HHS Public Access

Author manuscript

Am J Prev Med. Author manuscript; available in PMC 2018 October 01.

Published in final edited form as:

Am J Prev Med. 2017 October ; 53(4): 500–503. doi:10.1016/j.amepre.2017.02.019.

Potential Consequences of Not Using Live Attenuated Influenza Vaccine

Kenneth J. Smith, MD, MS[1], **Mary Patricia Nowalk, PhD, RD**[2], **Angela Wateska, MPH**[1], **Shawn T. Brown, PhD**[3], **Jay V. DePasse, BS**[3], **Jonathan M. Raviotta, MPH**[2], **Eunha Shim, PhD**[4], and **Richard K. Zimmerman, MD, MPH**[2]

[1]Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

[2]Department of Family Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

[3]Pittsburgh Supercomputing Center, Carnegie Mellon University, Pittsburgh, Pennsylvania

[4]Department of Mathematics, Soongsil University, Seoul, Republic of Korea

Abstract

Introduction—Decreased live attenuated influenza vaccine (LAIV) effectiveness in the U.S. prompted the Advisory Committee on Immunization Practices in August 2016 to recommend against this vaccine's use. However, overall influenza uptake increases when LAIV is available and, unlike the U.S., LAIV has retained its effectiveness in other countries. These opposing countercurrents create a dilemma.

Methods—To examine the potential consequences of the decision to not recommend LAIV, which may result in decreased influenza vaccination coverage in the U.S. population, a Markov decision analysis model was used to examine influenza vaccination options in U.S. children aged 2–8 years. Data were compiled and analyzed in 2016.

Results—Using recently observed low LAIV effectiveness values, fewer influenza cases will occur if LAIV is not used compared with having LAIV as a vaccine option. However, having the option to use LAIV may be favored if LAIV effectiveness returns to prior levels or if the absence of vaccine choice substantially decreases overall vaccine uptake.

Conclusions—Continued surveillance of LAIV effectiveness and influenza vaccine uptake are warranted given their importance in influenza vaccination policy decisions.

INTRODUCTION

The 2003 licensure of live attenuated influenza vaccine (LAIV), a nasal spray, introduced a new needle-sparing form of vaccine administration and led to vaccine acceptance among

Address correspondence to: Kenneth J. Smith, MD, MS, 200 Meyran Ave., Suite 200, Pittsburgh, PA 15213. smithkj2@upmc.edu.

needle-averse individuals.[1,2] Having a choice among vaccines and administration modes may increase uptake[1–5]; offering a choice between LAIV and inactivated influenza vaccine (IIV) to adults increased uptake by 5–7 percentage points.[6] However, potential positive effects of an LAIV option have been countermanded by changing recommendations for its use resulting from varying effectiveness estimates.

Effectiveness of LAIV has been highly variable in the U.S. Meta-analyses and reviews found LAIV more effective than IIV in children aged 2–8 years,[7–10] leading the Advisory Committee on Immunization Practices (ACIP) to preferentially recommend LAIV for this age group in 2014.[11] However, in the 2013–2014 and 2014–2015 seasons, LAIV was not effective against influenza A (H1N1) owing to heat instability.[12] Consequently, ACIP removed the LAIV preference for the 2015–2016 season.[13] The manufacturer changed the H1N1 construct for the 2015–2016 LAIV, but vaccine effectiveness remained low[14] and ACIP recommended against LAIV use in 2016.[15] Reasons for this continued loss of effectiveness in the U.S. are unclear. By contrast, LAIV effectiveness in other countries has been maintained.[16–18]

Conflicting effects between greater overall vaccine uptake with LAIV use and reduced LAIV effectiveness creates a dilemma. Using decision analysis, trade-offs among vaccine choice, uptake, and effectiveness in children aged 2–8 years were explored.

