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Letter in response to commentary by Small and Cronin

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Dear Vaccine,

The commentary by Small and Cronin [1] on the Advisory Committee on Immunization Practices (ACIP) recommendation that live attenuated influenza vaccine (LAIV) not be used during the 2016–17 influenza season [2] contains misconceptions concerning the basis of the ACIP recommendation and aspects of the test negative case-control (TNCC) design. Contrary to the statement that the recommendation was based upon CDC data that showed no protection against H1N1 viruses during the last influenza season (2015–16), the decision was reached following consideration of data for children aged 2 through 17 years from three U.S. studies (from CDC, the U.S. Department of Defense, and MedImmune) over three consecutive seasons [3]. These studies noted lack of significant effectiveness against H1N1pdm09 during the 2013–14 and 2015–16 seasons; during the latter season, despite replacement of the LAIV H1N1 vaccine virus to address the putative cause. During 2013–14 and 2015–16, inactivated influenza vaccines (IIVs) were significantly effective, with a higher point estimate than that for LAIV. Additional analysis of CDC data from the 2010–11 season revealed similarly low effectiveness of LAIV against H1N1pdm09 relative to IIV [4]. The authors note that previous “extensive studies demonstrate superior efficacy of LAIV in young children for both homologous and drifted viruses.” However, these studies were conducted prior to the 2009 pandemic, and the emergence of H1N1pdm09. Moreover, during the 2014–15 season, LAIV performed no better than IIVs against the predominant antigeni-cally-drifted H3N2 viruses, contrasting with observations from pre-pandemic trials [5].

The authors suggest superior prevention of infection and transmission by LAIV, citing evidence from animal studies to support sterilizing immunity induced by LAIV. We are unaware of human data suggesting that LAIV is superior to IIV in decreasing influenza transmission; a recent community-randomized study noted similar indirect effectiveness to that of IIV [6]. Moreover, lower effectiveness for LAIV relative to IIV observed in the CDC data was specific to H1N1pdm09 in 2010–11, 2013–14 and 2015–16. Lower effectiveness of LAIV was not observed against H3N2 or B in 2010–11 through 2012–13. If the authors’ assumptions regarding inherent biases in the TNCC design are correct, they should apply to all virus types/subtypes and to earlier seasons.

In most studies of older children and adults, LAIV has not been found to be more effective than inactivated vaccines, with some studies of adults indicating superiority of inactivated

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vaccines [7]. It is conceivable that previous exposure to influenza vaccines may impact replication and efficacy of LAIV, which may contribute to different experiences with LAIV in several other countries over the last several seasons. The introduction of quadrivalent LAIV in the 2013–14 season raises questions as to whether interference due to the additional B antigen could be a factor. ACIP will continue to review data; hopefully a reparable cause will be identified. While LAIV was attractive for school immunization programs, it is also important that effective vaccines are used, including vaccines against all circulating viruses.

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