recently vaccinated. More than a dozen papers have reported findings of declining vaccine effectiveness (VE) with increasing time since vaccination using the test-negative design [3]. We agree with Dr Lipsitch that caution is warranted when inferring that waning immunity is the mechanistic cause of the observed decline in VE.

Postvaccination antibody titers decline over time, and although titers usually remain at levels above those associated with protection for the duration of an influenza season [4–6], some degree of decline in VE may result from waning immunity. However, theoretical evidence suggests that an observed decline in VE may be an artifact [7–9]. As discussed by Dr Lipsitch, if influenza vaccine provides protection through a “leaky” mechanism, then vaccination reduces the risk of infection by a certain fraction without rendering complete immunity. Vaccinated individuals may be infected but at lower rates, with the practical implication being that rates of infection become similar between unvaccinated and vaccinated groups with passage of time, manifesting as a decline in observed VE. In short, the decline in VE, or some portion of it, identified by Ray et al and other observational studies could be from artifact and not waning.

It is difficult to disentangle waning from artifact related to the leaky vaccine effect. Ray et al used simulation to show that their observed waning effect was unlikely to be artifact, but similar calculations by Dr Lipsitch implied otherwise, suggesting that bias could contribute to the observed decline in VE, although its magnitude would likely be small. Numerous investigators have described the difficulty of elucidating temporal patterns of VE using empirical data due to uncertainty about mechanisms of vaccine protection, potential heterogeneity among vaccinated individuals, choice of VE measure, and other factors [10]. We reiterate the need for development of methodologic approaches in this area and agree with Dr Lipsitch that, in the

meantime, multiple sources of information, such as evidence of antibody decline and insights from theoretical expectations and simulation, are needed as corroborating evidence of biologic waning of protection.

A vaccine with significant waning of protection would raise important policy questions regarding optimal timing of vaccination campaigns. Delaying vaccination could offer improved protection later in an influenza season but risks lowering overall vaccination coverage and missing opportunities to vaccinate before influenza circulation, leaving individuals unprotected. Given uncertainty about the cause and extent of observed declines in VE and effect of a delay on vaccine coverage, we disagree with premature decisions that may affect vaccine policy, such as the suggestion by Ray et al that vaccination be postponed until November. To best inform policy decisions, a careful vetting of available evidence is required and a clearer understanding of the reasons for observed declines in intraseason VE is necessary—is it waning or is it artifact or some combination of both?

Note

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Reply to Ferdinands et al

TO THE EDITOR—We agree with Ferdinands et al that it would be premature to recommend delay of influenza vaccination until November. Although our study found that people vaccinated in November are better protected than people vaccinated earlier, we noted in the Discussion that delaying vaccination might reduce vaccine coverage and should not be recommended before careful consideration of potential harms as well as benefits [1].

We disagree with Ferdinands et al about the potential bias that was called to our attention by Dr Lipsitch [2]. This is an interesting bias—associated with “depletion of susceptibles”—but our findings cannot be attributed to it. This bias can arise as higher-risk individuals, called “susceptibles,” get infected and thereby depleted from the population still at risk. During influenza season the unvaccinated population loses more of its “susceptibles” (because it is unprotected by the vaccine) than does the vaccinated population. Consequently, influenza

incidence eventually falls faster among the unvaccinated than among vaccinees, bringing these 2 incidence rates closer together. Thus, later in the influenza season, vaccine effectiveness (VE) can artifactually seem to wane (unless susceptibility is measured and adjusted for).

For this kind of bias to arise, the groups compared must have differential depletion of their susceptible individuals. In our vaccinee-only study, the groups compared were persons vaccinated earlier in the year vs those vaccinated later in the year. Before influenza begins to circulate, there is no depletion of susceptibles. After influenza begins to circulate—and if there really is no waning of VE—the rate of depletion of susceptibles among the vaccinees will be the same regardless of when they were vaccinated. In this no-waning scenario, there is no potential for bias related to depletion of susceptibles.

(If VE really does wane, then the early vaccinees would be less protected than the later vaccinees and would get more depleted of their susceptibles. In this case, the amount of waning would be underestimated rather than exaggerated.)

However, bias in the direction of exaggerating waning is potentially introduced by the inclusion of persons who are vaccinated after the influenza season is under way and have less time to be depleted. To address this concern, we restricted our analysis to the 90% of our study population that was vaccinated before 1 December (before the influenza season ever started in Northern California during the 2010–2016 study period), and our estimate of waning changed very little. (Our estimate of the increased odds of influenza with every 28 days since vaccination went from 1.16 to 1.18.)

Notes

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Human Herpesvirus 6 Positivity on the FilmArray Meningitis/Encephalitis Panel Needs Clinical Interpretation

TO THE EDITOR—We read with interest the article by Green et al [1] regarding the clinical significance of human herpesvirus 6 (HHV-6) positivity on the FilmArray meningitis/encephalitis (ME) panel. We have had a similar experience and would like to add our own institution's findings to this interesting topic.

Our institution, Lehigh Valley Health Network (LVHN), is made up of 7 hospitals serving the suburban and rural areas surrounding Allentown, Pennsylvania. The ME panel was introduced 23 February 2016 to 3 of these hospitals, including our large 800-bed tertiary care center and children's hospital. Notably, LVHN performs kidney and pancreas solid organ transplants only. As previously described, this panel is a multiplex cerebrospinal fluid nucleic acid test that

detects 14 different targets with excellent sensitivity and specificity and a rapid turnaround time [1, 2].

We reviewed all of the cases of HHV-6 positive ME panel results from 23 February 2016 to 24 September 2018. Each patient's electronic medical record was reviewed for the following information: demographics, comorbidities, test results, radiology results, treatments, and 30-day mortality. Three providers reviewed the cases and then formulated a consensus to determine potential causality: an infectious disease specialist (A. K. S.), a transplant infectious disease specialist (T. L. R.), and a pediatric infectious disease specialist (T. V.). The authors assigned either (1) primary infection, including congenital infection, or the following regarding HHV-6 encephalitis: (2) unlikely, (3) possible, or (4) probable HHV-6 encephalitis [3–7]. This study was approved by the institutional review board at LVHN.

A total of 1516 ME panels were performed during the study period. Nineteen patients (1.3%) were identified with a positive HHV-6 result. HHV-6 was the fourth most common organism identified after enterovirus (60), herpes simplex virus type 2 (24), and varicella zoster virus (20), after excluding duplicate testing. Nine patients (47%) were ≤18 years of age and 10 (53%) were >18 years of age. Eight (88%) of the pediatric cases were thought to represent primary HHV-6 infection, resulting in a rapid discontinuation of antibiotics. Upon review, none of the adult cases was thought to represent HHV-6 encephalitis and the patients were discharged with a myriad of alternative diagnoses (Table 1). Interestingly, 3 of the adult patients were inappropriately treated with ganciclovir and in 1 patient this test result caused a delay in diagnosis of steroid-responsive encephalitis.

We support the authors' conclusions that this diagnosis should only be