WEB APPENDIX

Planning Control of Pandemic Influenza H1N1 in Los Angeles County and the United States

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Web Movies

Web Movie 1. Prevalence of pandemic H1N1 cases in the continental United States with and without vaccine. The top panel displays both a plot and a heat map of prevalence of cases by census tract in a simulation of the continental United States without vaccination. The bottom panel displays the corresponding plot for a simulation with vaccine distributed according to CDC estimates.

Web Movie 2. Prevalence of pandemic H1N1 cases in the continental United States with early arrival of vaccine. The top panel displays both a plot and a heat map of prevalence of cases by census tract in a simulation of the continental United States without vaccination. The bottom panel displays the corresponding plot for a simulation in which vaccine was distributed one month earlier than had actually occurred.

IMMUNITY FROM INFECTIONS OCCURING IN SPRING/SUMMER 2009

To determine the number of simulated individuals who should have immunity from prior exposure to pandemic H1N1, we estimated the number of individuals in the United States infected with pandemic H1N1 by early September. An estimated 3 million individuals in the United States were infected by late July of 2009 [1] (Web Table 1). The age-specific illness attack rates can be derived by dividing the age-specific numbers of cases by the size of the US population, as reported in US census resident estimates from July 2009 [2].

In late July, there were 5009 lab-confirmed hospitalizations and 302 lab-confirmed deaths in the United States. By early September, the Centers for Disease Control reported 9079 hospitalizations and 593 deaths (http://www.cdc.gov/h1n1flu/updates/090409.htm, posted Sept 4). Because there were approximately twice as many lab-confirmed deaths and lab-confirmed hospitalizations in early September as there were in late July, we estimate that twice as many people, or 6 million, had been infected by early September. We assume that 67% of those infected became symptomatic, as is the case with seasonal influenza [3, 4]. Therefore, the September infection attack rates are three times higher than the illness attack rates in July (Web Table 1).

To estimate the attack rate for the 19–29 age group, we take the weighted sum (based on the fraction of the July 2009 US population in the appropriate age groups) of the 5–24 and the 25–49 rates, which is 1.456% for July (and 4.37% for September). We used the same procedure to estimate the attack rate for the 30–64 age group and found it to be 0.476% for July (and 1.43% for September).

Web Table 1. Estimated Numbers and Proportions of Individuals Infected With Pandemic H1N1 in the United States by Late July and Early September.

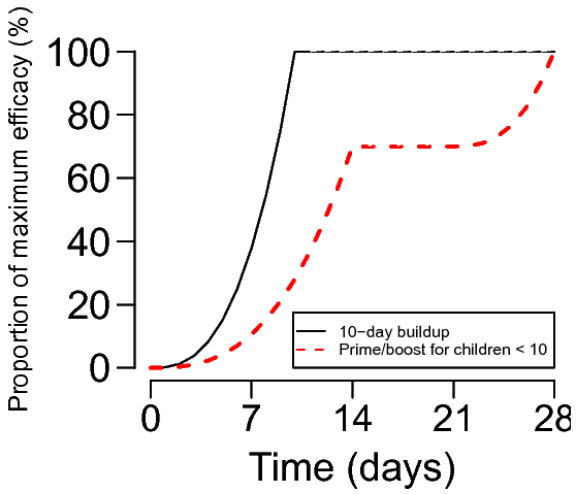
	late July cases	late July illness attack rate	early Sept infection attack rate
0–4 years	397033	1.87%	5.60%
5–24 years	1820284	2.19%	6.58%
25–49 years	612862	0.58%	1.73%
50–64 years	180297	0.32%	0.95%
65+ years	42292	0.01%	0.04%
Total	3052768	1.00%	2.99%

VACCINE EFFICACY

We use estimates from seasonal influenza vaccines [5] for pandemic H1N1 vaccine efficacy (summarized in Web Table 2). In our simulations, individuals acquire maximum protection 8–10 days after a single dose of vaccine (Web Figure 1). The live, attenuated vaccine has a slightly higher efficacy than inactivated vaccine in our simulations (Web Table 2). For all vaccines, children under 10 require 2 doses: the first confers 70% of the maximum efficacy after two weeks, and the second, which must be given at least three weeks after the first, takes one week to confer the remaining 30%. Vaccine may be less effective in the elderly (> 65 years), so the simulated vaccine efficacy is reduced by 40% in the elderly.