METHODS

A Markov model of influenza vaccination in children aged 2–8 years[19] was modified to consider two strategies: one where LAIV use is eliminated and another where either vaccine can be used. Thus, trade-offs were examined between: (1) no longer recommending LAIV, with potentially decreased vaccine uptake based on preference, needle phobia, and other factors; and (2) offering both vaccines and maintaining prior uptake, but with low LAIV effectiveness that could potentially improve. The model (detailed in the Appendix), constructed using TreeAge Pro, version 2016, followed identical hypothetical cohorts over a single influenza season, with influenza vaccination and illness occurring based on the product of U.S. seasonal population averages and monthly relative likelihoods of those events.[20,21] Influenza risk with or without vaccination was tracked, based on population attack rates, protective effectiveness of each vaccine, and vaccine uptake. Influenza illness and its severity, manifestations, costs, and outcomes occurred based on medical literature data (Appendix Table 1). The primary analytic outcome was influenza risk difference between strategies. A secondary analysis examined quality-adjusted life years lost and costs.

Removing LAIV, used in 38% of children aged 2–8 years, could decrease population vaccine uptake, which was modeled as a potential decrease in vaccination rate for the IIV-only strategy. When either vaccine could be used, vaccination rates were held at 2015 levels. The base case analysis assumed no decrease in vaccine uptake with the IIV-only strategy, but potential decreases in uptake were examined in sensitivity analyses. In 2015, vaccine uptake was 51.7% for children aged <5 years and 40.7% for those aged 5–12 years. The uptake of children aged <5 years was used in the base case analysis; rates of those aged 5–12 years were used in a sensitivity analysis. LAIV effectiveness has declined to low levels in the

U.S.,[14] but its effectiveness in other countries has remained relatively stable,[16–18] raising questions whether loss of effectiveness in the U.S. could be a transient phenomenon. In this analysis, the recently observed low LAIV effectiveness was modeled as the base case while examining the influence of potentially improved vaccine effectiveness in sensitivity analyses.

RESULTS

In the base case analysis, where vaccine uptake was identical for both strategies, the model estimated that 20.9% of children aged 2–8 years had influenza illness if only IIV were used, compared with 23.5% if both vaccines continued to be used (and LAIV has low effectiveness). In one-way sensitivity analyses, the IIV-only strategy prevented fewer cases than a choice between vaccines if LAIV effectiveness is >63% (base case, 3%) or if the absolute decrease in population vaccine uptake resulting from the absence of an LAIV option was >18.7% (base case, 0%). Individual variation of all other parameters, including influenza attack rates, through ranges listed in Appendix Table 1, did not change strategy favorability.

Figure 1 shows results when varying both sensitive parameters simultaneously in a two-way sensitivity analysis. When baseline influenza vaccination uptake was 51.7% (top panel), having both vaccines available prevented more influenza cases than the IIV-only strategy if overall vaccination uptake decreased by 5 percentage points and LAIV effectiveness was >46.5%, or if vaccine uptake decreased by 10 percentage points and LAIV effectiveness was >30.4%. When baseline vaccine uptake was set at 40.7% (bottom panel), having both vaccines available was favored if LAIV effectiveness was >42.1% or >21.8% and the IIV-only strategy decreased vaccination by 5 or 10 percentage points, respectively.

A secondary cost-effectiveness analysis compared costs and quality-adjusted life years between strategies. In the base case, which assumes unchanged vaccination rates, the IIV-only strategy was less costly and more effective than a strategy where either vaccine could be used (Appendix Table 2). Two-way sensitivity analyses varying LAIV effectiveness and potential decreased vaccine uptake showed somewhat greater ranges where IIV-only was favored (compared with Figure 1) when a $100,000 per quality-adjusted life year gained threshold was used (Appendix Figure 2); that area decreased when higher thresholds were used.

DISCUSSION

This analysis generally supports the ACIP decision to recommend against LAIV use, while showing how changes in overall vaccine uptake or LAIV effectiveness could undermine that decision. Decreased influenza vaccine uptake that could result from LAIV unavailability leads to higher disease burden, as does continuing to offer a low-effectiveness LAIV. Complicating the decision is the possibility of future improved LAIV effectiveness.

Although it is unlikely that a substantial change in just one of these parameters' values will occur and lead to continued LAIV use being favored, smaller changes in each parameter occurring jointly could plausibly lead to more illness under the new ACIP recommendations.

In any case, this analysis highlights the importance of timely vaccine effectiveness estimates via influenza surveillance, as well as the usefulness of examining reasons for vaccine acceptance or refusal and the effects of policy choices on vaccine uptake. In addition, this analysis shows the potential value of decision analytic techniques, along with surveillance data, in informing and assisting policy deliberations.

