Earlier and Faster Production of Influenza Vaccine For Pandemic Mitigation

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Introduction

As noted in the recent Centers for Disease Control and Prevention community planning guidance[1], the only intervention that can reasonably be expected to control an influenza pandemic is vaccination of a large fraction of the population with a strain-matched vaccine. Planners and modelers commonly assume that such a vaccine intervention would be similar to recent vaccination interventions for seasonal influenza, employing egg-based vaccine production technology. Thus analyses assume that pandemic influenza vaccine will not be available until four to six months after the onset of the pandemic, and that vaccine could not be produced faster than 4 million doses per week (corresponding to 100 million doses in 6 months). Under this view, several recent studies[2-5] have analyzed how various non-vaccine interventions might be able to control an influenza pandemic until vaccine can be delivered. Other studies[6] do not incorporate vaccination production and delivery because of the assumption that it would be too late.

Alternative approaches to egg-based vaccine production would grow virus in bioreactors using mammalian cell cultures, insect cell cultures (e.g. NovaVax, Inc. and Protein Sciences, Inc.), or **bacteria (e.g. PhageVax, Inc.).** These technology developments might reduce the lag time between identification of the influenza strain and initial vaccine production capability, and might also allow higher US production rates. This analysis considers the potential of these new technologies to mitigate a pandemic.

The effectiveness of a vaccine intervention to control an influenza pandemic will depend on 1) when the vaccine will first become available, 2) how many people can be treated per week once vaccination starts, 3) how effective the vaccine is, and 4) how many days following inoculation are required for immunity to build up. In addition, the impact of a vaccine intervention on the pandemic will depend on other interventions that are used in conjunction. This analysis compares the impact of vaccine distribution starting four months earlier than the seasonal influenza experience, comparing the impact of a range of vaccine production rates. It also compares the case of a two-dose course with a one-dose requirement. Most significantly, it examines the impact of early vaccine intervention used in conjunction with antiviral medication.

If a vaccine can be produced four months earlier relative to egg-based seasonal influenza vaccine production, at a production rate sufficient to vaccinate 95% of the

population within a one-month period, the impact on the pandemic would be enormous. In the absence of any other intervention, such a vaccine would reduce the mortality rate by a factor of five (from 614 deaths per 100,000 persons to 121 deaths per 100,000). Furthermore, if the existing strategic national stockpile (SNS) of 20 million courses of antiviral medication is used in conjunction with the vaccine intervention (for therapeutic treatment of diagnosed cases and prophylactic treatment of household members of diagnosed cases), the additional use of the early, rapidly produced vaccine would reduce the mortality from 550 per 100,000 to only 3 per 100,000, well below the mortality rate of seasonal influenza.

Scenario Assessment with the EpiSimS Simulation

The disease spread simulation engine EpiSimS[5] was used to simulate the course of influenza pandemics, with various assumptions about vaccine production rate. Details of the modeling assumptions and methodology were described in a previous article[5]. The EpiSimS simulations were run with a synthetic population constructed to statistically match the 2000 population demographics of southern California at the census tract level. The synthetic population contains 19 million individuals living in 6 million households, with an additional 938,000 locations representing actual schools, businesses, shops, or restaurant addresses. The age distribution, family size distribution, household income distribution and employment status of the synthetic population match the US census data at census tract level, in six southern California counties. On day 0 of the simulation, the population is seeded with 100 infected individuals, so that by day 3, 0.00035% of the population is symptomatic.

A basecase scenario was constructed for this analysis, to emulate the planning scenario used by DHHS[7,8]. This basecase scenario has vaccine as the only intervention, consistent with seasonal influenza vaccine production using egg-based technology. The vaccine begins to be distributed on day 150. The vaccine requires two doses, so 0.67% of the population can be treated per week beginning on day 150. The second dose is administered 4 weeks after the first, and 80% effectiveness is attained 2 weeks after the second dose.

The prevalence (fraction of the population that is symptomatic) reaches 0.1% on day 33±1. The peak in the number symptomatic cases is reached 30 days later (day 63, on average) when 9.92% of the population is symptomatic. The pandemic essentially runs its complete course before the egg-based vaccine begins to be distributed, and the pandemic trajectory the same as if there were no vaccine at all. For the whole pandemic in the basecase scenario, the clinical attack rate (i.e. the fraction of the population that ever became symptomatic) is 30.6%, and the mortality rate (i.e., the fraction of the population that dies) is 614 deaths per 100,000 population.