Web Table 2. Expected Efficacies (%) for Influenza Vaccines With a Homologous Match to the Wild Virus (From Basta, et al. [5]).

Vaccine efficacy parameter	Inactivated	Live attenuated
VES	40	40
VEP	67	83
VESP	80	90
VEI	40	50



Web Figure 1. Plot of modeled vaccine efficacies over time. Maximum attainable efficacy is reached 10 days after one dose of vaccine (solid black line). For the homologous inactivated vaccine (Web Table 2), the vaccine efficacy for infection (VES) reaches 40%; symptomatic illness given infection (VEP) reaches 67%; symptomatic illness with infection (VESP) reaches 80%; infectiousness (VEI) reaches 40%; and finally combined efficacy (VEC) reaches 78% after the second. Children under 10 require a booster shot 21 days after the first dose (red dashed line). We assume that 70% of maximum efficacy is achieved after the first dose.

VACCINE RESTRICTIONS

Nine different pandemic H1N1 vaccine formulations produced by five manufacturers were distributed in the United States during the 2009–2010 influenza season. Influenza vaccines are licensed for specific age groups, and some are prohibited for use in pregnant women. Live, attenuated vaccine is likely to be used mostly in children (up to 18 years old) (because it is easier to administer and it may be more effective in children than adults [6]), and only in those without certain medical conditions, which restricts its use to about 80% of children between 0–18. It is also licensed for adults < 50, so in the simulation it is administered to adults between 19–29 who are not pregnant. Multi-dose vials of inactivated vaccine contain thimerosol, so are not given to children under 5 or to pregnant women. Fluzone pre-filled syringes (PFS) 7.5 μg/dose are given only to children under 5. Pre-filled syringes containing 15 μg of Fluzone or Fluvirin are given only to individuals 5 and older, while PFS 15 μg of Afluria are given to those 19 and up. No vaccine is licensed for infants (<6 months), so they are never vaccinated in the simulations.

VACCINE AVAILABILITY

The vaccine supply in the simulation followed the CDC's vaccine allocation schedule released on December 25, 2009 (Web Table 3). Vaccine is distributed pro rata, so LA County received a portion proportionate to its population (3.195% of the total supply for the United States). We assumed that the amount of vaccine allocated each week would be deployed in LA County 9 days later, and 1/7 of the week's supply would be administered each day starting that day. Although the projections indicated that there would be enough vaccine to cover half of the US population, estimates indicate that only 20% of the population was vaccinated [7]. Therefore, we ignored vaccine allocations after November 27, 2009.

Web Table 3. US Pandemic H1N1 Vaccine Supply (From [8]).

