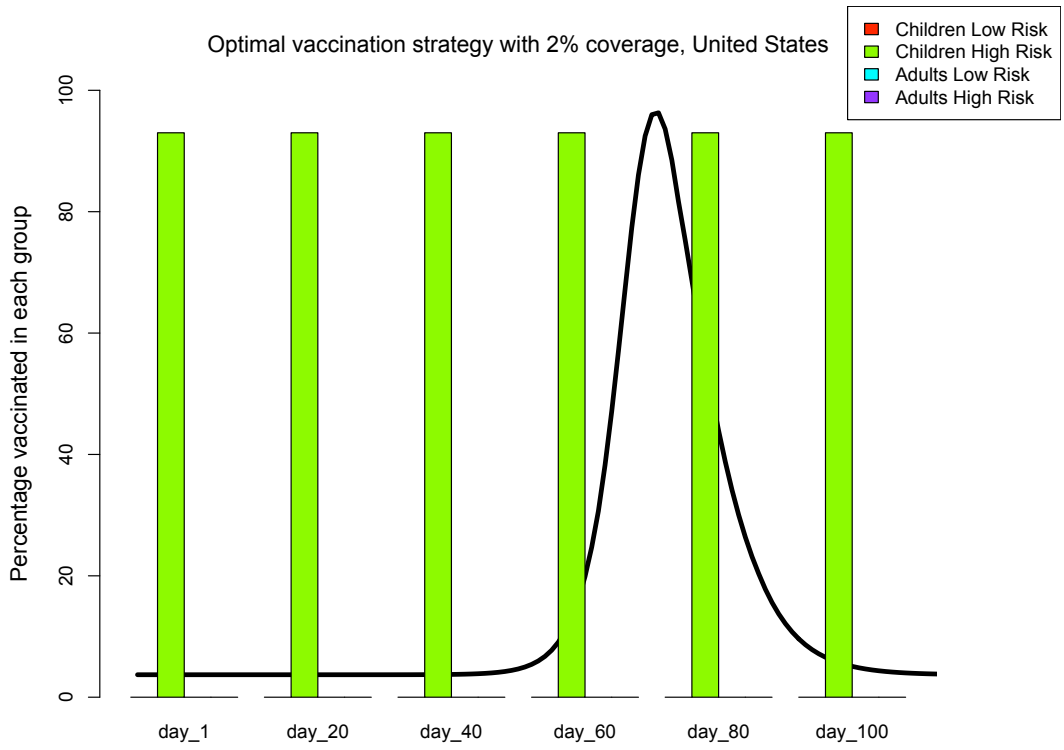

Figure 2: Optimal vaccination policy when there is enough vaccine to cover 2% of the population in United States starting one, 20, 40, 60, 80, or 100 days after the beginning of transmission. The epidemic curve for the symptomatic infections is shown in black.

