A Theoretic Framework to Consider the Effect of Immunizing Schoolchildren Against Influenza: Implications for Research

AUTHOR: Ira M. Longini Jr, PhD

Program of Biostatistics and Biomathematics, Fred Hutchinson Cancer Center, Seattle, Washington

KEY WORDS

human influenza, influenza vaccines, communicable disease control, mass immunization

ABBREVIATIONS

ACIP—Advisory Committee on Immunization Practices
ILI—influenza-like illness
LAIV—live attenuated influenza vaccine

Because there were no contributors to this article, the author made all intellectual contributions to this published study and met the following criteria: (1) made all contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafted the article or revising it critically for important intellectual content; and (3) approved its final version to be published.

Dr Longini's current affiliation is Department of Biostatistics, Colleges of Public Health and Health Professions, and Medicine, University of Florida, Gainesville, Florida.

www.pediatrics.org/cgi/doi/10.1542/peds.2011-0737D

doi:10.1542/peds.2011-0737D

Accepted for publication Nov 29, 2011

Address correspondence to Ira M. Longini, Jr, PhD, Department of Biostatistics, Colleges of Public Health and Health Professions, and Medicine, 22 Buckman Drive, 452 Dauer Hall, University of Florida, Gainesville, FL, 117450. E-mail: ilongini@ufl.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: *The author has indicated he has no financial relationships relevant to this article to disclose.*

abstract

The illness attack rate and annual morbidity caused by infection with influenza is high in schoolchildren. Because schoolchildren are 1 of the most important sources of community-wide transmission of influenza, vaccinating them could have a major effect on reducing morbidity and mortality in older adults. Stochastic modeling shows that a vaccination rate as low as 20% in schoolchildren reduces overall mortality in adults aged ≥64 years more effectively than a vaccination rate of 90% for older adults. Additional modeling shows that vaccinating schoolchildren against influenza is optimal for reducing morbidity and mortality caused by influenza in the overall population. Although supported by simulated models, the benefits of mass vaccination need to be confirmed in a real-world setting. The best way to demonstrate the effectiveness of mass vaccination of schoolchildren is to implement the process in several localities in several states by using properly designed studies that incorporate accurate viral surveillance with at least 10 pairs of intervention and comparison populations. *Pediatrics* 2012;129:S63–S67

JUSTIFICATION FOR IMMUNIZING SCHOOLCHILDREN ANNUALLY AGAINST INFLUENZA

The annual economic burden caused by influenza infection in the United States has been estimated to be $10 billion in direct costs alone. Infection with influenza virus is responsible for as many as 334 000 hospitalizations and 41 000 deaths per year.[1] Mortality rates associated with infection with influenza virus are highest among infants and adults aged ≥65 years.[2] Influenza-associated hospitalization rates for children aged 3 through 14 years with high-risk conditions can be 2 to 4 times higher than comparable rates for otherwise healthy children in the same age group.[3,4] For adults aged 18 to >65 years with high-risk conditions, influenza-associated hospitalization rates can be 3 to 8 times higher compared with those of otherwise healthy adults in the same age group.[5] Past recommendations by the American Academy of Pediatrics' Committee on Infectious Diseases and the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention regarding vaccination against influenza focused on vaccinating those at higher risk of developing complications from influenza infection, including adults and children with chronic cardiovascular or pulmonary disease, as well as those with hematologic, hepatic, metabolic, or renal disorders.[6] However, the most recent ACIP recommendation called for annual vaccination of all children aged 6 months through 18 years, beginning in the 2008–2009 influenza season if possible, but no later than the 2009–2010 influenza season.[7]

Vaccination of schoolchildren not only benefits the children vaccinated but also could lower the incidence of disease in the community, although the latter is not as well established. Even though schoolchildren and young adults have not been considered at high risk for complications or death from influenza, annual morbidity is high; illness attack rates in schoolchildren is higher than that of adults.[8] Analysis of influenza activity during the 1918 and 1957 pandemics showed that influenza virus activity increased at the start of the school year and peaked once schools had been in session for ~2 months. In addition, during the course of an influenza epidemic, the distribution of patients positive for influenza by culture shifted from school-age children to children aged <5 years plus adults, further explaining why schoolchildren are generally considered to be the most important source of community-wide transmission of influenza.[8] Because the immune systems of children respond better to influenza vaccination than adults, vaccination of schoolchildren could have important indirect effects in reducing morbidity and mortality in older adults.[9] Ecologic evidence for this was shown by a mandatory influenza vaccination program for schoolchildren in Japan during the mid-1970s through the 1980s that reached a vaccination coverage rate of 50% to 85% and was associated with a reduction in influenza disease among older adults and a population-wide reduction in all-cause mortality of 37 000 to 49 000 deaths per year.[10]

