



# Repeated Vaccination May Protect Children From Influenza Infection

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Influenza infections in children are problematic not only for the immediate symptoms they cause but also for their potentially large contribution to influenza infections in other age groups. Since 2008, the Advisory Committee on Immunization Practices has recommended that all children at least 6 months old be vaccinated annually against influenza. By historical standards, vaccination coverage in children in the United States is high, with nearly 60% of children younger than age 18 years and 76% of children aged 6 to 23 months receiving an influenza vaccine in the 2016-2017 season.<sup>1</sup> Vaccination coverage in children has also expanded in the United Kingdom, where indirect benefits on other age groups have been observed.<sup>2</sup>

The recent expansion of vaccination coverage has coincided with increased attention to the vexing problem of why the vaccine is not more effective, and especially to scattered observations that the vaccine may be less effective in frequent recipients.<sup>3</sup> Although many analyses of repeated vaccination included children in their study populations, they were underpowered to examine effects by age, and their statistical conclusions were inevitably heavily influenced by adults. Young children and adults can respond to vaccines differently, however, partly because they share different exposure histories.

The study by McLean et al<sup>4</sup> fills an important gap by measuring the association of repeated vaccination with vaccine effectiveness in children. From the 2013-2014 to the 2015-2016 seasons, the investigators enrolled 3369 children presenting with an acute respiratory illness at 4 sites in the United States. Using a retrospective, test-negative case-control design, the authors then estimated the ratio of vaccinated to unvaccinated children among the influenza test-positive cases and the same ratio among the influenza test-negative cases. The ratio of these ratios yields the exposure odds ratio of vaccination associated with being an influenza case and is one measure of vaccine effectiveness. The authors examined whether vaccine effectiveness changed with individuals' recent histories of influenza vaccination while adjusting for sex, age group, and other factors.

In no case was repeated vaccination associated with lower effectiveness than vaccination in the current season only. In other words, there was no evidence of diminished vaccine effectiveness in frequent vaccinees, even though the study included seasons in which such effects had been reported elsewhere. But there were intriguing differences in the effects of vaccination history by type. For influenza B, vaccination at any time—this season, last season, or both—was associated with similar effectiveness. This points to a high degree of residual protection for the B component of both the live attenuated influenza vaccines (LAIV) and inactivated influenza vaccines (IIV), which the study was able to examine separately. For influenza A(H3N2), prior vaccination appeared to enhance the effectiveness of LAIV. In this study influenza A(H3N2) cases occurred primarily in 2014-2015, a season in which a well-described antigenic mismatch lowered vaccine effectiveness.<sup>5</sup> Notably, significant protection against influenza A(H3N2) in children vaccinated with LAIV was only associated with previous vaccination, and prior vaccination with IIV was associated with higher effectiveness. The effects of repeated vaccination with LAIV were thus in the opposite direction of what had been found in some older populations that season.<sup>3,6</sup> Prior vaccination had no significant effect on the effectiveness of IIV against influenza A(H3N2), but like LAIV, the highest effectiveness was observed in repeated vaccinees. With influenza A(H1N1)pdm09, which circulated in the 2013-2014 and 2015-2016 seasons, IIV and LAIV were not significantly associated with vaccination history, but for LAIV, effectiveness was significantly associated with repeat vaccinees only.

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The results thus suggest additional support for the current Advisory Committee on Immunization Practices' recommendation that children be vaccinated annually against influenza. Although annual vaccinations may do little to enhance protection against influenza B, regular vaccinations might improve performance of the influenza A(H3N2) and influenza A(H1N1)pdm09 components. Despite the mismatch of a major immunodominant epitope between the vaccine and circulating strains of influenza A(H3N2) in 2014-2015, successively vaccinated children experienced the highest protection with LAIV and suggestively high protection with IIV. One possibility is that repeated vaccination boosted responses to conserved but less dominant sites on the virus. Children, whose first infections (compared with adults) were probably with viruses more closely resembling the vaccine strain, may have a better ability to target these subdominant sites.<sup>7</sup> For both influenza A(H1N1)pdm09 and influenza A(H3N2), LAIV tended to be less effective than IIV for children vaccinated only in the current season. This was ascribed to poor replicative capacity of the vaccine strain, which has apparently been reformulated for the 2018-2019 season. The trend of higher effectiveness in children with repeated vaccination hints that priming might boost the immunogenicity of LAIV.

