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Interpretation of Relative Efficacy and Effectiveness for Influenza Vaccines

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Background. Relative vaccine effectiveness (rVE) are metrics commonly reported to compare absolute VE (aVE) of 2 vaccine products.

Methods. Estimates of rVE for enhanced influenza vaccines (eIV) vs standard inactivated influenza vaccine (IIV) have been assessed across different seasons, influenza-specific endpoints, and nonspecific endpoints (eg, all-cause cardiovascular hospitalizations). To illustrate the challenges of comparability across studies, we conducted a scenario analysis to evaluate the effects of varying absolute VE (aVE) of IIV (ie, as compared with placebo) on the interpretation of rVE of eIV vs IIV.

Results. We show that estimates of rVE might not be comparable across studies because additional benefits commensurate with a given estimate of rVE are dependent on the aVE for the comparator vaccine, which can depend on factors such as host response to vaccine, virus type, and clinical endpoint evaluated.

Conclusions. These findings have implications for interpretation of rVE across studies and for sample size considerations in future trials.

Keywords. vaccine efficacy; vaccine effectiveness; influenza; vaccines.

Influenza vaccines were first developed over 80 years ago to help prevent morbidity and mortality associated with seasonal influenza viruses. Purified versions of standard-dose inactivated influenza vaccines (IIV) grown in embryonated chicken eggs are used today in most countries, with pooled protection of 33–67% against all influenza illness [1]. Newer, enhanced influenza vaccines (eIV) have been developed in the pursuit of improving immune responses, improving clinical vaccine effectiveness, particularly among elderly populations, and reducing manufacturing timelines by relying less on eggs. In the United States, several eIVs (eg, high-dose, adjuvanted, recombinant, or tissue cell-culture derived vaccines) have been approved for use during recent years, including 2 (high-dose and adjuvanted) approved and marketed specifically for persons aged ≥ 65 years [2]. Although recent years have seen an expansion of studies comparing benefits of different influenza vaccines relative to one another, rVE estimates vary from season to season, and data for some specific vaccine comparisons are limited. Given these complexities, currently no preferential recommendation exists for eIVs in the United States, although evidence has accumulated for superior efficacy of some high-dose eIVs compared to standard-dose IIVs in adults aged ≥ 65 years [3].

Although randomized controlled trials (RCTs) typically aim to compare a vaccine intervention with an unvaccinated or placebo cohort, which in turn provides an estimate of absolute vaccine efficacy (aVE), these comparator cohorts are not feasible when a vaccine is indicated for broad use as a necessary preventive intervention in the general population [4]. Relative vaccine efficacy or effectiveness (herein referred to as rVE), which compares disease incidence between groups receiving 2 different vaccines, is a metric commonly reported to demonstrate the additional preventive benefit of eIVs vs IIVs [5–10]. Efficacy estimates are generated through RCTs and effectiveness estimates through observational case-control or cohort studies in the post-marketing period [11]. Although rVE here refers to relative efficacy and relative effectiveness interchangeably, the RCTs and observational studies from which rVE can be derived have different biases; for example, more exclusions of medically compromised persons in RCTs generating higher efficacy estimates, compared with effectiveness estimates. For practical reasons (eg, infrequency of both a standard and enhanced vaccine being included in an RCT), most estimates of rVE for influenza both (1) use data from observational studies and (2) are derived from comparing the aVE of 2 different vaccines. As rVE is the incremental improvement in the efficacy of eIV relative to the standard vaccine (IIV), it can be interpreted only with knowledge of the aVE, or simply VE, of IIV.

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First, absolute VE of any vaccine can vary substantially by viral factors such as influenza virus type and subtype/lineage, antigenic match of vaccine strains to circulating viruses, including from season to season, and by host factors [1]. Second, aVE can vary depending on whether the clinical endpoint assessed is influenza-specific (eg, laboratory-confirmed influenza, influenza-specific hospitalization) or a nonspecific endpoint such as all-cause cardiovascular (CV) hospitalization or death [10, 12]. Despite these limitations, findings of rVE from sentinel trials have often been used as benchmarks for comparison in future trials and post-licensure evaluations [5–10]. In addition, findings of rVE against laboratory-confirmed influenza have also been applied for sample size considerations in trials with nonspecific endpoints [5].

As the menu of influenza vaccines will potentially be expanded during the next decade [13], better understanding of how rVE is interpreted across endpoints, populations, and time may be useful. Here we conduct a scenario analysis to evaluate and illustrate the effects of varying aVE of the IIV (ie, the comparator standard vaccine) and the endpoints assessed in the studies on the interpretation of rVE of the new vaccine.

