School-Based Influenza Vaccination: Health and Economic Impact of Maine's 2009 Influenza Vaccination Program

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Objective. To estimate the societal economic and health impacts of Maine's school-based influenza vaccination (SIV) program during the 2009 A(H1N1) influenza pandemic.

Data Sources. Primary and secondary data covering the 2008–09 and 2009–10 influenza seasons.

Study Design. We estimated weekly monovalent influenza vaccine uptake in Maine and 15 other states, using difference-in-difference-in-differences analysis to assess the program's impact on immunization among six age groups. We also developed a health and economic Markov microsimulation model and conducted Monte Carlo sensitivity analysis.

Data Collection. We used national survey data to estimate the impact of the SIV program on vaccine coverage. We used primary data and published studies to develop the microsimulation model.

Principal Findings. The program was associated with higher immunization among children and lower immunization among adults aged 18–49 years and 65 and older. The program prevented 4,600 influenza infections and generated \$4.9 million in net economic benefits. Cost savings from lower adult vaccination accounted for 54 percent of the economic gain. Economic benefits were positive in 98 percent of Monte Carlo simulations.

Conclusions. SIV may be a cost-beneficial approach to increase immunization during pandemics, but programs should be designed to prevent lower immunization among nontargeted groups.

Key Words. Pandemics, immunization, economic evaluation

Influenza transmission rates are high in schools, and school-aged children play an important role in the spread of the disease (National Center for Immunization and Respiratory Diseases 2010). Vaccinations among young children are usually administered by primary care physicians, but coverage among school-age children is lower than among younger children. A significant increase in office visits would be needed to achieve higher coverage among school-age children, which would impose an additional burden on the health care system and on households (Szilagyi et al. 2003; Burns and Zimmerman 2005; Cawley, Hull, and Rousculp 2010). School-based influenza vaccination (SIV) has been suggested as an effective strategy not only to increase vaccination among children (King et al. 2006; Lindley et al. 2008), but also to reduce costs relative to vaccination at traditional settings (White, Lavoie, and Nettleman 1999; Schmier et al. 2008).

In 2009, during the influenza A (H1N1) pandemic, several U.S. states reported holding SIV clinics, but only a handful implemented statewide SIV efforts (U.S. Department of Health and Human Services 2010). Months before the pandemic, Maine's public health and education authorities had planned to pilot SIV clinics for seasonal influenza vaccination. With the emergence of the pandemic influenza A(H1N1)pdm09 virus, state authorities enabled all public and private K-12 schools in the state to conduct SIV clinics. By some estimates, 98 percent of schools participated in these clinics (unpublished data, collected by Lorick et al. [2014]). Maine's SIV experience during this pandemic constitutes an important case study. Not only was the program an impressive logistical exercise but also, unlike other states where A(H1N1)pdm09 vaccine may have arrived too late, vaccine delivery in Maine coincided with peak influenza activity. Thus, effective vaccine coverage may have increased if vaccine was administered quickly and efficiently. However, because A(H1N1)pdm09 vaccine distribution in Maine was prioritized such that most early supplies were allocated to SIV clinics, the program may have unintentionally led to lower uptake among adults and the elderly.

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In this evaluation, we set out to estimate the health and economic impact of Maine's SIV program across age groups. Our results may help public health officials in other jurisdictions plan and prepare for future influenza pandemics.

METHODS

This study included two analyses. First, we estimated the effects of the SIV program on vaccine uptake using a statistical approach that contrasted vaccination in Maine during the first 9 weeks after A(H1N1)pdm09 vaccination started (October 11 to December 12, 2009) to (1) uptake in Maine during the first 9 weeks of vaccination in the previous season (September 1 to November 1, 2008); (2) uptake in 15 other states during the first 9 weeks of vaccination in both seasons; and (3) uptake in all 16 states after the first 9 weeks of vaccination during both seasons. Second, we estimated the health and economic impact of the program using simulation modeling, projecting outcomes among the population of Maine under a hypothetical scenario without the program.

SIV Impact on Vaccine Coverage

We used data from two national surveys: the 2009–2010 Behavioral Risk Factor Surveillance System (BRFSS) and the National 2009 H1N1 Flu Survey (NHFS) (Centers for Disease Control and Prevention 2008–2010; U.S. Department of Health and Human Services 2012) to estimate influenza vaccine uptake in Maine and 15 other states (Alaska, Connecticut, Illinois, Iowa, Kansas, Michigan, Nevada, New Mexico, Ohio, Texas, Utah, Washington, West Virginia, Wisconsin, and Wyoming) that reported vaccination for children and adults and did not implement statewide A(H1N1)pdm09 SIV programs (see Appendix SA2 for details). We applied Kaplan–Meier survival methods (Setse et al. 2011) to these data to estimate the monthly cumulative proportion of individuals who received one or more doses of seasonal (2008–09) or A(H1N1)pdm09 (2009–10) influenza vaccine for six age groups (6 months–4, 5–12, 13–17, 18–49, 50–64, and 65 and older). Because our microsimulation model used weekly transition periods, we used linear interpolation to estimate weekly vaccine uptake for each state–age group combination.

In our statistical analysis, we used a difference-in-difference-in-differences (DDD) approach (Meyer 1995), exploiting three features of our data: (1)

the existence of intervention (Maine) and control (15 states) groups; (2) the availability of data for both groups over two influenza seasons, one during which the intervention (SIV) was not implemented; and (3) the indication that over 95 percent of A(H1N1)pdm09 doses administered during the SIV intervention were given during the first 9 weeks after vaccine was available (data collected as part of this evaluation and described in Graitcer et al. [2012]).