Allocation date	FluZone PFS 7.5µg	FluZone PFS 15µg	FluZone MDV	FluVirin PFS	FluVirin MDV	Afluria PFS	Afluria MDV	FluLaval MDV	FluMist	Total	Cumulative total
10/02/09	0	0	0	0	0	0	0	0	2,380,300	2,380,300	2,380,300
10/09/09	0	0	3,149,400	183,700	0	0	0	0	2,039,200	5,372,300	7,752,600
10/16/09	0	0	2,928,100	336,400	0	0	0	0	1,351,600	4,616,100	12,368,700
10/23/09	0	0	1,619,500	672,600	0	0	0	0	1,420,300	3,712,400	16,081,100
10/30/09	1,318,900	0	4,411,500	1,707,000	1,128,800	464,700	0	0	1,574,400	10,605,300	26,686,400
11/06/09	960,700	0	1,732,500	2,159,400	4,214,600	492,200	0	0	1,792,300	11,351,700	38,038,100
11/13/09	1,080,500	0	1,262,800	813,600	884,800	278,000	0	0	651,600	4,971,300	43,009,400
11/20/09	811,700	194,900	3,208,200	465,900	4,479,600	152,800	322,400	0	1,500,400	11,135,900	54,145,300
11/27/09	305,600	322,100	1,740,400	299,700	3,341,900	0	0	0	2,182,800	8,192,500	62,337,800
12/04/09	9,000	667,000	1,338,600	1,326,800	4,310,000	0	0	0	2,624,700	10,276,100	72,613,900
12/11/09	0	1,164,500	7,869,100	412,500	2,589,100	0	0	0	2,194,000	14,229,200	86,843,100
12/18/09	0	1,323,800	7,882,300	490,000	1,321,000	191,900	155,700	0	1,874,900	13,239,600	100,082,700
12/25/09	0	2,384,100	3,002,900	904,900	2,053,900	627,800	217,100	0	1,204,300	10,395,000	110,477,700
01/01/10	0	2,100,000	8,500,000	325,000	1,900,000	1,122,130	129,800	0	2,300,000	16,376,930	126,854,630
01/08/10	0	900,000	8,200,000	900,000	4,000,000	388,300	0	630,000	3,500,000	18,518,300	145,372,930
01/15/10	0	943,600	930,000	902,500	2,076,300	0	0	630,000	2,100,000	7,582,400	152,955,330
01/23/10	0	0	2,800,000	0	0	0	0	3,810,000	2,100,000	8,710,000	161,665,330
01/30/10	0	0	3,100,000	0	0	0	0	0	2,100,000	5,200,000	166,865,330

VACCINE PRIORITIZATION

The Advisory Committee on Immunization Practices (ACIP) recommended that the following groups be prioritized for pandemic H1N1 vaccination in the 2009 season if a large amount of vaccine were available: pregnant women, people who live with or care for children younger than 6 months of age, health care and emergency services personnel with direct patient contact, children 6 months through 4 years of age, children 5 through 18 years of age who have chronic medical conditions, and people from ages 25 through 64 years who are at higher risk for complications from novel H1N1 because of chronic health disorders or compromised immune systems [9]. If there was sufficient vaccine, the first priority tier was expanded to include: health care and emergency services personnel without direct patient contact and persons between the ages of 6 months through 24 years of age.

In our simulations, we implemented a three-tier priority system that reflects the actual distribution of vaccine in the fall of 2009. The highest priority individuals were pregnant women, family members of children less than six months old, health care and emergency services personnel with direct patient contact, and high-risk individuals from 6 months to 64 years old. The second tier included healthy children (ages 6 months to 18 years), and the third tier was the remaining population, which included healthy adults and the elderly.

We matched the prioritized categories of individuals to our simulator's by taking the estimated fraction of the US population in a category and randomly assigning that proportion of simulated individuals of the appropriate age to be prioritized. The simulation has US population of about 279,583,437 (based on the 2000 continental US), while the current US population is about 307,000,000.

Infants (<6 months) can not get vaccinated, but their family members are prioritized to receive vaccine. In 2000, 3,805,648 individuals in the US were under 1 year old, and we assume that half of them are under 6 months old. 19,175,798 individuals were under 5. Therefore, 9.923% of individuals under 5 are under 6 months old, so this percentage of 0–4 year olds in the simulation are designated to be "infants".

There are an estimated 9 million health care and emergency services personnel with direct patient contact [10]. The simulation has about 118,420,000 employed adults in the continental US so 6.9% of them are randomly selected to be "essential."

There are an estimated 4 million pregnant women in the US [10]. In the simulation, we assigned a fraction of individuals who were from 19–29 years old and 30–64 years old to be pregnant. We took the number of women in the different age groups from the 2000 Census and multiplied these by pregnancy rates [11] to determine the proportion of pregnant women from different age groups. To compute the number of pregnant 19-year-olds, we assumed that they comprised 1/5 of the US 2000 Census population of 15-19 year-olds and multiplied by the 18–19 year-old pregnancy rates. Our estimates of the number of pregnant women in each age group in 2000 is summarized in Web Table 4.

An estimated 6 million children 5 through 18 years of age have chronic medical conditions [10]. If children 5–18 are about 22% of the population, then 8.884% are in this category.

