No Clinical Association of Live Attenuated Influenza Virus with Nasal Carriage of Bacteria or Acute Otitis Media

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We write this note to clarify the article "Live Attenuated Influenza Vaccine Enhances Colonization of *Streptococcus pneumoniae* and *Staphylococcus aureus* in Mice" by Mina et al. (1) in order that patients or clinicians not misinterpret the study's clinical relevance.

Mina et al. described interactions between a novel live attenuated influenza virus (LAIV) strain and pathogenic bacteria at the murine respiratory mucosa. Mina et al. demonstrated that their novel attenuated virus could promote colonization of the upper respiratory tract of mice with *S. pneumoniae* and *S. aureus* but had no effect on severe bacterial disease or mortality within the lower respiratory tract. Based on that finding, the authors speculated that the FDA-approved LAIV may, like wild-type influenza virus, condition the site of replication in the upper respiratory tract for enhanced secondary bacterial colonization and noted that the immediate effects of their novel LAIV on bacterial replication and disease have never before been described.

The findings in mice reported by Mina et al. are not supported by clinical trial data for the Ann Arbor strain LAIV licensed for use. In a recent randomized placebo-controlled study of LAIV in 151 children conducted by investigators at the University of Bristol, there was no difference in rates or densities of nasal carriage of *S. pneumoniae* on day 7 or 28 following receipt of LAIV or a placebo (2). Furthermore, multiple large randomized clinical trials in children have not demonstrated any increase in bacterial upper respiratory tract disease following vaccination with LAIV. More specifically, in 6 placebo-controlled studies (14,109 subjects), the incidences of acute otitis media (AOM) during days 0 to 10 postvaccination were not significantly different between LAIV and placebo recipients in any individual study or when study results were pooled (3). In 2 inactivated influenza vaccine (IIV)-controlled studies (9,937 subjects), AOM incidences during days 0 to 28 postvaccination were similar between LAIV and IIV recipients with one exception: the rate of AOM following the second LAIV dose in one study (4) was significantly lower in LAIV recipients than in IIV recipients (7.1% versus 8.6%; $P = 0.028$) (3).

In contrast to results obtained with mice, the licensed Ann Arbor strain LAIV did not enhance *S. pneumoniae* carriage in clinical studies and there was no evidence of an increased risk of bacterial upper respiratory tract disease following vaccination. LAIV has been shown to reduce influenza-associated AOM and all-cause AOM during the influenza season and to reduce the severity of AOM in breakthrough cases (3, 5). As the authors correctly state, vaccines may have unintended consequences on other important human pathogens unrelated to the vaccine target. As a result, it is important that they are carefully studied in clinical trials prior to licensure. The safety of the licensed LAIV has been demonstrated in multiple clinical studies and in the postmarketing setting (6, 7).

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