The data in each of six regressions (one for each age group) had one observation per-week, per-state over the 2008–09 and 2009–10 influenza seasons (34 weeks in each season), for a total of 1,088 observations per regression model. The outcome variable was the proportion of a group's population that received the vaccine in that particular week. In addition to the intercept, all variables in the right-hand side were binary (yes/no) indicators for (1) the state of Maine; (2) the period including the first 9 weeks after vaccination started in each season; (3) the 2009–10 influenza season; (4) the interaction between the Maine and first 9 weeks variables; (5) the interaction between the Maine and 2009–10 season variables; (6) the interaction between the first 9 weeks and 2009–10 season variables; and (7) the triple interaction between the Maine, first 9 weeks, and 2009–10 season variables.

The equation below describes each regression model. In this equation, w is an index for weeks and s is an index for states. We estimated each regression using the *xtreg* command in Stata version 13.1 (StataCorp LP, College Station, TX), with robust standard errors and random effects for each state.

$$\begin{aligned} \text{uptake}_{w,s} = & \beta_0 + \beta_1 \text{Maine}_{w,s} + \beta_2 \text{first9weeks}_{w,s} + \beta_3 \text{2009season}_{w,s} \\ & + \beta_4 (\text{Maine}_{w,s} \times \text{first9weeks}_{w,s}) + \beta_5 (\text{Maine}_{w,s} \\ & \times \text{2009season}_{w,s}) + \beta_6 (\text{first9weeks}_{w,s} \times \text{2009season}_{w,s}) + \\ & \beta_7 (\text{Maine}_{w,s} \times \text{first9weeks}_{w,s} \times \text{2009season}_{w,s}) \end{aligned}$$

Within each group, we tested the null hypothesis $\beta_7 = 0$. A rejection of this hypothesis implies that A(H1N1)pdm09 vaccine uptake during the 2009–10 season was different in Maine from uptake in the other 15 states, after accounting for the potential confounders listed above. Under the assumption that this model captured the effects of the SIV program on vaccination uptake, we used regression results to project counterfactual vaccine coverage in Maine in the absence of a SIV program—that is, removing the estimated effects of the program on vaccine coverage. This statistical approach reduces bias due to pre-existing differences in vaccine uptake rates between Maine and the other states; changes in vaccine uptake between the two seasons that were

common to all states; pre-existing differences between Maine and the other states in vaccine uptake during the first 9 weeks of vaccination; and changes in vaccine uptake during the first 9 weeks of A(H1N1)pdm09 vaccination relative to the first 9 weeks of vaccination in the previous season that were common to all states.

SIV Impact on Health Outcomes

We used TreeAge Pro 2014 (TreeAge Software Inc., Williamstown, MA) to develop a Markov microsimulation decision model of health outcomes (influenza infections, outpatient visits, hospitalizations, and deaths due to influenza) over the influenza season. We projected outcomes under scenarios with and without the SIV program. In the first scenario, weekly vaccination uptake was taken directly from the Kaplan–Meier interpolated estimates described above. In the second scenario, vaccine coverage was estimated using the results of the DDD regressions, removing the effect of the SIV program.

A simplified representation of the simulation model is shown in Figure 1. Individuals transition over time through six different health states: (1) nonvaccinated, susceptible to influenza; (2) vaccinated, susceptible to influenza; (3) nonvaccinated, immune due to infection; (4) vaccinated, immune due to infection; (5) vaccinated, immune due to vaccination; and (6) dead due to infection. All individuals entered the model in state (1). Over 34 weekly cycles, individuals remained in that state or transitioned to other states, depending on whether they became infected and/or received the vaccine. For example, state (2) was reached when vaccination was ineffective and did not result in immunity to infection. If influenza infection occurred before vaccination and did not result in death, state (3) was reached. State (4) was reached in several ways: due to ineffective vaccination followed by infection; when vaccination occurred after infection, which could be due to an asymptomatic infection or unawareness that symptoms were due to influenza; or from infection during the same week of vaccination, which was possible due to a lag between vaccination and the development of protective immunity. Effective vaccination led to state (5). Death, not shown for simplicity, could follow any influenza infection.

Differences in health outcomes between the two scenarios arise from differences in vaccine uptake. Increased vaccination led to a larger immune population. The model did not account for possible herd immunity resulting from higher vaccine coverage; therefore, weekly probabilities of *infection* for susceptible individuals were the same in both scenarios. Model parameters were

Figure 1: Simplified Structure of Markov Decision Model

Note. For simplicity, the health status of death is not shown. See text for further details. Additional graphs are shown in Appendix SA2.

derived from surveillance data, published studies, unpublished data collected by the CDC, and expert opinion (Table 1).

Economic Costs and Benefits

We also used the Markov model for cost–benefit calculations. We estimated direct and indirect costs due to influenza vaccination and treatment from the societal perspective. We defined economic benefits using the human capital approach (Grosse, Krueger, and Mvundura 2009); that is, the economic value of child and adult health was determined by averted productivity losses due to adult illness or adults taking time off to care for ill children. As acute influenza illness is typically a self-limiting infection that causes symptoms for several days, we did not discount any costs or benefits, except for the lifetime value of lost productivity due to premature death, which was discounted annually at 3 percent (Weinstein et al. 1996; Grosse, Krueger, and Mvundura 2009).