About 52.23% of the 2000 population was between 25 and 64. If we assume 52.23% of the current population is between 25 and 64 and 34 million have chronic health disorders or compromised immune systems [10], then 21.20% of individuals within these ages are at high risk. Web Table 5 summarizes these values.

Web Table 4. US Pregnancy Rates and Numbers by Age.

Census Age Group	Female Pop (2000)	Pregnancy Rate (2004)	% of Pregnant Pop	# Pregnant
19	9828886/5	119/1000	4.03%	146613
20–24	9276187	164/1000	26.19%	953412
25–29	9582576	169/1000	27.88%	1014971
30–34	10188619	135/1000	23.68%	861970
35–39	11387968	76/1000	14.90%	542496
40–44	11312761	17/1000	3.311%	120538
total			100.00%	3640000

Web Table 5. High-risk Segments of the Simulated Population by Age.

Age Category	Ages	% of Population	% High Risk	% Pregnant
Pre-school children	0–4 years	6.80%	8.90%	—
School-age children	5–18 years	22.00%	8.90%	—
Young adults	19–29 years	28.90%	21.20%	2.62%
Middle adults	30–64 years	30.00%	21.20%	1.82%
Old adults	65+ years	12.40%	—	—

HOSPITALIZATION AND CASE FATALITY RATIOS

To estimate the pandemic H1N1 age-specific case fatality ratios (the proportion of symptomatic H1N1 cases that are fatal) and the age-specific case hospitalization ratios (the proportion of symptomatic cases due to H1N1 that require hospitalization), we draw on estimates of the total number of age-specific H1N1 cases, total number of age-specific H1N1 hospitalizations, and total number of age-specific H1N1 deaths in the US as reported by in [12] (Web Table 6).

We estimate the H1N1 hospitalization and mortality ratios by risk group (Web Table 7). Starting with the ratios in Web Table 6, we assume that some proportion of each group is "high risk" and their ratios of hospitalization and mortality are 6.4, 17.0, and 8.1 times higher than the rest of their age groups in 0–4 year olds, 5-18 year olds, and 19-64 year olds, respectively [13]. [13] assumes that 10% of children, 17% of younger adults, and all older adults are "high risk". This is close to the ACIP estimates in which 8.9% of children and 21.2% of adults are high risk [10], which is what we use. We assume that high-risk individuals are no more likely to become infected or symptomatic than healthy individuals. Using the age-specific hospitalization and mortality ratios in Web Table 6, our ACIP estimates of the proportion of individuals who are high risk, and the ratio of high-risk to healthy hospitalization and mortality ratios from [13], we estimate the hospitalization and mortality ratios for high-risk and healthy individuals.

To calculate the number of deaths based on a simulation's output, we use the mortality estimates for "healthy" individuals for the non-high risk, non-pregnant symptomatic individuals and the high-risk estimates for the high-risk and pregnant individuals, remembering not to double-count those who are both high risk and pregnant.

Web Table 6. Age-specific Pandemic H1N1 Influenza-related Cases, Hospitalizations, and Deaths in the USA From April 2009–April 10, 2010 (From Reference (1)).

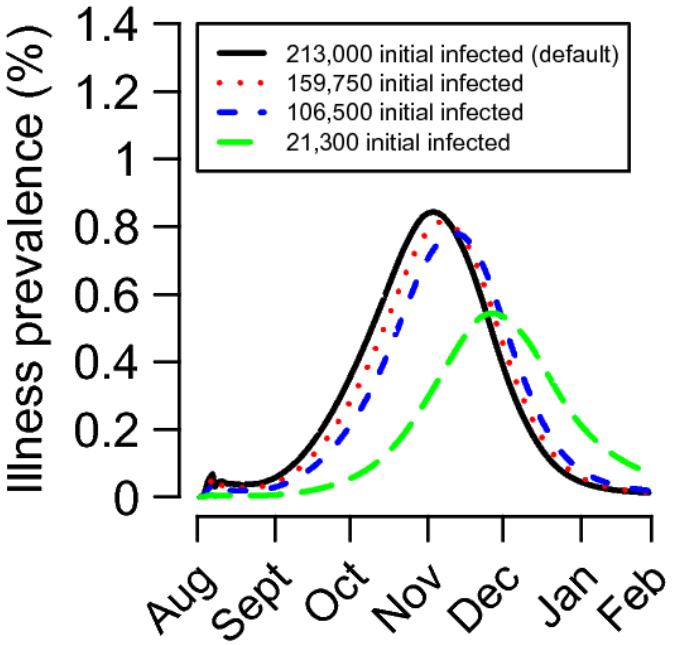
Age Group	Cases[1]	Hospitalizations	Deaths
0–17 years	20 million	87,000	1,280
18–64 years	35 million	160,000	9,570
65 years and older	6 million	27,000	1,620
Total	60 million	274,000	12,470