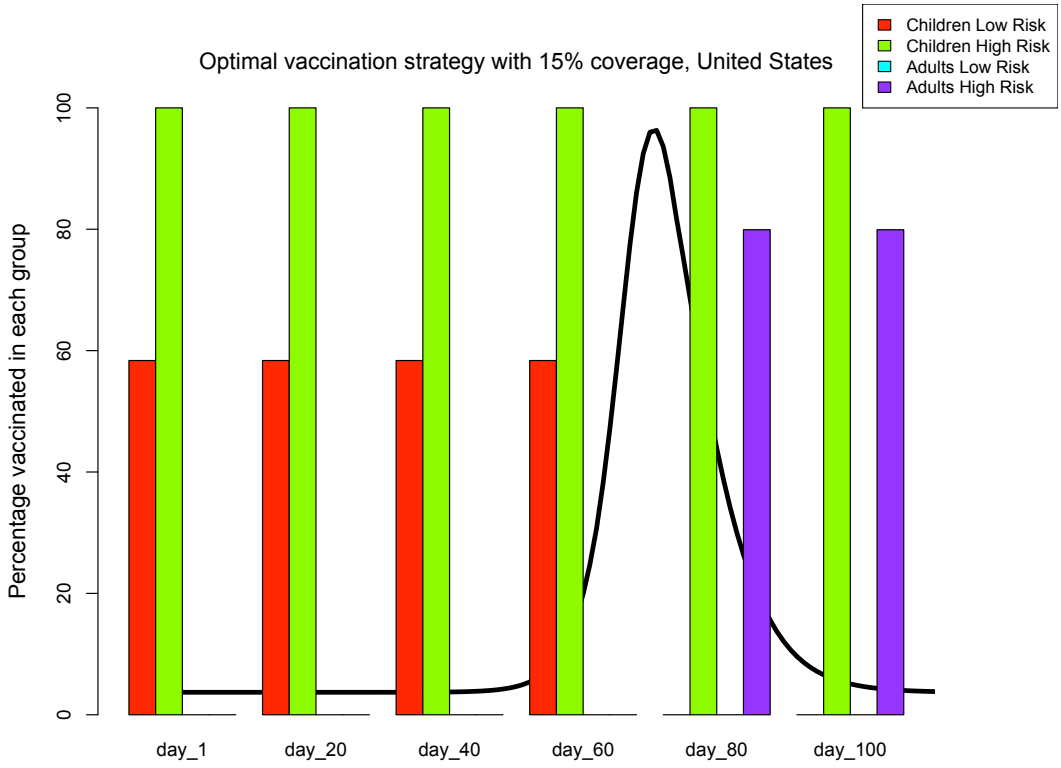

Figure 3: Optimal vaccination policy when there is enough vaccine to cover 15% of the population in United States starting one, 20, 40, 60, 80, or 100 days after the beginning of transmission. The epidemic curve for the symptomatic infections is shown in black.

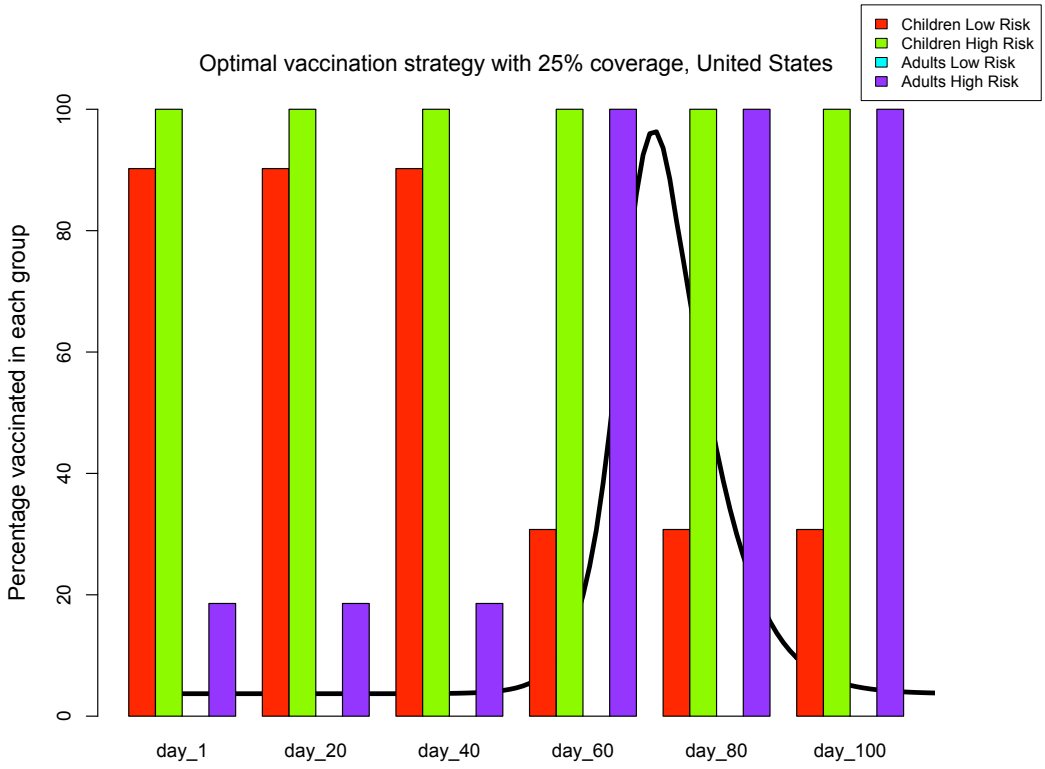

Figure 4: Optimal vaccination policy when there is enough vaccine to cover 25% of the population in United States starting one, 20, 40, 60, 80, or 100 days after the beginning of transmission. The epidemic curve for the symptomatic infections is shown in black.