Table 1: Input Parameters in Markov Model to Estimate Impact of School-Based Vaccination Program

<i>Variable</i>	<i>Base-Case Value*</i>	<i>Sensitivity Analysis[‡]</i>	<i>Sources</i>
Population size			
Ages 6 months–4 years	70,716	–	CDC (2009)
Ages 5–12 years	114,487	–	CDC (2009)
Ages 13–17 years	87,202	–	CDC (2009)
Ages 18–49 years	534,077	–	CDC (2009)
Ages 50–64 years	278,425	–	CDC (2009)
Ages 65 + years	195,100	–	CDC (2009)
Probability a child was vaccinated at school clinic in SIV scenario			
Ages 6 months–4 years	0.25	[L] –1.44, 0.32	‡
Ages 5–12 years	0.73	[L] –0.31, 0.01	§
Ages 13–17 years	0.79	[L] –0.24, 0.02	§
Probability of receiving A (H1N1)pdm09 vaccine	Varied by week, age, scenario	[T] 0.75x, x, 1.25x	CDC (2008–2010); DHHS (2012)
Probability of A(H1N1)pdm09 virus infection among susceptible individuals	Varied by week, age	[T] 0.75x, x, 1.25x	¶
Probability of asymptomatic influenza infection	0.50	[T] 0.35, 0.5, 0.65	Aho et al. (2010); Bandaranayake et al. (2010)
Vaccine effectiveness against A(H1N1)pdm09 virus infection			
Ages 6 months–12 years	0.51	[L] –0.70, 0.23	Griffin et al. (2011)
Ages 13–49 years	0.59	[L] –0.54, 0.16	Griffin et al. (2011)
Ages 65 + years	0.22	[L] –1.79, 0.76	Griffin et al. (2011)
Probability of outpatient visit symptomatic A(H1N1)pdm09 virus infection			
Ages 6 months–4 years	0.67	[L] –0.40, 0.024	CDC (2009)
Ages 5–17 years	0.51	[L] –0.65, 0.022	CDC (2009)
Ages 18–64 years	0.37	[L] –0.98, 0.030	CDC (2009)
Ages 65 + years	0.56	[L] –0.58, 0.034	CDC (2009)
Probability of hospitalization symptomatic A(H1N1)pdm09 virus infection			
Ages 6 months–4 years	0.027	[L] –3.70, 0.413	Presanis et al. (2009)
Ages 5–17 years	0.007	[L] –5.11, 0.409	Presanis et al. (2009)
Ages 18–64 years	0.030	[L] –3.57, 0.377	Presanis et al. (2009)
Ages 65 + years	0.024	[L] –4.00, 0.706	Presanis et al. (2009)
Probability of death symptomatic A(H1N1)pdm09 virus infection			
Ages 6 months–4 years	0.00030	[L] –8.36, 0.697	Presanis et al. (2009)
Ages 5–17 years	0.00012	[L] –9.25, 0.597	Presanis et al. (2009)
Ages 18–64 years	0.00161	[L] –6.51, 0.413	Presanis et al. (2009)
Ages 65 + years	0.00263	[L] –6.83, 1.330	Presanis et al. (2009)
Cost of symptomatic uncomplicated influenza (not medically attended)	15.6	[T] 11.7, 15.6, 19.5	Lee et al. (2011)

Continued

Table 1. *Continued*

<i>Variable</i>	<i>Base-Case Value*</i>	<i>Sensitivity Analysis[†]</i>	<i>Sources</i>
Cost of outpatient visit due to influenza			
Ages 6 months–4 years	211	[L] 4.61, 1.215	Molinari et al. (2007)
Ages 5–17 years	120	[L] 3.73, 1.457	Molinari et al. (2007)
Ages 18–49 years	158	[L] 3.77, 1.608	Molinari et al. (2007)
Ages 50–64 years	190	[L] 3.60, 1.815	Molinari et al. (2007)
Ages 65 + years	306	[L] 3.86, 1.931	Molinari et al. (2007)
Cost of hospitalization due to influenza			
Ages 6 months–4 years	13,750	[L] 8.28, 1.578	Molinari et al. (2007)
Ages 5–17 years	18,975	[L] 8.08, 1.881	Molinari et al. (2007)
Ages 18–49 years	24,028	[L] 9.15, 1.369	Molinari et al. (2007)
Ages 50–64 years	28,188	[L] 8.76, 1.722	Molinari et al. (2007)
Ages 65 + years	14,472	[L] 8.77, 1.275	Molinari et al. (2007)
Present value of productivity losses due to death			
Ages 6 months–4 years	1,233,932	–	Grosse, Krueger, and Mvundura (2009)
Ages 5–12 years	1,437,082	–	Grosse, Krueger, and Mvundura (2009)
Ages 13–17 years	1,639,189	–	Grosse, Krueger, and Mvundura (2009)
Ages 18–49 years	1,421,706	–	Grosse, Krueger, and Mvundura (2009)
Ages 50–64 years	630,629	–	Grosse, Krueger, and Mvundura (2009)
Ages 65 + years	189,646	–	Grosse, Krueger, and Mvundura (2009)
Market and household productivity			
Ages 18–49 years and caregivers for ill children	164	–	Grosse, Krueger, and Mvundura (2009)
Ages 50–64 years	157	–	Grosse, Krueger, and Mvundura (2009)
Ages 65 + years	59	–	Grosse, Krueger, and Mvundura (2009)
Probability of missing work days child ill with symptomatic A(H1N1)pdm09 virus infection	0.53	[L] –0.63, 0.046	[§]
Adult productivity days missed to care for child ill with A(H1N1)pdm09 virus infection	3.2	[L] 1.002, 0.574	[§]
Adult productivity days missed due to symptomatic A(H1N1)pdm09 virus infection	1.03	[T] 0.5, 1.09, 1.5	Lee et al. (2011)

Continued

Table 1. *Continued*

<i>Variable</i>	<i>Base-Case Value*</i>	<i>Sensitivity Analysis[‡]</i>	<i>Sources</i>
Per-dose administration costs of vaccination in usual setting	31.7	[T] 12.7, 31.7, 50.6	Prosser et al. (2006)
Per-dose cost of school-based vaccination (planning, clinic staff, other personnel, materials, operations, and postoperations)	27.1	Random sampling from tables**	Asay et al. (2012); Cho et al. (2012)
Household nonmedical costs of vaccination at usual setting (HHCV)	40.5	[T] 0, 40.5, 78.5	Prosser et al. (2006)
Household nonmedical costs of school-based vaccination ^{††}			
Ages 6 months–4 years	HHCV	Same as HHCV	Assumed
Ages 5–12 years	0.25 × HHCV	Varied with HHCV	‡
Ages 13–17 years	0.12 × HHCV	Varied with HHCV	‡

*All costs and productivity values are in 2009 dollars. Medical costs were inflated using the medical services component of the consumer price index; nonmedical costs were adjusted using the overall consumer price index.