RESULTS OF VACCINATING SCHOOLCHILDREN

In an ongoing open-labeled, nonrandomized, community-based trial in children vaccinated with cold-adapted live attenuated influenza vaccine (LAIV) in Temple-Belton, Texas, over the past 5 years, comparisons have been made between the intervention communities and similar comparison communities. Results from this study have shown that vaccination of children aged from 5 through 18 years with LAIV was associated with a statistically significant reduction of medically attended acute respiratory illnesses in adults aged ≥35 years.[11] Similarly, in an earlier community-based trial in 1968 in Tecumseh, Michigan, 86% of schoolchildren and 89% of school staff members were vaccinated against influenza. The adjusted community-based influenza attack rate among all age groups in Tecumseh during the 1968–1969 influenza season was one-third that of a neighboring comparison community, Adrian, Michigan.[12]

A school-based vaccine intervention study was conducted during the 2004–2005 influenza season in 28 elementary schools in Maryland, Minnesota, Texas, and Washington, during which approximately half (47%) of the schoolchildren in intervention schools received LAIV.[13] During a prospectively defined week of peak influenza activity, a questionnaire was sent to households with children in intervention and control schools to gather data on the demographics, influenza vaccination rates, and influenza-like illness (ILI) outcomes pertaining to these households. Households in which a child had been vaccinated had a significant reduction of influenza-like illness (~11%), medication use, and medical visits for adults and children living there compared with households with children enrolled in control schools (all $P < .001$). Thus, vaccinating an elementary school child appeared to be associated with a lower household-based incidence of influenza and its associated medical needs. Any indirect effect on community influenza incidence was not studied.

SIMULATIONS OF INFLUENZA TRANSMISSION AND OUTCOMES

To address the question of indirect effects of vaccinating children on a community, we developed and refined a stochastic simulation epidemic model of influenza infection transmission that simulated outcomes in a hypothetical population.[14] The model population consisted of 10 000 people; each person in the community was assigned to a variable-sized household and stratified among 4 age groups (young children [aged 0–4 years], older children [aged 5–18 years], younger adults [aged 19–64 years], and older adults [aged $\geq$65 years]). Additional refinement involved assigning each person to a social group (such as a playgroup, day-care center, school, work, community) depending on age and household composition. Population demographics regarding the distribution among the 4 age groups were modeled using the year 2000 US Census,[15] and health status (ie, "high-risk" or "healthy") was estimated from ACIP data from 2002.[16] The risks for influenza illness and influenza infection were estimated by using the infection rate of the initial infected persons, probability of disease transmission, and the susceptibility of the unvaccinated persons. Influenza-related death rates were estimated from published data.[2] Protective efficacy of the vaccine was assumed to be 70% for those aged $\leq$64 years and 50% for those aged $\geq$65 years.[16] The transmission of influenza was simulated by a few initial unvaccinated infected persons who were able to infect those persons who have not yet been vaccinated for that influenza season.

Initial simulations were performed by using assumed US vaccination rates against influenza of 5%, 23%, and 68% for young and older children, young adults, and older adults, respectively. Persons at high risk were assumed to be vaccinated at rates two- and 1.5-fold higher than those for children and young adults, respectively, compared with their healthy counterparts. Simulations were run assuming higher vaccination rates (20%, 40%, 60%, and 80%) for children aged 6 months to 18 years, keeping the initial coverage levels for the other populations constant. One thousand stochastic simulations were run for each scenario to examine the expected spread of influenza throughout the community. Results from our stochastic influenza simulator model suggest that vaccinating merely 20% of the schoolchildren would reduce overall mortality in adults aged $>$65 years more effectively than vaccinating 90% of the adults aged $>$65 years.[9,14] In this model, additional increases in vaccination rates result in incremental declines in death rates (Fig 1).

Keeping vaccine coverage of persons at high risk at its current rate and using the rest of the influenza vaccine supply to vaccinate schoolchildren is an alternative strategy that combines protection of persons at highest risk with the ability to slow the spread of the virus by limiting infection of the most active reservoir. Additional simulations using different model parameters also suggest that mass vaccination of schoolchildren is optimal for reducing overall morbidity and mortality caused by infection with influenza, especially for influenza strains that transmit well among children and in situations in which vaccine quantities are limited.[17] Although these models suggest how to proceed in the future, they are not a substitute for studies of real communities during influenza season.