METHODS

Our primary objective was to demonstrate, through hypothetical numerical examples, how a fixed value of rVE could have different practical meanings under differing estimates of aVE and study endpoints. To achieve our objective, we assumed (1) 2 different constant rVE estimates for eIV relative to IIV, (2) a range of aVE estimates for IIV, and (3) burden estimates of influenza-specific and all-cause CV hospitalizations. Using these inputs, we calculated outputs as additional benefits provided by eIV in terms of averted hospitalizations associated with each endpoint. For simplicity, we assumed a fully vaccinated US population to illustrate the effects of rVE on averted hospitalizations in relation to a range of aVE estimates. To isolate the effects of rVE on disease burden and for purposes of illustration, we assumed that all input parameters were true unbiased estimates.

We simulated 2 scenarios.

Scenario 1: Here we address the question of additional benefit provided by eIV beyond that provided by IIV in terms of averted influenza-specific hospitalizations.

Scenario 2: Here we address the question of additional benefits provided by eIV beyond that provided by IIV in

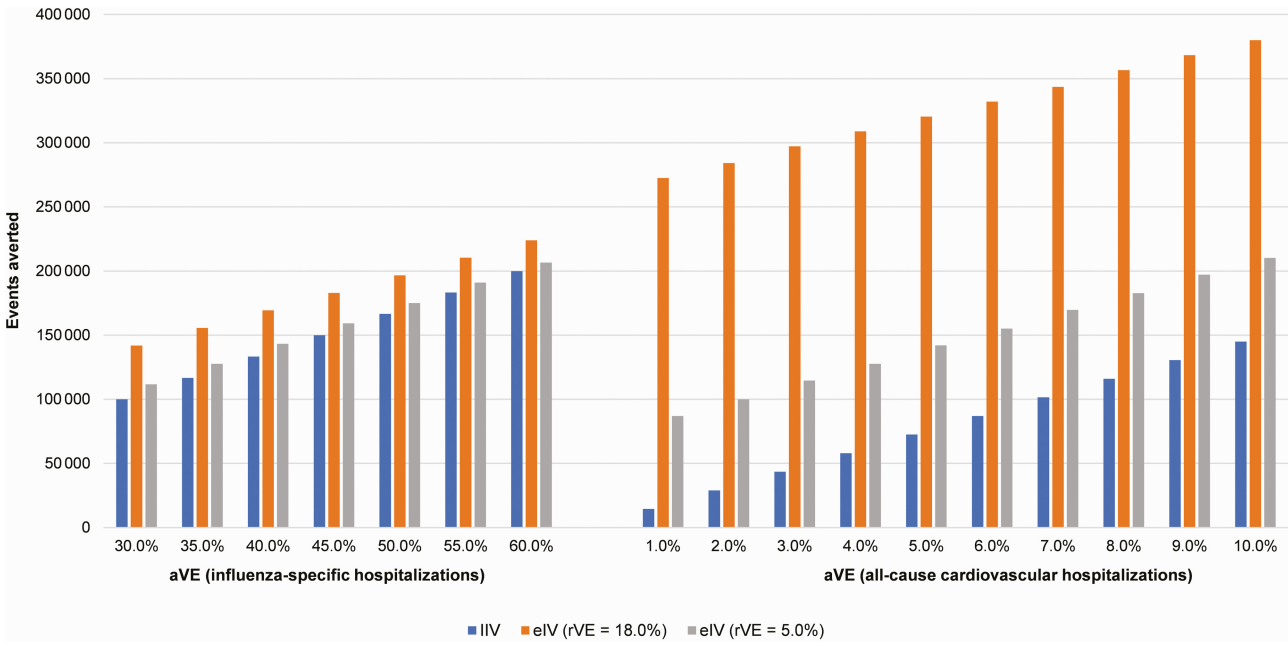

Figure 1. Hypothetical effects of varying (5% vs 18%) rVE estimates on averted events for influenza-specific hospitalizations and all-cause cardiovascular hospitalizations. *A*, We calculated aVE for eIV under scenarios of 18% and 5% rVE, compared with IIV, using the following equation: $aVE_{eIV} = rVE \times (1—aVE_{IIV}) + aVE_{IIV}$, where aVE_{eIV} denotes absolute efficacy for an enhanced influenza vaccine; rVE denotes relative efficacy; and aVE_{IIV} denotes absolute efficacy for a standard influenza vaccine. *B*, Total events averted annually were the product of total influenza hospitalizations and aVE of each respective vaccine. Annual influenza hospitalizations during the study were based on CDC estimates (total = 999 915) during 2015–2016, 2016–2017, and 2017–2018 divided by 3 (total = 333 305) [https://www.cdc.gov/flu/about/burden/past-seasons.html]. *C*, Total events averted annually were the product of total all-cause cardiovascular hospitalizations and aVE of each respective vaccine. Total all-cause cardiovascular hospitalizations were based on annual rates (60.5 per 1000) among persons aged ≥ 65 years (47.8 million) during 2015–2017 (total = 2 900 000) [https://nccd.cdc.gov/DHDSPAtlas/Reports.aspx]. We divided these estimates by 2 (total = 1 450 000) to reflect the ~6-month event monitoring period typical of randomized controlled vaccine trials. Abbreviations: aVE, absolute vaccine efficacy; CDC, Centers for Disease Control and Prevention; eIV, enhanced influenza vaccine; IIV, inactivated influenza vaccine; rVE, relative vaccine efficacy or effectiveness.

terms of averted all all-cause cardiovascular (CV) hospitalizations. We use this scenario because studies have specifically evaluated this endpoint in RCTs, and it has been highlighted as a priority for evaluation in future rVE trials of influenza vaccines [5, 10]