[†]Parameter order is [T]riangular distribution: minimum, likeliest, maximum; [L]ognormal distribution: mean of logs, SD of logs.

[‡]Unpublished data collected during a separate study (Lorick et al. 2014).

[§]Unpublished data collected during a separate study (Graitcer et al. 2012).

[†]Estimated using data from CDC's Influenza-Like Illness Surveillance Network (ILINet) and Influenza Incidence Surveillance Project (IISP); details provided in Appendix SA2.

**Costs randomly sampled from tables summarizing vaccination costs in individual school-based influenza vaccination (SIV) clinics, collected during a separate study (Asay et al. 2012; Cho et al. 2012).

^{††}We assumed that household costs of SIV were the same as vaccination in regular settings at clinics that required parental presence. For clinics not requiring parental presence, we assumed zero household costs. See Methodology for further details.

We assumed that parental presence was required in SIV clinics for children under 5 years old and, based on primary data collected by Lorick et al. (2014), for 25 percent of children aged 5–12 and 12 percent of children aged 13–17. When parental presence was not required, we assumed no productivity losses due to vaccination. When parental presence was required, we assumed that productivity losses were the same as for vaccination in traditional settings. Estimates of SIV labor, materials, planning, and implementation costs were taken from a cost analysis conducted as part of the same evaluation effort (Asay et al. 2012; Cho et al. 2012). In a survey of Maine school nurses, 25 percent of nurses in schools that offered SIV clinics reported their schools either

had preschool-age students or offered vaccination to children younger than their own students (unpublished data collected by Lorick et al. [2014]); therefore, we assumed that 25 percent of vaccinations among children aged 0–4 occurred in SIV clinics and the rest occurred in regular settings. Other direct costs in the model and their sources are described in Table 1.

We provide additional details on the costs included in our analysis in Appendix SA2, which also provides an explanation of why we excluded the cost of vaccine dose supplies—funded by the federal government, but still part of societal costs—from our analysis.

Sensitivity Analysis

Results from the baseline analysis described above may be vulnerable to underlying uncertainty in our assumptions. For example, we assumed that 73 percent of children ages 5–12 were vaccinated at an SIV clinic, but this value was estimated using data from four Maine counties that account for less than 60 percent of the state's population (see footnote in Table 1); thus, the true value for the state's population in this age group could have been lower or higher.

To assess how robust our results were to uncertainty in our assumptions, we assigned probability distributions to most model parameters and ran 10,000 Monte Carlo simulations for synthetic populations of 25,000 individuals in each age group. That is, in each simulation, individual parameters were randomly sampled from the probability distributions described in Table 1 and all costs and outcomes were estimated for 25,000 individuals within each age group, using the set of sampled parameter values. We used probability distributions found in previous studies, adjusting them for inflation and also so they matched the distributional characteristics of our data; for example, if a previous study of vaccine effectiveness used a lognormal distribution with mean of logs X and standard deviation of logs S , we assumed a lognormal distribution in our sensitivity analysis, but using parameter values that matched the available information regarding the effectiveness of the A(H1N1)pdm09 vaccine. To aggregate simulation results for the entire population, a random seed was used to generate the same set of pseudorandom parameter values across age groups.

To estimate total costs and outcomes, the average of each simulation within an age group was multiplied by the group's population size. In our findings below, we reported the mean results of the 10,000 simulations and, to illustrate the potential variability of results due to uncertainty, the 5 and 95

percentiles, which represent the 500th lowest and 500th highest results among the 10,000 simulations, respectively. We should remark that (1) as they are estimated from simulated populations, not from data sampled from a population, the 5 and 95 percentiles are not measures of statistical significance (i.e., they cannot be interpreted as confidence intervals, and thus, no statistical significance can be inferred from whether they cross zero or not); and (2) other simulation studies report more conservative measures of outcome variability, such as the interquartile range (25 and 75 percentiles) or the 10 and 90 percentiles.

RESULTS

Vaccine Coverage

We provide the results of our DDD regressions in Table 2. Holding everything else constant, vaccine uptake during the 2008–09 season among children was not significantly different in Maine from that in other states (p -values $> .05$ for *Maine* and *Maine* $\times$ *First 9 Weeks* in all three regressions for ages < 18). This pattern changed in the first 9 weeks of the 2009–10 season when vaccine coverage among children was significantly higher in Maine than in the other states (p -values $< .001$ for the triple interaction term *Maine* $\times$ *First 9 Weeks* $\times$ *2009–10 Season*, the key variable of interest in our analysis). Moreover, this increase in uptake among children in Maine during the 2009–10 season appears largely limited to the first 9 weeks after vaccination started, as two of three coefficients for the interaction term *Maine* $\times$ *2009–10 Season*—which represents the differences in uptake between Maine and the other states after the first 9 weeks—were not statistically significant. Examining patterns among adults and the elderly in the 2009–10 season, we see evidence that their uptake in Maine was lower during the first 9 weeks (two of three coefficients for the *triple interaction term* were negative and their p -values $< .001$) and higher in the period after the first 9 weeks (all three coefficients for the term *Maine* $\times$ *2009–10 Season* were positive and p -values $< .001$).