Assessment of Early Vaccine at Various Production Rates

For consistency with seasonal influenza experience, the early vaccine scenarios assume that the vaccine requires a single dose, that it provides complete immunity in 80% of recipients, and that this immunity is developed 14 days after inoculation. We further assume that of the 20% of inoculated persons that don't develop immunity, if they do become infected, they would be only one fifth as infectious as their unvaccinated

counterparts. We also assume that every unvaccinated individual has an equal chance of receiving the next available dose—i.e. this analysis did not examine strategies where the early vaccine is given preferentially to at-risk demographic categories or to healthcare workers, or to students.

Whereas the basecase scenario begins delivery of vaccine on day 150, a set of early vaccine scenarios begin vaccination on day 33, which is the day on which 0.1% of the population is symptomatic. This represents a four month advance on when vaccine can start production, relative to egg-based technology. Four early vaccine scenarios then produce and deliver 4, 8, 12 or 75 million doses per week, nationwide. These production rates would enable inoculation of 0, 1.33%, 2.66%, 4%, or 25% of the US population per week, respectively. **Note that 75 million doses per week might be produced by 300 local production facilities, each producing 1 million doses per month**. Table 1 shows the peak symptomatic fraction of the population, the clinical attack rate, and the mortality, for each vaccine production/delivery rate that result from EpiSimS simulation of these early vaccination scenarios. The percentage of the population that is currently symptomatic is shown against time for each vaccination scenario in Fig. 1.

Assumed US vaccine production rate, doses per week	Percentage of population vaccinated per week	Symptomatic percentage of population at pandemic peak	Clinical Attack Rate	Mortality, deaths per 100,000 population
0	0	9.92%	30.6%	614
4 million	1.3%	9.51%	29.2%	573
8 million	2.7%	9.03%	27.6%	532
12 million	4.0%	8.45%	25.8%	486
75 million	25%	4.48%	11.4%	**121**

Table 1. Summary of simulation results for various early vaccine production rates.

At distribution rates typical of seasonal influenza vaccine, even this four month advancement in production time only produces a 7% reduction in mortality. However, if vaccination distribution can be initiated one month after 0.1% of the population is symptomatic, and can be delivered to 95% of the population within one month of initial distribution, then the mortality rate of pandemic influenza can be reduced more than five-fold.