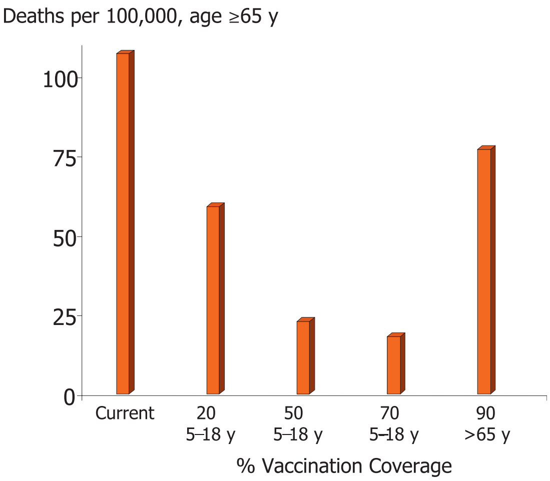

FIGURE 1

Simulated mean number of deaths per 100 000 in the elderly population under the current vaccination coverage in the United States and under different additional levels of vaccination coverage in school-age children or the older adults. Adapted with permission from Halloran ME, Longini IM Jr. Public health. Community studies for vaccinating schoolchildren against influenza. *Science.* 2006; 311(5761): 616.

SUGGESTED FUTURE RESEARCH DIRECTION

Confirmation of the real-world effectiveness of vaccinating schoolchildren through herd immunity is of high importance. The suggested study design would be a community trial of communities, families, or schools. One approach would be to conduct large-scale community studies in which all eligible children in 1 community are offered vaccinations, comparing outcomes with those of a similar control community. This approach resembles the Temple-Belton study in which vaccinated schoolchildren had fewer medically attended acute respiratory illnesses than the unvaccinated (control) schoolchildren.[11] Our models predict that $\sim$50% to 70% coverage in children would be required to see strong indirect protection at the community level. The Tecumseh study showed an increase in indirect protection against influenza infection by two-thirds,[12] but this increase occurred in association with an 85% vaccine coverage rate, and during a pandemic, when community influenza attack rates and susceptibility were high. Whether one would see this level of benefit without an influenza pandemic is unknown. In contrast, the Temple-Belton study found that successful indirect protection occurred against influenza B infection when the vaccination rate of the intervention group was only ∼30%.[18,19] Approximately 6 to 7 matched pairs of communities would need to be studied to achieve satisfactory statistical precision using this study design.

Another approach would be to perform such studies in schools and families other than entire communities, similar to the study design used by King and colleagues[13] described earlier. The households of vaccinated and unvaccinated children could be observed for the incidence of ILI among family members. The families (households) would be treated as mini-cohorts to prospectively assess the effect of vaccination in families. Studies such as this will estimate the extent to which influenza is prevented in the schools and households by vaccination. Observations of influenza illness in both intervention and control schools would help to evaluate the presence and strength of herd effects in such schools. Inferences could be made about the potential effect on the entire community, because according to our models, schools and families account for ∼60% of the influenza transmission in a community.

Both of these community trial approaches require accurate determination of true influenza illness. Because occurrence of ILI is a nonspecific outcome, surveillance cultures or serology will need to be conducted for some proportion of the people to assess validity in both limbs of the study. These validation sets would be used to adjust for nonspecific outcomes. If adjustments are not made for a nonspecific outcome, the realized effect may be underestimated, making an effective intervention appear to be ineffective. For example, in the Temple-Belton study previously described, the direct protective effectiveness of LAIV was estimated to be 18% (95% confidence interval: 18–24) by using the nonspecific case definition, but 79% (95% confidence interval: 51–91) when surveillance culture data were included.[20]

Large-scale community trials are an important component of assessing the effectiveness of mass vaccination of children. These trials should be done in a controlled manner, complete with careful evaluation. The most meaningful demonstration would be to implement mass vaccination of schoolchildren in several communities in geographically diverse states over several seasons, which it is hoped would encompass a range of influenza illness severity. Such a study should use appropriate viral surveillance methods in at least 10 pairs of intervention and comparison populations. To yield meaningful results, ideally 50% to 70% vaccine coverage should be achieved and maintained for several years in the intervention populations. A gradual buildup of vaccination rates would allow ample time to observe any safety problems that may arise and also would provide ongoing data to help reduce the effect of chance on the analysis. Positive results from these studies would lend a great deal of support for implementing a mass vaccination program of schoolchildren nationally.[20]