A graphical illustration that largely confirms these findings is provided in Figure S3 in the Appendix SA2, which shows Kaplan–Meier estimates of cumulative vaccine coverage in Maine and the 15 comparison states during the 2008–09 and 2009–10 influenza seasons. Figure S3 in Appendix SA2 shows that vaccine uptake in Maine was similar to uptake in the other states during the 2008–09 season. However, during the first 9 weeks of the 2009–10 season vaccine uptake among children was significantly higher in Maine than in the other states, while no appreciable differences can be seen among adults

Table 2: Regression Results: Impact of School Vaccination Program on Influenza A(H1N1)pdm09 Virus Vaccine Coverage in Maine between October 11 and December 12, 2009, by Age Group

Variable/Interaction	Ages 6 m–4 years				Ages 5–12 years				Ages 13–17 years				Ages 18–49 years				Ages 50–64 years				Ages > 64 years			
	Coeff	(p-value)	Coeff	(p-value)	Coeff	(p-value)	Coeff	(p-value)	Coeff	(p-value)	Coeff	(p-value)	Coeff	(p-value)	Coeff	(p-value)	Coeff	(p-value)	Coeff	(p-value)	Coeff	(p-value)	Coeff	(p-value)
Intercept	1.064	(<.001)	0.539	(<.001)	0.428	(<.001)	0.575	(<.001)	0.802	(<.001)	1.077	(<.001)	0.802	(<.001)	1.077	(<.001)	0.802	(<.001)	1.077	(<.001)	0.802	(<.001)	1.077	(<.001)
Maine	0.042	(.544)	0.067	(.257)	0.018	(.750)	0.078	(<.001)	0.223	(<.001)	0.222	(<.001)	0.078	(<.001)	0.222	(<.001)	0.223	(<.001)	0.222	(<.001)	0.223	(<.001)	0.222	(<.001)
First 9 vaccination weeks	1.237	(<.001)	0.916	(<.001)	0.725	(<.001)	0.765	(<.001)	1.761	(<.001)	3.473	(<.001)	0.765	(<.001)	1.761	(<.001)	1.761	(<.001)	3.473	(<.001)	1.761	(<.001)	3.473	(<.001)
2009–10 season	–0.508	(<.001)	–0.036	(.528)	0.074	(.207)	–0.150	(.001)	–0.376	(<.001)	–0.399	(<.001)	–0.150	(.001)	–0.376	(<.001)	–0.376	(<.001)	–0.399	(<.001)	–0.376	(<.001)	–0.399	(<.001)
Maine × First 9 weeks	–0.114	(.641)	0.037	(.831)	0.062	(.519)	–0.178	(.008)	–0.260	(<.001)	0.094	(.391)	–0.178	(.008)	–0.260	(<.001)	–0.260	(<.001)	0.094	(.391)	–0.260	(<.001)	0.094	(.391)
Maine × 2009–10 season	0.108	(.114)	0.169	(.003)	0.090	(.124)	0.285	(<.001)	0.184	(<.001)	0.360	(<.001)	0.285	(<.001)	0.184	(<.001)	0.184	(<.001)	0.360	(<.001)	0.184	(<.001)	0.360	(<.001)
First 9 weeks × 2009–10 season	1.838	(<.001)	1.875	(<.001)	0.930	(<.001)	0.198	(.024)	–0.606	(<.001)	–2.620	(<.001)	0.198	(.024)	–0.606	(<.001)	–0.606	(<.001)	–2.620	(<.001)	–0.606	(<.001)	–2.620	(<.001)
Maine × First 9 weeks × 2009–10 season	2.419	(<.001)	2.807	(<.001)	2.327	(<.001)	–0.628	(<.001)	0.089	(.351)	–0.627	(<.001)	–0.628	(<.001)	0.089	(.351)	0.089	(.351)	–0.627	(<.001)	0.089	(.351)	–0.627	(<.001)
R-square	0.31		0.45		0.35		0.21		0.29		0.38		0.21		0.29		0.29		0.38		0.29		0.38	
Percentage point change in uptake due to SIV program (95% CI)	21.8 [16.9, 26.7]		25.3 [21.8, 28.7]		20.9 [17.6, 24.2]		–5.7 [–7.2, –4.1]		0.8 [–0.9, 2.5]		–5.6 [–7.8, –3.5]		–5.7 [–7.2, –4.1]		0.8 [–0.9, 2.5]		0.8 [–0.9, 2.5]		–5.6 [–7.8, –3.5]		0.8 [–0.9, 2.5]		–5.6 [–7.8, –3.5]	
Change in number of vaccine doses received (95% CI)	15,395 [11,935, 18,856]		28,927 [24,956, 32,898]		18,267 [15,391, 21,144]		–30,167 [–38,470, –21,863]		2,225 [–2,455, 6,905]		–11,006 [–15,258, –6,753]		–30,167 [–38,470, –21,863]		2,225 [–2,455, 6,905]		2,225 [–2,455, 6,905]		–11,006 [–15,258, –6,753]		2,225 [–2,455, 6,905]		–11,006 [–15,258, –6,753]	

Notes. All explanatory variables are binary (yes/no). The symbol × denotes an interaction term between two or more variables. The data for each regression (column) included one observation per-week, per-state over the 2008–09 and 2009–10 influenza seasons, 34 weeks each season, for a total of 1,088 observations per regression. The outcome variable was the percentage of the population, within each age group, that received the A(H1N1)pdm09 monovalent influenza vaccine each week on average. The coefficient of the triple interaction term (highlighted in bold typeface) can be interpreted as the additional weekly percentage of each age group's population in Maine that received the vaccine due to Maine's SIV program. Regression models were estimated using robust standard errors and random effects for each state.

and the elderly. Conversely, after the first 9 weeks, vaccine uptake among children in Maine and other states appears to increase at roughly the same rate, while it increased faster among older groups in Maine than in other states.