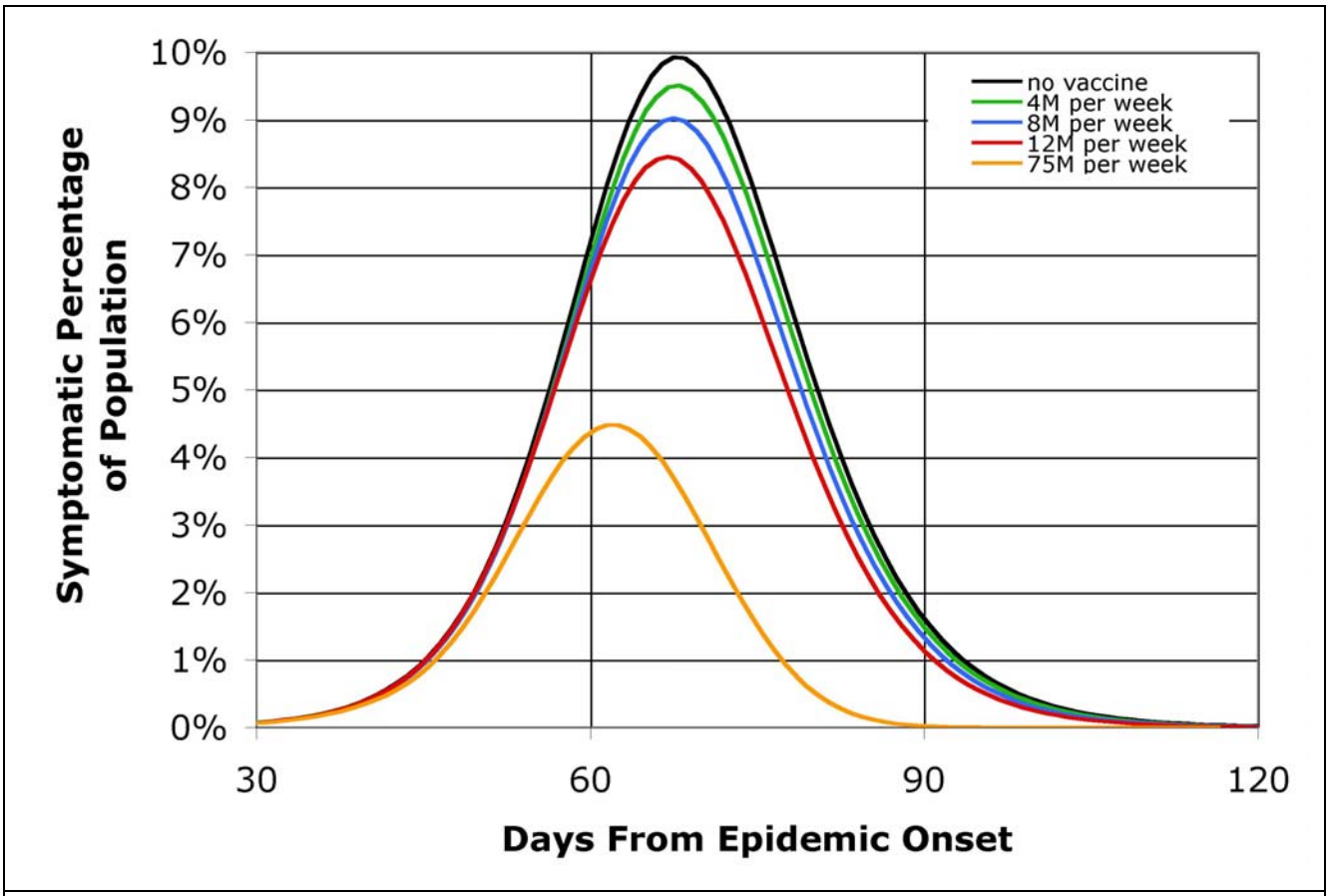

Fig. 1. The current percentage of the population that is symptomatic during an influenza pandemic, using a vaccine intervention beginning on day 33 and continuing at several vaccine production rates.

Assessment of Early Vaccine Combined with SNS Antiviral Medication

At the end of 2006, the US Strategic National Stockpile (**SNS**) held 20 million courses of antiviral medications (Tamiflu and Relenza), enough to treat 6.7% of the population. Presumably, administration of these antivirals would begin as soon as an influenza pandemic is recognized. The assumed antiviral treatment strategy is that all diagnosed cases would receive a therapeutic course of treatment (five doses), and that 95% of household members of diagnosed persons would receive a prophylactic course (10 doses), beginning between 12 and 24 hours after the diagnosis of the household index case. As with vaccination, there will likely be a small fraction of the population that will refuse medication.

Three scenarios were constructed for EpiSimS simulation to assess the effectiveness of combined early vaccine and antiviral interventions. The first scenario uses antivirals as the only intervention. The second has a combined intervention using antivirals and early vaccine at a moderate production rate sufficient to vaccinate 4% of the population per week. The third has a combined intervention using antivirals and early vaccine at a high production rate, sufficient to vaccinate 25% of the population per week. In both combined scenarios, vaccination production and distribution begins on day 34.

In the antiviral-only scenario, the strategy of treating diagnosed cases and their household members slows the disease spread but does not control the pandemic. The pandemic growth rate is found to be reduced to about 9% per day while the antiviral stockpile lasts, compared to about 17% per day with no intervention. A prevalence of 0.1% of the population being symptomatic is attained on day 51. The SNS antiviral stockpile is exhausted on day 81. At the time the SNS antiviral stockpile is exhausted, 1.34% of the population is symptomatic. The pandemic then explodes, reaching a peak symptomatic fraction of 8.1% on day 105. Even with the SNS antivirals, the pandemic still essentially runs its complete course before the egg-based vaccine would have any impact. For the whole pandemic in the SNS antiviral intervention scenario, the clinical attack rate (i.e. the fraction of the population that ever became symptomatic) obtained by EpiSimS simulation is 28.5%, and the mortality rate (i.e., the fraction of the population that dies) is 541 deaths per 100,000 population.

In the combined intervention scenarios, vaccine distribution begins on day 34, and is delivered thereafter at a rate of 4% (moderate production rate) or 25% (high production rate) of the population per week. Due to the assumed two week period to develop immunity, the vaccination intervention does not begin to provide any protection until day 48. The results are tabulated in Table 2. At a moderate vaccine delivery rate of 4% of the population per week beginning on day 34, the antiviral stockpile lasts an additional 7 days, not running out until day 88 instead of day 81. The clinical attack rate is reduced to 13.2%, and the mortality rate drops to 191 deaths per 100,000.