REFERENCES

1. Molinari NA, Ortega-Sanchez IR, Messonnier ML, et al. The annual impact of seasonal influenza in the US: measuring disease burden and costs. *Vaccine*. 2007;25(27):5086–5096
2. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA*. 2003;289(2):179–186
3. Neuzil KM, Mellen BG, Wright PF, Mitchel EF, Jr, Griffin MR. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. *N Engl J Med*. 2000a;342(4):225–231
4. Neuzil KM, Wright PF, Mitchel EF, Jr, Griffin MR. The burden of influenza illness in children with asthma and other chronic medical conditions. *J Pediatr*. 2000b;137(6):856–864
5. Mullooly JP, Bridges CB, Thompson WW, et al. Vaccine Safety Datalink Adult Working Group. Influenza- and RSV-associated hospitalizations among adults. *Vaccine*. 2007;25(5):846–855
6. Fiore AE, Shay DK, Haber P, et al. Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2007. *MMWR Recomm Rep*. 2007;56(RR-6):1–54
7. Fiore AE, Shay DK, Broder K, et al. Centers for Disease Control and Prevention; Advisory Committee on Immunization Practices. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008. *MMWR Recomm Rep*. 2008;57(RR-7):1–60
8. Glezen WP. Emerging infections: pandemic influenza. *Epidemiol Rev*. 1996;18(1):64–76
9. Halloran ME, Longini IM Jr. Public health. Community studies for vaccinating schoolchildren against influenza. *Science*. 2006;311(5761):615–616
10. Reichert TA, Sugaya N, Fedson DS, Glezen WP, Simonsen L, Tashiro M. The Japanese experience with vaccinating schoolchildren against influenza. *N Engl J Med*. 2001;344(12):889–896
11. Piedra PA, Gaglani MJ, Kozinetz CA, et al. Herd immunity in adults against influenza-related illnesses with use of the trivalent-live attenuated influenza vaccine (CAIV-T) in children. *Vaccine*. 2005;23(13):1540–1548
12. Monto AS, Davenport FM, Napier JA, Francis T Jr. Modification of an outbreak of influenza in Tecumseh, Michigan by vaccination of schoolchildren. *J Infect Dis*. 1970;122(1):16–25
13. King JC, Jr, Stoddard JJ, Gaglani MJ, et al. Effectiveness of school-based influenza vaccination. *N Engl J Med*. 2006;355(24):2523–2532
14. Weycker D, Edelsberg J, Halloran ME, et al. Population-wide benefits of routine vaccination of children against influenza. *Vaccine*. 2005;23(10):1284–1293

15. United States Census Bureau. United States Census 2000. Available at: www.census.gov/main/www/cen2000.html. Accessed October 26, 2007
16. Bridges CB, Fukuda K, Uyeki TM, Cox NJ, Singleton JA. Centers for Disease Control and Prevention, Advisory Committee on Immunization Practices. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2002;51(RR-3):1–31
17. Longini IM, Jr, Halloran ME. Strategy for distribution of influenza vaccine to high-risk groups and children. *Am J Epidemiol*. 2005;161(4):303–306
18. Piedra PA, Gaglani MJ, Kozinetz CA, et al. Prevention of the influenza B outbreak during the 2005–2006 influenza season through a universal vaccination program in children. Presented at the European Society for Paediatric Research Annual Meeting; October 6–8, 2007; Prague, Czech Republic
19. Piedra PA, Gaglani MJ, Kozinetz CA, et al. Prevention of the influenza B outbreak during the 2005–2006 influenza season through a universal vaccination program in children. Presented at the Pediatric Academic Societies' Annual Meeting; May 5–8, 2007; Toronto, Canada
20. Halloran ME, Longini IM, Jr, Gaglani MJ, et al. Estimating efficacy of trivalent, cold-adapted, influenza virus vaccine (CAIV-T) against influenza A (H1N1) and B using surveillance cultures. *Am J Epidemiol*. 2003;158(4):305–311

A Theoretic Framework to Consider the Effect of Immunizing Schoolchildren Against Influenza: Implications for Research

Ira M. Longini Jr

Pediatrics 2012;129;S63
DOI: 10.1542/peds.2011-0737D

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

A Theoretic Framework to Consider the Effect of Immunizing Schoolchildren Against Influenza: Implications for Research

Ira M. Longini Jr

Pediatrics 2012;129;S63

DOI: 10.1542/peds.2011-0737D