In short, Figure S3 in Appendix SA2 and Table 2 suggest that the SIV program increased vaccine coverage among children but decreased it among some adults. The last two rows in Table 2 provide estimates of the overall impact of the SIV program, ranging from an increase in coverage of 21.8 percentage points (pp) among children aged 13–17 years ($p < .001$) to 25.3 pp among children aged 5–12 years ($p < .001$), and a decrease in coverage of 5.7 pp among adults aged 18–49. In terms of number of vaccine doses administered, we estimate that Maine's SIV program increased A(H1N1)pdm09 uptake among children by about 62,600 doses and decreased coverage among adults 18–49 years and the elderly by 41,200 doses. We show counterfactual vaccine coverage, derived from the results of the DDD regressions, in Appendix SA2, Figure S4.

SIV Health Impact

Based on microsimulation models, we estimated that Maine's SIV program prevented 4,609 (5; 95 percentiles: 2,989; 6,760) cases of influenza and 1,434 (5; 95 percentiles: 900; 2,131) outpatient visits (Table 3). Effects on hospitalizations and deaths (not shown) were small.

Most of these benefits occurred among children: the SIV program prevented 10.2 percent (5; 95 percentiles: 6.2 percent; 16.0 percent) infections among children aged 0–4 years; 9.5 percent (5; 95 percentiles: 5.8 percent; 14.8 percent) among children aged 5–12 years; and 7.8 percent (5; 95 percentiles: 5.8 percent; 10.6 percent) among children aged 13–17 years. Among adults, we estimated that the program led to 2.0 percent (5; 95 percentiles: 1.4 percent; 2.6 percent) more infections among adults aged 18–49 years, and it had only small impacts on adults aged 50–64 and 65 and older. The estimated effects on outpatient visits and hospitalizations showed similar patterns (Table 3).

SIV Economic Impact

Our cost–benefit analyses suggested that school-based vaccination in Maine during the 2009 pandemic had a positive economic impact (Table 4). The total net benefit for the state's population of children aged 5–12 years was \$0.96 million (5; 95 percentiles: \$0.3; \$2.1 million), and for children aged

Table 3: Simulation Results: Health Care Outcomes under Maine’s School-Based Influenza Vaccination Program and a Scenario with Usual Vaccination Practices, by Age Group

Ages	Influenza Cases			Outpatient Visits			Hospitalizations		
	Mean Change [5; 95 percentiles]	Mean %Change [5; 95 percentiles]	Mean Change [5; 95 percentiles]	Mean %Change [5; 95 percentiles]	Mean Change [5; 95 percentiles]	Mean %Change [5; 95 percentiles]	Mean Change [5; 95 percentiles]	Mean %Change [5; 95 percentiles]	Mean %Change [5; 95 percentiles]
0 to 4	-1,463 [-2,198; -919]	-10.2% [-16.0%; -6.2%]	-494 [-756; -291]	-10.2% [-16.1%; -6.1%]	-3 [-6; -1]	-12.8% [-27.3%; -2.0%]			
5 to 12	-2,716 [-4,103; -1,706]	-9.5% [-14.8%; -5.8%]	-766 [-1,186; -458]	-10.0% [-15.5%; -6.1%]	-2 [-4; -1]	-15.2% [-30.8%; -5.9%]			
13 to 17	-1,279 [-1,759; -922]	-7.8% [-10.6%; -5.8%]	-346 [-494; -232]	-7.9% [-10.6%; -5.9%]	-2 [-3; -1]	-21.7% [-33.3%; -10.0%]			
18 to 49	837 [590; 1,154]	2.0% [1.4%; 2.6%]	163 [90; 256]	2.0% [1.2%; 2.9%]	5 [0; 13]	4.2% [0.0%; 8.6%]			
50 to 64	-4 [-26; 20]	-0.1% [-0.3%; 0.2%]	-2 [-9; 7]	-0.1% [-0.5%; 0.4%]	0 [0; 0]	0.0% [0.0%; 0.0%]			
≥65	15 [-22; 81]	0.4% [-0.5%; 2.1%]	11 [-3; 29]	0.9% [-0.3%; 2.7%]	0 [0; 2]	0.4% [0.0%; 11.0%]			
All ages	-4,609 [-6,760; -2,989]	-4.0% [-5.9%; -2.6%]	-1,434 [-2,131; -900]	-5.1% [-7.5%; -3.4%]	-1 [-8; 7]	-0.8% [-5.1%; 3.0%]			

Notes. Means and percentiles estimated from 10,000 probabilistic draws of model parameters from distributions shown in Table 1. In each draw, outcomes were simulated for a synthetic population of 25,000 individuals in each age group. Mean values are shown in bold typeface for easier reading.

Table 4: Total Incremental Costs and Benefits of Maine’s 2009–2010 School-Based Vaccination Program, Compared to the Usual Vaccination Strategy, by Age Group (in 2009 dollars)

<i>Ages</i>	<i>Incremental Cost (A) Mean \$ [5; 95 percentiles]</i>	<i>Incremental Benefit (B) Mean \$ [5; 95 percentiles]</i>	<i>Net Benefit (B–A) Mean \$ [5; 95 percentiles]</i>	<i>Simulations with Net Benefit > \$0 (%)</i>
0 to 4	554,900 [203,200; 976,500]	882,100 [117,500; 1,903,800]	327,100 [–633,700; 1,460,000]	63
5 to 12	–964,800 [–2,060,500; 258,300]	412,700 [164,500; 763,900]	1,377,500 [152,400; 2,550,900]	96
13 to 17	–649,700 [–1,372,700; 112,100]	191,900 [79,600; 338,800]	841,600 [79,000; 1,574,400]	97
18 to 49	–2,052,600 [–3,055,800; –1,104,500]	–235,600 [–976,600; –58,500]	1,817,100 [850,500; 2,894,200]	96
50 to 64	153,600 [86,600; 224,000]	700 [–2,700; 4,100]	–152,900 [–226,700; –49,000]	3
≥65	–776,900 [–1,121,700; –445,700]	–3,400 [–4,900; 500]	773,500 [438,400; 1,120,700]	99
Overall	–\$ 3,735,600 [–6,465,700; –964,800]	\$ 1,248,400 [243,100; 2,565,700]	\$ 4,983,900 [1,771,000; 7,999,800]	98

Notes: Means and percentiles estimated from 10,000 probabilistic draws of model parameters from distributions shown in Table 1. In each draw, outcomes were simulated for a synthetic population of 25,000 individuals in each age group and then rescaled to represent the total population in the state for the respective age group. Amounts are rounded to nearest \$100. Row and column means may not add up to shown totals due to rounding. Mean values are shown in bold typeface for easier reading.