This analysis did not account for herd immunity, likely an important component of LAIV effectiveness.[18,22] However, this omission's effect is probably low when LAIV effectiveness is low and when herd immunity can occur with IIV use. Absence of LAIV options in other age groups, which was not accounted for in this analysis, could have greater or lesser effects than those observed in children aged 2–8 years. Use of cohort simulation limits the ability to account for population heterogeneity. It is felt that the most likely cause of poor LAIV protection is reduced replicative effectiveness of H1N1 strains in LAIV,[25] but definitive reasons for regional effectiveness differences are not yet available. Decision analysis models depend on parameter estimates; this analysis was based on a published model[19] incorporating vaccine effectiveness data from the same data source that informed Centers for Disease Control and Prevention recommendations.[14] Continued surveillance of LAIV effectiveness and influenza vaccine uptake is warranted, given their importance and influence in future influenza vaccination policy choices.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Research reported in this publication was supported by the National Institute of General Medical Sciences of NIH under Award Number R01GM111121. The content is solely the responsibility of the authors and does not necessarily represent the official views of NIH.

Richard Zimmerman has active research grants from Merck & Co., Inc., SanofiPasteur, and Pfizer, Inc. and in January 2012 received an honorarium from MedImmune, LLC. Mary Patricia Nowalk has received or currently receives grant funding from Merck & Co., Inc., Pfizer, Inc., and MedImmune, LLC. Jonathan Raviotta currently receives grant funding from Pfizer, Inc. No other financial disclosures were reported by the authors of this paper.

References

1. Flood EM, Block SL, Hall MC, et al. Children's perceptions of influenza illness and preferences for influenza vaccine. J Pediatr Health Care. 2011; 25(3):171–179. https://doi.org/10.1016/j.pedhc.2010.04.007. [PubMed: 21514492]
2. Flood EM, Ryan KJ, Rousculp MD, et al. Parent preferences for pediatric influenza vaccine attributes. Clin Pediatr (Phila). 2011; 50(4):338–347. https://doi.org/10.1177/0009922810391247. [PubMed: 21196417]
3. Shea KM, Edelsberg J, Weycker D, Farkouh RA, Strutton DR, Pelton SI. Rates of pneumococcal disease in adults with chronic medical conditions. Open Forum Infect Dis. 2014; 1(1):1–9. https://doi.org/10.1093/ofid/ofu024.
4. Arnou R, Frank M, Hagel T, Prebet A. Willingness to vaccinate or get vaccinated with an intradermal seasonal influenza vaccine: a survey of general practitioners and the general public in France and Germany. Adv Ther. 2011; 28(7):555–565. https://doi.org/10.1007/s12325-011-0035-z. [PubMed: 21626269]