The study by McLean et al<sup>4</sup> also serves as a reminder of how much epidemiological work needs to be done. There are 3 major challenges to understand influenza vaccine effectiveness. The first is to measure effectiveness accurately. Observational studies are intrinsically at risk for bias from unmeasured and unadjusted confounding, for instance, if people at higher risk of infection are vaccinated more often. Additionally, it has been shown that test-negative case-control approaches might lead to biased estimates of effectiveness, especially if vaccines are leaky, eg, confer protection from severe but not moderate infection, and if people vary in their susceptibility.<sup>8</sup> The second challenge is to measure exposure history adequately. Most studies of the seasonal influenza vaccine do not have the capacity to probe individuals' vaccination histories more than a few years in the past, self-reports may be sensitive to recall bias, and infections are almost never directly observed. But there is ample evidence that infections early in life are associated with risk decades later<sup>9</sup> and that vaccine responses are shaped by exposure histories.<sup>10</sup> The third challenge is to identify the basis of vaccine-induced protection from infection, which would start by identifying correlates. Overcoming these challenges will require longitudinal cohorts, randomized controlled trials, and continued surveillance, and will provide critical insight into the development of better vaccines and vaccination strategies. This study is important progress.

## ARTICLE INFORMATION

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## REFERENCES

1. Santibanez TA, Zhai Y, O'Halloran A, et al. Flu vaccination coverage, United States, 2016-17 influenza season. <https://www.cdc.gov/flu/fluview/coversage-1617estimates.htm>. Accessed September 15, 2018.
2. Pebody RG, Green HK, Andrews N, et al. Uptake and impact of vaccinating school age children against influenza during a season with circulation of drifted influenza A and B strains, England, 2014/15. *Euro Surveill*. 2015;20(39). doi:[10.2807/1560-7917.ES.2015.20.39.30029](https://doi.org/10.2807/1560-7917.ES.2015.20.39.30029)
3. Belongia EA, Skowronski DM, McLean HQ, Chambers C, Sundaram ME, De Serres G. Repeated annual influenza vaccination and vaccine effectiveness: review of evidence. *Expert Rev Vaccines*. 2017;16(7):1-14. doi:[10.1080/14760584.2017.1334554](https://doi.org/10.1080/14760584.2017.1334554)

4. McLean HQ, Caspard H, Griffin MR, et al. Association of prior vaccination with influenza vaccine effectiveness in children receiving live attenuated or inactivated vaccine. *JAMA Netw Open*. 2018;1(6):e183742. doi:[10.1001/jamanetworkopen.2018.3742](https://doi.org/10.1001/jamanetworkopen.2018.3742)
5. Flannery B, Zimmerman RK, Gubareva LV, et al. Enhanced genetic characterization of influenza A(H3N2) viruses and vaccine effectiveness by Genetic Group, 2014-2015. *J Infect Dis*. 2016;214(7):1010-1019. doi:[10.1093/infdis/jiw181](https://doi.org/10.1093/infdis/jiw181)
6. Skowronski DM, Chambers C, Sabaiduc S, et al. A perfect storm: impact of genomic variation and serial vaccination on low influenza vaccine effectiveness during the 2014-2015 season. *Clin Infect Dis*. 2016;63(1):21-32. doi:[10.1093/cid/ciw176](https://doi.org/10.1093/cid/ciw176)
7. Lewnard JA, Cobey S. Immune history and influenza vaccine effectiveness. *Vaccines (Basel)*. 2018;6(2):E28. doi:[10.3390/vaccines6020028](https://doi.org/10.3390/vaccines6020028)
8. Lewnard JA, Tedijanto C, Cowling BJ, Lipsitch M. Measurement of vaccine direct effects under the test-negative design [published online August 7, 2018]. *Am J Epidemiol*. doi:[10.1093/aje/kwy163](https://doi.org/10.1093/aje/kwy163)
9. Gostic KM, Ambrose M, Worobey M, Lloyd-Smith JO. Potent protection against H5N1 and H7N9 influenza via childhood hemagglutinin imprinting. *Science*. 2016;354(6313):722-726. doi:[10.1126/science.aag1322](https://doi.org/10.1126/science.aag1322)
10. Davenport FM, Hennessy AV. Predetermination by infection and by vaccination of antibody response to influenza virus vaccines. *J Exp Med*. 1957;106(6):835-850. doi:[10.1084/jem.106.6.835](https://doi.org/10.1084/jem.106.6.835)