13–17 years, it was \$0.65 million (5; 95 percentiles: \$0.11; \$1.4 million). Although the average net impact for children aged 0–4 years was positive, this result was not consistent across simulations, as demonstrated by the variability of this outcome in the sensitivity analysis (5; 95 percentiles: $-\$0.63$; \$1.5 million) and the fact that only in 63 percent of simulations the net economic benefit was positive. Among adults aged 18–49 years, the reduction in immunization coverage of over 30,000 vaccine doses (Table 2) resulted in a positive net economic benefit due to \$2.1 million lower direct and indirect costs of vaccination (5; 95 percentiles: \$1.1; \$3.1 million), which were only partially offset by the \$0.24 million (5; 95 percentiles: \$0.06; \$0.98 million) higher productivity losses due to the increase in infections among people in this age group. The overall impact on adults 50–64 years was an economic loss of \$0.15 million (5, 95 percentiles: \$0.05; \$0.23 million). Those aged ≥ 65 years experienced \$0.78 million lower costs (5; 95 percentiles: \$0.45; \$1.1 million) and a small incremental benefit.

Overall, we estimate Maine's SIV program resulted in a positive societal economic gain of \$4.98 million (5; 95 percentiles: \$1.8; \$8.0 million). This result was largely robust to parameter uncertainty, as the overall net gain was positive in 98 percent of all simulations. Cost savings due to lower adult vaccination (\$2.7 million) accounted for 54 percent of total economic net benefits.

CONCLUSIONS

Our findings suggest that SIV programs can significantly increase vaccine coverage among children, when compared to vaccination in traditional clinic-based settings, leading to positive economic benefits to society. However, we also found evidence that, because most early A(H1N1)pdm09 vaccine shipments in Maine were allocated to SIV clinics, the increase in immunization coverage among children may have come at the expense of lower coverage among adults and the elderly.

Among the key inputs in our analysis were the costs of planning and implementing school-based vaccination clinics. Some of the estimated economic benefits arise from lower average costs of immunization at SIV clinics compared with those associated with influenza vaccination in more traditional settings (Table 1). It should be noted that the SIV costs presented here were calculated from data collected at a small sample of Maine SIV clinics (Asay et al. 2012; Cho et al. 2012). Thus, it is not clear how accurate or generalizable this estimate may be. Few published estimates of costs are available for

comparison and costs reported in these few studies range from \$12 per dose for a program in one county in Florida to \$53 per dose in New York City (Tran et al. 2010; Kansagra et al. 2012). Nevertheless, our main result of a positive economic benefit from the SIV program was robust in sensitivity analyses where per-dose SIV costs ranged from \$6.8 to \$51.7 (not shown in Table 1 because SIV costs were sampled from tables of cost data collected in SIV clinics). Moreover, several nurses who managed Maine's SIV clinics stated that SIV costs would likely be lower in the future due to the expertise they developed in 2009 (Asay et al. 2012).

An important finding of our evaluation was that more than half of the estimated economic benefits of Maine's SIV program were associated with cost savings due to lower immunization rates among adults and the elderly (Table 4). Although some of these savings were offset by higher medical costs and productivity losses due to more influenza infections, the net effect was still a positive economic benefit. While further exploring these effects is outside the scope of this study, we hypothesize that these results are due to the relatively low attack rates during the 2009 pandemic among adults (e.g., 8 percent for ages 18–49 years, according to data used in our simulation model, discussed in detail in Appendix SA2). Higher infection rates among adults would have increased health care costs and productivity losses among adults. Therefore, unless programs are designed to ensure that vaccine delivery among adults is not affected, the economic benefits of SIV programs might not be positive in a future influenza pandemic if symptomatic attack rates among adults are high.

Because we used a human capital approach to value health, we likely underestimated the economic benefits associated with Maine's SIV program. In our analysis, we account for the value of time lost by adults due to illness or caring for a sick child, but we ignore the intangible value of avoided pain and suffering due to a person not being sick, as well as the associated reduction in the burden and inconvenience borne by parents of a sick child. In addition, we did not account for other effects of immunization that have been found in previous studies, but that are difficult to value, such as lower school absenteeism (Graitcer et al. 2012). Methods used to capture intangible costs and benefits—for example, willingness-to-pay—usually result in larger estimates of the economic benefits of preventing illnesses. Furthermore, because we used relatively low vaccine effectiveness values (22–59 percent), the estimated health and economic benefits of the program would likely have been larger had we used higher effectiveness values reported in other published studies (Wichmann et al. 2010; Valenciano et al. 2011; Simpson et al. 2012). On the

other hand, because we only had access to cost data at the clinic level, our cost analysis ignored state-level administrative and implementation costs; it is unlikely that these costs exceeded the estimated net benefits of \$5 million, but future studies should attempt to include them to provide more robust assessments.

Our results are consistent with previous evaluations of SIV programs. For example, in their analysis of a large school-based program providing live attenuated influenza vaccine (LAIV) in four states, King et al. (2006) found that the program decreased influenza-like illness rates among children by 8.3 pp and outpatient visits by 3.4 pp, but it had no statistically significant impact on hospitalizations. In a subsequent cost–benefit analysis of the same program, Schmier et al. (2008) estimated that the program saved \$172 per household, after accounting for vaccination costs, health care costs, and indirect costs (productivity losses). Similarly, a modeling study concluded that both individual and group-based influenza vaccination of school-aged children are cost-saving compared to no vaccination, but group-based vaccination saved \$31 (1999 dollars) per *child* compared to individual vaccination, with the savings arising primarily from averted indirect costs (White, Lavoie, and Nettleman 1999).