Web Table 7. Age-specific Pandemic H1N1 Influenza-related Hospitalization and Mortality in the USA by Risk Group.

		0–4 years	5–18 years	19–29 years	30–64 years	65+ years	Total
Hospitalization ratios (per 100 cases)	Overall	0.4350	0.4350	0.4571	0.4571	0.4500	0.4492
	Healthy	0.2938	0.1795	0.1825	0.1825	–	
	High risk	1.8803	3.0507	1.4781	1.4781	–	
Case fatality ratios (per 100 cases)	Overall	0.0064	0.0064	0.0273	0.0273	0.0270	0.0204
	Healthy	0.0043	0.0026	0.0109	0.0109	–	
	High risk	0.0277	0.0449	0.0884	0.0884	–	

SENSITIVITY OF RESULTS TO THE INITIAL NUMBER OF INFECTED INDIVIDUALS

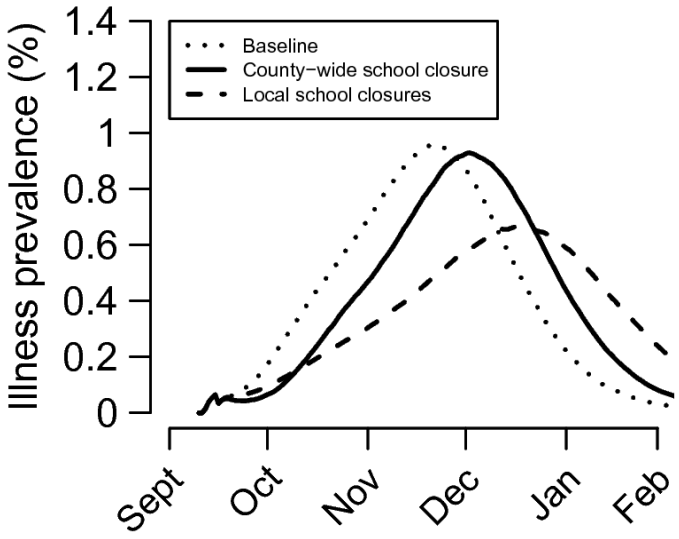
In the Results section of the text, we describe the results of simulations of the continental United States in which 213,000 (0.08% of the population) are initially infected. Here, we show that this number can be reduced by 25% (159,750 infected) to 50% (106,500 infected) without greatly affecting the results (Web Figure 2). When the number is reduced by 90% (21,300), the epidemic is noticeably slowed (Web Figure 2).



Web Figure 2. Plot of simulated illness prevalence in the continental United States for different numbers of initially infected people.

EFFECT OF SCHOOL CLOSURES

We simulated the effect of closing schools for a week in Los Angeles County (Web Figure 3). Local transmission of influenza appeared to slow or stop when schools were closed, then resume when schools reopened. If all schools in the county are closed simultaneously for seven days, the epidemic curve shifts one week back. If each school closes reactively for seven days after a single student falls ill, then school closures slow but does not stop the epidemic. These simulations show that schools are a catalyst for community-wide influenza transmission, and that short-term school closures delay, but do not necessarily diminish influenza epidemics.



Web Figure 3. The effect of school closure on illness prevalence in simulations of Los Angeles County. The dotted line plots the baseline illness prevalence in which there is no vaccination or school closure. The solid line plots illness prevalence when all schools in the county are simultaneously closed for seven days. The dashed line plots illness prevalence when each school closes for seven days after a single student becomes ill in each one.

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