Estimates of rVE

We used a base rVE estimate of 18% for both scenarios based on estimates used for sample size calculations in a recent trial of rVE of high-dose eIV vs standard dose IIV against all-cause cardiovascular hospitalizations [5]and findings from a larger meta-analysis of clinical trials assessing high-dose eIV vs standard dose IIV clinical trials [10]. To illustrate additional benefits with lower estimates of rVE, we repeated the simulations for both scenarios with rVE estimates of 5%.

In trials, rVE of an eIV is based on aVE of a new vaccine vs a comparator vaccine, where aVE for each product is measured as the inverse of: the probability of an outcome in the vaccinated population ($[risk]_{vaccinated}$) as a proportion of the probability of the same outcome in the unvaccinated population ($[risk]_{unvaccinated}$), or:

$$aVE = 1 - \frac{(Risk\ among\ vaccinated)}{(Risk\ among\ unvaccinated)} \times 100\%$$

The rVE comparing an eIV with an IIV then is the difference between the absolute VE of enhanced vaccine ($aVE_{enhanced}$) and the absolute VE of the standard-dose vaccine ($aVE_{standard}$), as a proportion of the inverse of $aVE_{standard}$, or:

$$rVE = \frac{aVE_{enhanced} - aVE_{standard}}{1 - aVE_{standard}} \times 100\%$$

Estimates of aVE

In scenario 1, for aVE we used a range of 30–60% to reflect the range observed in studies of influenza-specific hospitalizations [14–19]. As compared with influenza-specific hospitalizations, aVE is expected to be substantially decreased for nonspecific endpoints. Thus, for scenario 2, we used an aVE range of 1–10% to reflect the lower expected efficacy against all-cause CV hospitalizations.

Disease Burden Estimates for Influenza-Specific Hospitalizations and All-Cause Cardiovascular (CV) Hospitalizations

Disease burden estimates were obtained for the US population for influenza-specific hospitalizations and for all-cause cardiovascular hospitalizations [20, 21]. We use data from 2015–2018 for this analysis and focused on adults aged ≥ 65 years, the main population using eIV (eg, high-dose IIV or adjuvanted IIV), and thus more represented among published estimates of rVE. For influenza-specific hospitalizations, we used annual average estimates of total influenza hospitalizations published by the US Centers for Disease Control and Prevention (CDC) during the 2015–2016, 2016–2017, and 2017–2018 influenza seasons (n = 3 33 305 per year) [20]. For total all-cause cardiovascular hospitalizations, we used CDC's Interactive Atlas of Heart Disease and Stroke to calculate burden based on the annual rate (60.5 per 1000) among persons aged ≥ 65 years (47.8 million) during 2015–2017 (29 00 000 in total annually) [21].

Because these were annual estimates of all-cause CV hospitalizations, and influenza circulates predominantly during fall, winter, and spring months in the United States, we divided these estimates by 2 (n = 14 50 000) to reflect the ~6-month event monitoring period during influenza seasons for RCTs using nonspecific endpoints.