There are limitations to our estimation of the impact of the SIV program on vaccine coverage. Our regression models assume that all estimated differences in vaccine uptake during the first 9 weeks of the 2009–10 season can be attributed to the SIV program, but other policies to increase vaccination could have been implemented at the same time as the SIV program. Even if this was the case, our results would be biased only if these other policies affected coverage *only* among children and *only* during the first 9 weeks of the season. Perhaps of more significance, early vaccine supplies were primarily LAIV, which is not indicated for persons aged 50 years and older. Therefore, it is likely that vaccine coverage in the absence of the SIV program would not have increased as much as we estimate for individuals aged 65 and older (Table 2). Maine's SIV program was heterogeneous: School districts had significant flexibility in the operation and timing of vaccination clinics (Lorick et al. 2014). Thus, it is likely that some approaches were more effective than others, but our data did not allow us to examine this heterogeneity. Finally, we had imperfect information on the proportion of children aged 5 years or younger vaccinated in SIV clinics, and thus, it is unclear if our estimates of the impact of the SIV program on vaccination among this age group are reliable.

Our simulation models were associated with further limitations. First, the model does not account for the lower (higher) infection rates that could

result from higher (lower) immunization coverage (i.e., herd immunity); thus, we may underestimate the benefits of higher vaccination among children, as well as the costs of lower coverage among adults. Second, we only consider two possible vaccination results for each individual (full immunization or no immunization), ignoring other possibilities discussed in the literature, such as partial protection or reduced infectiousness (Halloran, Haber, and Longini 1992; Newall, Dehollain, and Wood 2012). However, because the largest estimated intervention impact was among children, accounting for these effects would likely increase the estimated benefits of the intervention. Third, because our model required weekly estimates of influenza burden beginning with infections and continuing to hospitalizations and deaths, our approach to influenza burden estimation (described in detail in the Appendix SA2) was different from methods recently used by CDC, which start with hospitalization data to then estimate influenza infections and deaths (Kostova et al. 2013; Reed et al. 2015); however, because many of our parameters are similar (e.g., case-hospitalization ratio, death-hospitalization ratio), both methods should be consistent as long as influenza-like illness surveillance data are consistent with hospitalization surveillance data. Unfortunately, because our estimates of influenza burden are limited to Maine, a side-by-side comparison of results using both methods is not possible. Finally, we did not account for behavioral determinants of vaccine uptake that could lead to different outcomes in other settings or situations, such as patients' decisions to seek vaccination depending on their risk perceptions and available public information, as well as the incentives of health care providers or schools to cooperate with SIV efforts.

Vaccination remains the preferred strategy to mitigate pandemic influenza transmission. Unfortunately, because of unpredictable shifts in the influenza genome, there is no guarantee that large amounts of stockpiled influenza vaccine will actually match the strain causing the next pandemic, and thus be of use. Thus, one of the many important decisions public health officials need to plan for as they prepare for the next influenza pandemic is how to allocate the vaccine, given circumstances impossible to predict in advance—for example, vaccine and strain match, attack rates among different age groups, and time available to produce (if needed) and distribute vaccine supplies. Our results, along with those of other studies (King et al. 2006; Lindley et al. 2008), suggest that school-based vaccination during pandemics can substantially increase vaccine coverage among children. When clinical influenza attack rates are higher among children than among adults, increasing vaccination rates among children is likely associated with increased disease control, which, in turn, is associated with a likely positive economic benefit to society.

This approach may be most beneficial during future influenza pandemics, particularly when achieving rapid vaccine coverage among children is judged to be of special importance. It is less clear how relevant our results are to seasonal influenza vaccination, when schools may be more reluctant to participate in these efforts, rapid vaccination is usually not crucial, and traditional vaccination strategies may be sufficient. Future studies should seek to assess whether SIV programs produce positive health and economic benefits during nonpandemic situations. Our findings clearly suggest that the prioritization of vaccine supplies to SIV clinics in Maine led to lower vaccine coverage among adults and the elderly. In considering the implementation of SIV or other mass-immunization approaches targeted at specific populations, policy makers should carefully consider the potential impacts on supplies made available to other populations. Finally, future studies should build upon our findings by studying how vaccines should be allocated among (1) different venues (medical facilities, mobile clinics, SIV clinics, etc.), (2) different age groups, and (3) groups with different infection risks, to minimize both the health and economic burden of future pandemics.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the supporting information tab for this article:

Appendix SA1: Author Matrix.

Appendix SA2: Estimation of SIV Impact on Vaccination Coverage.

Table S1: Influenza Vaccine Coverage in Maine and Fifteen Other U.S. States, 2008–09 and 2009–10 (A(H1N1)pdm09) Seasons, by Age Group.

Table S2: Results of Markov Probabilistic Microsimulation of Health-care Outcomes under Maine's School-Based Influenza Vaccination Program and a Scenario with Usual Vaccination Practices, by Age Group.

Figure S1: Partial Representation of Markov Decision-Analytic Model, All Age Groups.

Figure S2: Partial Representation of Markov Decision-Analytic Model, Age Group 5–12.

Figure S3: Estimated Cumulative Influenza Vaccine Coverage by Age Group, 2008–2010, Maine versus Fifteen Other U.S. States.^{a,b}

Figure S4. Estimated Mean Cumulative Influenza A(H1N1)pdm09 virus Vaccination under School-Based (Actual) and Usual Setting Scenarios, Maine 2009–2010.^{a,b}