For the scenario combining the SNS antiviral intervention with the early vaccine at high production rate, the pandemic is controlled to such an extent that the antivirals never run out. Where the SNS holds sufficient courses of antivirals to treat 6.7% of the population, the combined use of early high-production-rate vaccine reduces the need for antivirals to only 1.31% of the population. **The clinical attack rate drops to 0.48%, and the mortality rate drops to 2.7 deaths per 100,000 persons, well below the mortality rate associated with seasonal influenza.**

Assumed US vaccine production rate, doses per week	Percentage of population vaccinated per week	Symptomatic percentage of population at pandemic peak	Clinical Attack Rate	Mortality, deaths per 100,000 population
0	0	8.1%	28.5%	541
12 million	4%	2.65%	13.2%	191
75 million	25%	0.16%	0.48%	**2.7**

Table 2. Summary of simulation results for combined antiviral and early vaccine intervention scenarios.

The time trajectories of the current symptomatic percentage of the population are shown in Fig. 2, for the basecase scenario, the SNS antiviral intervention scenario, and the combined antiviral & early vaccine intervention scenarios.

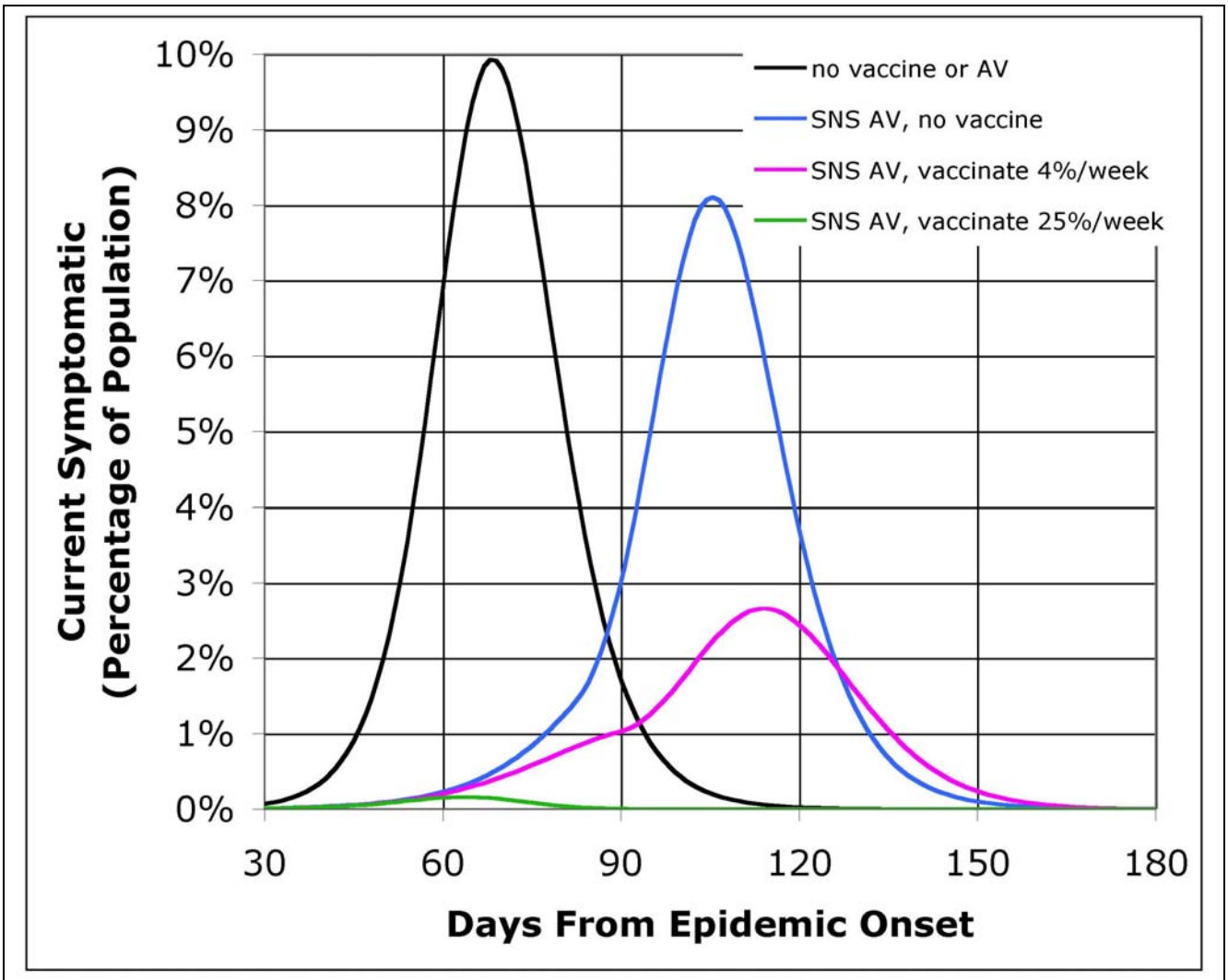

Fig. 2. EpiSimS simulation results for no intervention, SNS antiviral intervention alone, and SNS antiviral intervention combined with moderate and high production rate, early vaccine scenarios.