5. Reygrobellet C, Viala-Danten M, Meunier J, Weber F, Nguyen VH. Perception and acceptance of intradermal influenza vaccination: Patient reported outcomes from phase 3 clinical trials. Hum Vaccin. 2010; 6(4):336–345. https://doi.org/10.4161/hv.6.4.10753. [PubMed: 20372083]
6. Nowalk MP, Lin CJ, Toback SL, et al. Improving influenza vaccination rates in the workplace: a randomized trial. Am J Prev Med. 2010; 38(3):237–246. https://doi.org/10.1016/j.amepre.2009.11.011. [PubMed: 20036102]
7. Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. Lancet Infect Dis. 2012; 12(1):36–44. https://doi.org/10.1016/S1473-3099(11)70295-X. [PubMed: 22032844]
8. Andersohn, F., Bornemann, R., Damm, O., Martin, F., Mittendorf, T., Theidel, U. Vaccination of children with a live-attenuated, intranasal influenza vaccine – analysis and evaluation through a Health Technology Assessment; GMS Health Technol Assess. 2014. p. 10www.ncbi.nlm.nih.gov/pmc/articles/PMC4219018/pdf/HTA-10-03.pdf
9. .CDC. Influenza vaccines for healthy children aged 2 through 8 years—review of comparative studies of live attenuated influenza vaccine (LAIV) and inactivated influenza vaccine (IIV). www.cdc.gov/vaccines/acip/recs/grade/laiv-child.pdf
10. Jefferson T, Rivetti A, Di Pietrantonj C, Demicheli V, Ferroni E. Vaccines for preventing influenza in healthy children. Cochrane Database Syst Rev. 2012; 8:CD004879. https://doi.org/10.1002/14651858.cd004879.pub4.
11. Grohskopf LA, Olsen SJ, Sokolow LZ, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP)-United States, 2014–15 influenza season. MMWR Morb Mort Wkly Rep. 2014; 63(32):691–697.
12. Caspard H, Gaglani M, Clipper L, et al. Effectiveness of live attenuated influenza vaccine and inactivated influenza vaccine in children 2–17 years of age in 2013–2014 in the United States. Vaccine. 2016; 34(1):77–82. https://doi.org/10.1016/j.vaccine.2015.11.010. [PubMed: 26589519]
13. Zimmerman RK, Nowalk MP, Chung J, et al. 2014–2015 influenza vaccine effectiveness in the United States by vaccine type. Clin Infect Dis. 2016; 63(12):1564–1573. https://doi.org/10.1093/cid/ciw635. [PubMed: 27702768]
14. Flannery, B., Chung, J. Influenza Vaccine Effectiveness, including LAIV vs IIV in Children and Adolescents, U.S. FluVE Network. 2015–16. www.cdc.gov/vaccines/acip/meetings/downloads/slides-2016-06/influenza-05-flannery.pdf
15. CDC. ACIP votes down use of LAIV for 2016–17 flu season. www.cdc.gov/media/releases/2016/s0622-laiv-flu.html
16. Public Health England. Influenza vaccine effectiveness in adults and children in primary care in the UK: provisional end-of-season results 2015–16. www.gov.uk/government/uploads/system/uploads/attachment_data/file/530756/Influenza_vaccine_effectiveness_in_primary_care_in_children.pdf
17. Ambrose, CS. 2015–16 US Influenza Vaccine Effectiveness Influenza Clinical Investigation for Children (ICICLE) Study. www.cdc.gov/vaccines/acip/meetings/downloads/slides-2016-06/influenza-06-ambrose.pdf
18. Loeb M, Russell ML, Manning V, et al. Live attenuated versus inactivated influenza vaccine in hutterite children: a cluster randomized blinded trial. Ann Intern Med. 2016; 165(9):617–624. https://doi.org/10.7326/M16-0513. [PubMed: 27538259]
19. Smith KJ, Raviotta JM, DePasse JV, et al. Cost effectiveness of influenza vaccine choices in children aged 2–8 years in the U.S. Am J Prev Med. 2016; 50(5):600–608. https://doi.org/10.1016/j.amepre.2015.12.010. [PubMed: 26868283]
20. CDC. [Accessed November 19, 2014] Influenza-Associated Pediatric Mortality. http://gis.cdc.gov/GRASP/Fluview/PedFluDeath.html
21. CDC. [Accessed November 19, 2014] FluView. National and regional level outpatient illness and viral surveillance. http://gis.cdc.gov/grasp/fluview/fluportaldashboard.html
22. Glezen WP, Gaglani MJ, Kozinetz CA, Piedra PA. Direct and indirect effectiveness of influenza vaccination delivered to children at school preceding an epidemic caused by 3 new influenza virus variants. J Infect Dis. 2010; 202(11):1626–1633. https://doi.org/10.1086/657089. [PubMed: 21028955]

23. Rodgers L, Pabst LJ, Chaves SS. Increasing uptake of live attenuated influenza vaccine among children in the United States, 2008–2014. Vaccine. 2015; 33:22–24. https://doi.org/10.1016/j.vaccine.2014.11.006. [PubMed: 25448098]

24. CDC. National Early Season Flu Vaccination Coverage, United States. Nov. 2015 Flu Vax View.

25. Ambrose CS, Bright H, Mallory R. Potential causes of the decreased effectiveness of the influenza A(H1N1)PDM09 strain in live attenuated influenza vaccines. Euro Surveill. 2016; 21(45) pii=30394. https://doi.org/10.2807/1560-7917.ES.2016.21.45.30394.