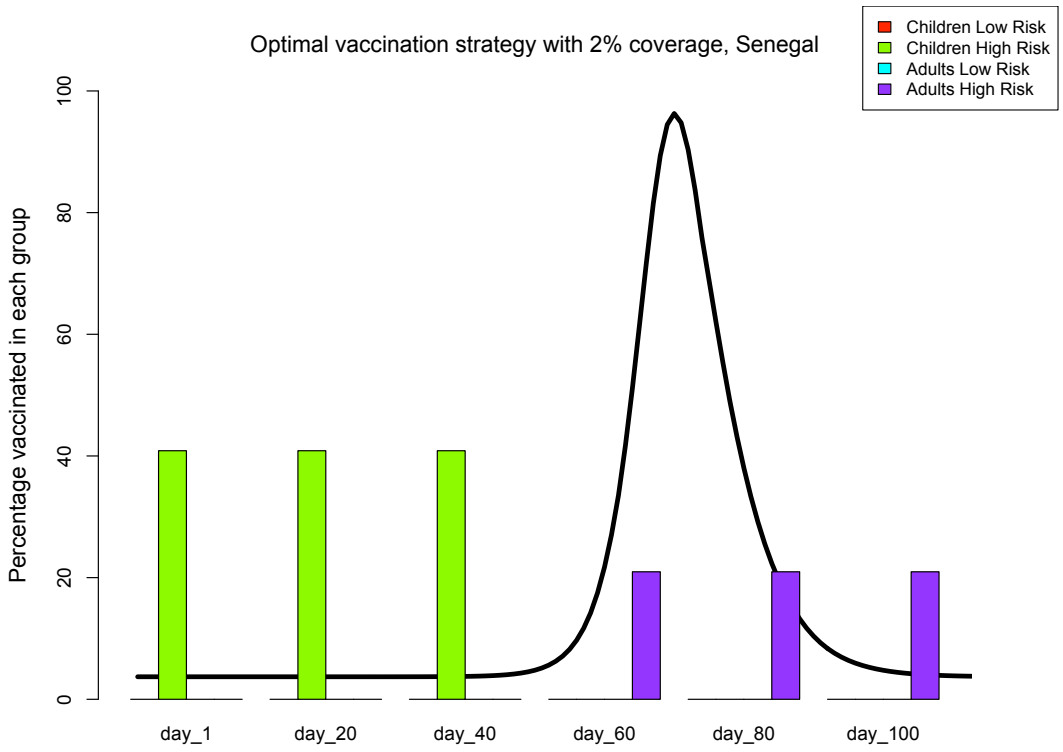

Figure 5: Optimal vaccination policy when there is enough vaccine to cover 2% of the population in Senegal starting one, 20, 40, 60, 80, or 100 days after the beginning of transmission. The epidemic curve for the symptomatic infections is shown in black.