Comparison of One versus Two Vaccine Dose Requirement

Two scenarios were constructed to compare the cases in which either one or two vaccine doses are needed to produce 80% effectiveness. In both scenarios, the vaccine is produced at 8 million doses per week, and the distribution begins on day 34. For the one-dose case, an 80% immune response is attained 14 days after inoculation. For the two-dose case, the 80% immune response is attained 42 days after the first inoculation (14 days after the second inoculation). **Since the dose production rate is the same in both cases, the one-dose case will enable 2.6% of the population to be treated per week, while the two-dose case will only enable 1.3% of the population to be treated per week.**

The EpiSimS simulation of the two-dose early vaccine scenario, where 1.3% of the population is treated per week beginning on day 34, finds essentially no reduction in the pandemic

relative to the basecase scenario. The clinical attack rate is 30.6%, which is the same found for the basecase. The mortality rate is reduced from 614 to 609 per 100,000 population.

For the one-dose scenario, where 2.6% of the population is treated per week beginning on day 34, the EpiSimS simulation find a slight impact relative to egg-based or no vaccine production. The clinical attack rate is reduced to 27.6%, and the mortality rate is reduced to 532 deaths per 100,000 population. This scenario is illustrated in Fig. 1 as the 8 million doses per week case.

Conclusion

Several vaccine production platforms (based on mammalian cells, caterpillar cells, or bacterial cultures) show potential to enable the US to produce influenza vaccine four months earlier, and at **15 to 20 times faster** than the egg-based platform used for seasonal influenza vaccine production. With a good vaccine (a single dose providing 80% efficacy within 14 days of inoculation) becoming available for distribution within one month of isolation of the pandemic strain, detailed disease spread simulation finds that: at a production rate of 75 million doses of vaccine per week in the US, the mortality rate can be reduced **from 614 per 100,000 to 121 per 100,000.**

A more telling assessment of the impact of early, high-production vaccine takes into consideration the probable use of the SNS antiviral stockpile. The use of the current antiviral stockpile alone would delay the pandemic, but when the antivirals run out, the pandemic will explode. A scenario which combines the SNS antiviral stockpile with early, high-production vaccine, is assessed to be very effective, **reducing the mortality rate to only 2.7 deaths per 100,000 population**, which is well below the mortality rate for seasonal influenza in the US **of 12 deaths per 100,000 people per flu season.**

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References

1. Centers for Disease Control and Prevention, *Interim Pre-PAndemic Planning Guidance: Community Strategy for Pandemic Influenza Mitigation in the United States – Early, Targeted, Layered Use of Nonpharmaceutical Interventions*, Feb 2007.
2. Ferguson NM, Cummings DAT, Fraser C, Cajka JC, Cooley PC, Burke DS, *Strategies for mitigating an influenza pandemic*, doi 10:1038/nature04795.
3. Germann TC, Kadau K, Longini IM, Macken CM, *Mitigation strategies for pandemic influenza in the United States*, *Proc. Natl. Acad. Sci. U.S.A.* **103**, 5935-5940 (2006).
4. Longini IM, et.al. *Containing Pandemic Influenza with Antiviral Agents*, Am. J. of Epidemiology, Vol. 159, No. 7, April 1, 2004.
5. Stroud PD, Del Valle SY, Mniszewski SM, Riese JM, Sydoriak SJ, *Pandemic Influenza Impact Analysis Report: Simulation of Disease Spread and Intervention Effectiveness*, Los Alamos National Laboratory Report LAUR-06-7966, Nov 10, 2006.
6. Glass RJ, Glass LM, Beyeler WE, Min HJ, *Targeted Social Distancing Design for Pandemic Influenza, Emerging Infectious Diseases*, 12 (Nov 2006).
7. U.S. Department of Health and Human Services, *HHS Pandemic Influenza Plan*, Nov 2005.
8. U.S. Homeland Security Council, *National Strategy for Pandemic Influenza - Implementation Plan*, May 2006.