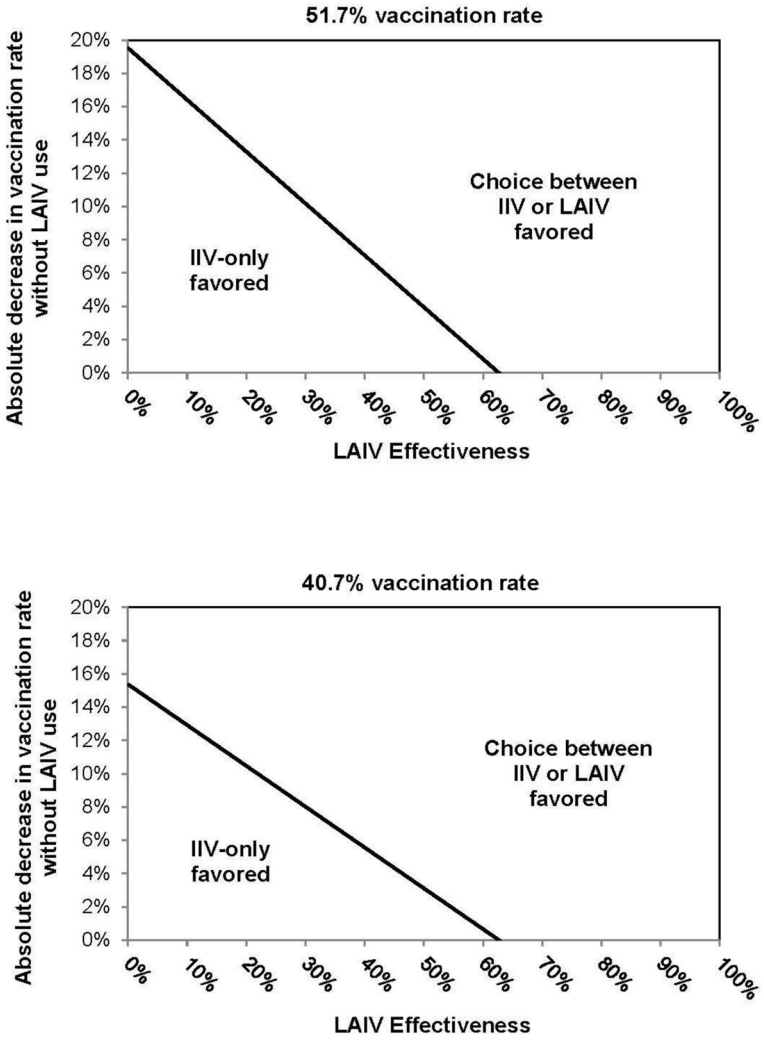

Figure 1.

Two-way sensitivity analysis.

Notes: Varying LAIV effectiveness (x-axis) and the absolute decrease in vaccination rates when LAIV is not used (y-axis) for prior population vaccination rates of 51.7% (observed influenza vaccine uptake for children aged <5years, top panel) and 40.7% (uptake for children aged 5–12 years, bottom). Within each panel, areas depict where strategies are favored due to fewer influenza cases compared to the other strategy. The option to use either vaccine was favored when LAIV effectiveness is high or when the decrease in vaccination rate is high after LAIV is no longer an option. At the base case LAIV effectiveness of 3%, the vaccination rate would have to decrease by almost 19% (top) or 15% (bottom) as a result of removing LAIV for the both vaccines option to be favored.

LAIV, live attenuated influenza vaccine; IIV, inactivated influenza vaccine

Table 1

Key Parameter Values Examined in the Model

Parameter	Base case (range)	Source
Relative likelihood of LAIV use (vs. IIV)	38% (0–50%)	[23]
Vaccination likelihood		
Base case (6 months–4 years)	51.7% (+/− 6.1%)	[24]
Alternative case (5–12 years)	40.7% (+/− 3.6%	[24]
Vaccine effectiveness – Age 2–17 years		
LAIV	3% (0–70%)	[14]
IIV	63% (40–80%)	[14]

LAIV, live attenuated influenza vaccine; IIV, inactivated influenza vaccine