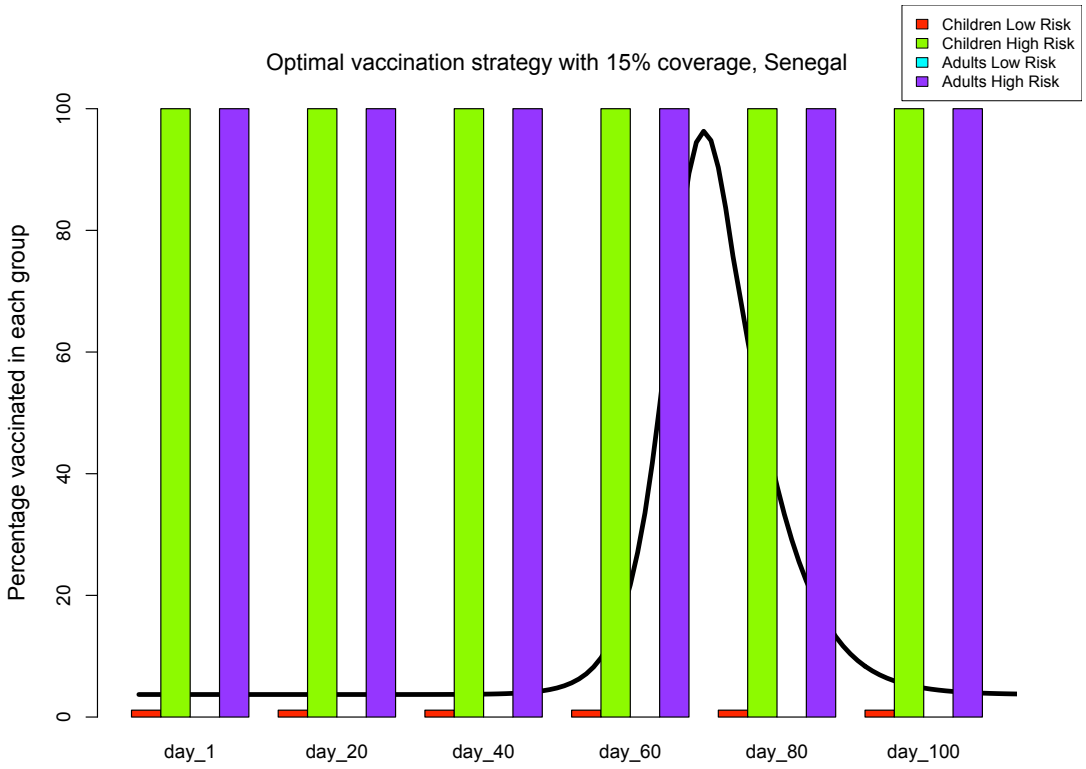

Figure 6: Optimal vaccination policy when there is enough vaccine to cover 15% of the population in Senegal starting one, 20, 40, 60, 80, or 100 days after the beginning of transmission. The epidemic curve for the symptomatic infections is shown in black.

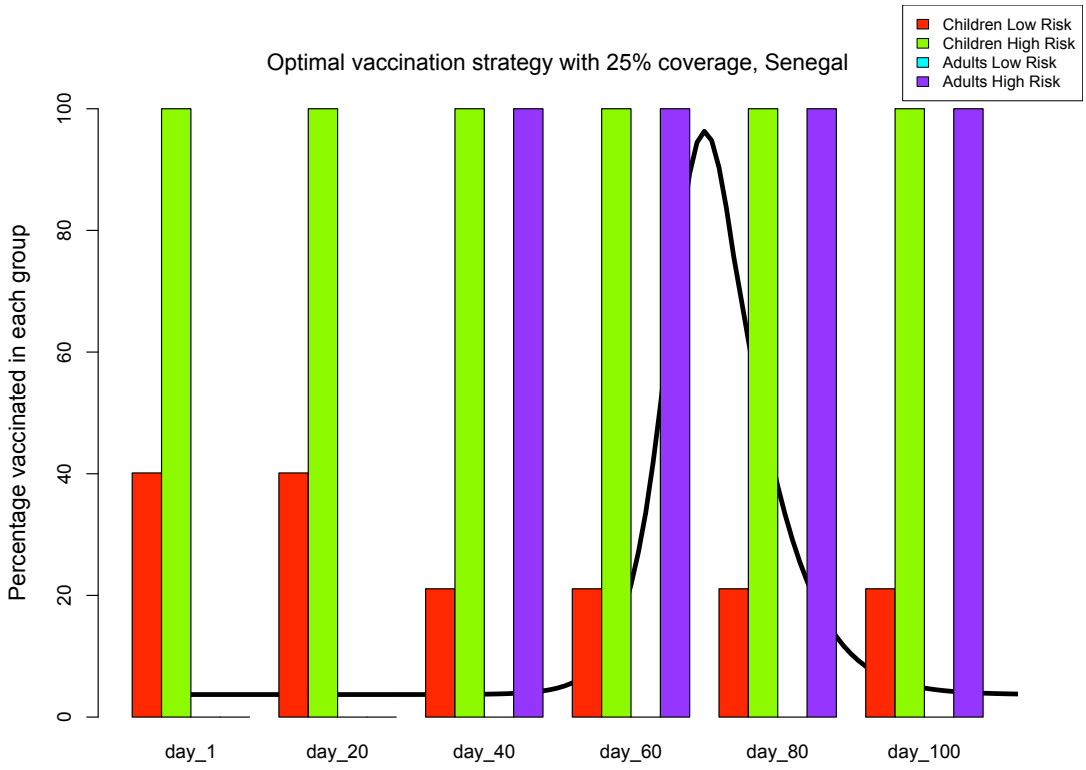

Figure 7: Optimal vaccination policy when there is enough vaccine to cover 25% of the population in Senegal starting one, 20, 40, 60, 80, or 100 days after the beginning of transmission. The epidemic curve for the symptomatic infections is shown in black.

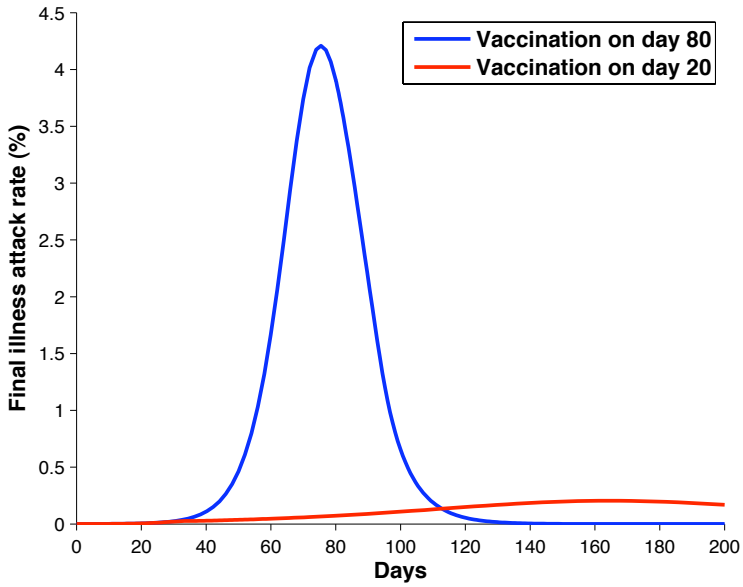

Figure 8: Epidemic curve for Senegal with 25% of the population coverage. The vaccine has been administered to children at high-risk (100% coverage of this group) and children at low risk (40% coverage of this group) starting 20 days (red curve) or 80 days (blue curve) after the beginning of transmission. This strategy is optimal before the exponential rise of the epidemic and controls the outbreak but it is suboptimal after it.

Discussion

We use a mathematical model to find the optimal vaccine allocation at different time points of an epidemic. For both developed and developing countries, when faced with low supplies of vaccines, it is better to allocate vaccine to the high risk groups. For developed countries, as more vaccine becomes available, it is optimal to allocate vaccine to high-transmission groups earlier in the epidemic, but to concentrate in high-risk groups during or after the exponential phase of the epidemic. In contrast, for developing countries, it is better to allocate vaccine in the high-risk groups first and then cover high-transmission groups. Once vaccine supplies reach a certain coverage level, then it becomes important to vaccinate the high-transmission groups in the earlier stages of the epidemic, but this policy becomes suboptimal once the peak of the epidemic has passed. These results highlight two important features: first, the population structure is extremely important. For a country like Senegal, where the high-transmission group accounts for the majority of the population, one needs large amounts of vaccine to indirectly protect the high-risk groups by vaccinating the high-transmission ones. However, in a country like the US, where high-risk groups represent a smaller fraction of the population, it is possible to reduce transmission by vaccinating the high-transmission groups, if this is done early in the epidemic. The second important point is that timing of the vaccination is extremely important and greatly determines where the efforts should be concentrated.

The optimal results presented here are sensitive to the population structure, both in the percentages of each group and subgroup and in the contact pattern among them. Given the uncertainty of these parameters for pandemic influenza A(H1N1), we agree with Dushoff et al. [7] that one should be cautious in interpreting the results offered by simple models. Here, the only difference considered between US and Senegal is the proportion of children and adults in each country. While this is a key factor, there are many other important features that make these countries different and would give rise to different optimal solutions. For instance, it could be important to incorporate more detailed data for Senegal including influenza-related case fatality ratios, the composition and percentages of high-risk groups, and vaccine availability and distribution patterns. Senegal has a higher infant and child mortality rate than the US, so one could imagine that the fraction of children at high risk in Senegal will be greater than in the US. Moreover, differences in the health system in both countries might be a crucial factor in minimizing the number of deaths. Adding more groups to the populations will make a more realistic model. Finally, one could expect very different results if the objective function was different, such as final illness attack rates, remaining years of life lost, hospitalizations, economic burden or a combination of these.

Previous work [2, 13, 25] has suggested that in presence of low vaccine supplies, high-risk groups should be prioritized but high-transmission groups should be vaccinated with

larger quantities of vaccine. Our results agree with this strategy for a population with a structure similar to the one in the US as long as vaccination starts before the peak of the epidemic. However, we suggest that there is a threshold in the time when a switch in the optimal strategy occurs, after which, the resources will be more useful if allocated directly to the high-risk groups. This is in agreement with the results found by others [14, 16, 29]. The particular time for this threshold is strongly dependent on the values of the model parameters, in particular on the vaccination coverage and the structure of the population, but in general, occurs some time during the exponential phase of the epidemic or right at the peak.

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