Calculations for Additional Benefits Provided by eIV

Applying the hypothetical estimates of rVE and aVE for IIV, we first computed aVE for eIV using the following equation:

$$aVE_{eIV} = rVE \times (1 - VE_{IIV}) + aVE_{IIV}$$

Averted burden by eIV and IIV were calculated separately as the products of estimated product-specific aVE and (1) influenza-specific hospitalizations (scenario 1) and (2) all-cause cardiovascular hospitalizations (scenario 2). To provide an estimate of additional benefit from eIV, we calculated the difference between the events averted by eIV vs IIV for each of the 2 endpoints.

RESULTS

With rVE held constant, the added benefit of an eIV in terms of additional averted events decreased as aVE of a comparator IIV increased (Figure 1). In the first scenario for influenza-specific hospitalizations, respectively, for IIV with aVE of 30%, 45%, and 60%, rVE estimates of 18% for eIV vs IIV translated to eIV averting 42 000, 33 000, and 24 000 more influenza-specific hospitalizations compared with IIV (Table 1). When rVE was changed to 5% in these calculations, eIV averted 11 670, 9330,

Table 1. Additional Benefits in Terms of Averted Influenza-Specific Hospitalizations Based on Varying aVE Estimates[a] for IIV (30–60%) and eIV (42.6–67.2%) Under Hypothetical Assumptions of 18% rVE of eIV vs IIV

aVE of IIV	aVE of eIV (rVE = 18%)	Difference	Additional Hospitalizations Averted
30.0%	42.6%	12.6	42 000
35.0%	46.7%	11.7	39 000
40.0%	50.8%	10.8	36 000
45.0%	54.9%	9.9	33 000
50.0%	59.0%	9.0	30 000
55.0%	63.1%	8.1	27 000
60.0%	67.2%	7.2	24 000

Abbreviations: aVE, absolute vaccine efficacy; eIV, enhanced influenza vaccine; rVE, relative vaccine efficacy or effectiveness; IIV, inactivated influenza vaccine.

[a]Under the assumption that the entire United States population aged ≥ 65 years was vaccinated IIV) or eIV during the 2015–2018 influenza seasons, calculated as $aVE_{eIV} = rVE \times (1—aVE_{IIV}) + aVE_{IIV}$.

and 6670 more influenza-specific hospitalizations, respectively, compared with IIV (Supplementary Table 1).

In the second scenario for all-cause CV hospitalizations, for IIV with aVE of 1%, 5%, and 10%, rVE estimates of 18% for eIV vs IIV translated into 258 100, 248 000, and 234 900 more all-cause CV hospitalizations averted, respectively, compared with IIV (Table 2). When rVE was changed to 5% in these calculations, eIV averted 72 500, 69 600, and 65 250 more all-cause CV hospitalizations, respectively, compared with IIV (Supplementary Table 2).

Table 2. Additional Benefits in Terms of Averted All-Cause Cardiovascular Hospitalizations Based on Varying aVE Estimates[a] for IIV (1–10%) eIV (18.8–26.2%) Under Hypothetical Assumptions of 18% rVE of eIV vs IIV

aVE of IIV	aVE of eIV (RVE = 18%)	Difference	Additional Hospitalizations Averted
1.0%	18.8%	17.8	2 58 100
2.0%	19.6%	17.6	2 55 200
3.0%	20.5%	17.5	2 53 800
4.0%	21.3%	17.3	2 50 900
5.0%	22.1%	17.1	2 48 000
6.0%	22.9%	16.9	2 45 100
7.0%	23.7%	16.7	2 42 200
8.0%	24.6%	16.6	2 40 700
9.0%	25.4%	16.4	2 37 800
10.0%	26.2%	16.2	2 34 900

Abbreviations: aVE, absolute vaccine efficacy; eIV, enhanced influenza vaccine; rVE, relative vaccine efficacy or effectiveness; IIV, inactivated influenza vaccine.

[a]Under the assumption that the entire US population aged ≥ 65 years was vaccinated with standard dose inactivated influenza vaccine (IIV) or enhanced influenza vaccine (eIV) during the 2015–2018 influenza seasons, calculated as $aVE_{eIV} = rVE \times (1—aVE_{IIV}) + aVE_{IIV}$.

DISCUSSION

We showed that the meaning and interpretation of rVE (eg, 5% or 18%) changes considerably based on the aVE of the comparator product as determined by factors such as the endpoint evaluated in the study, influenza virus characteristics, or the host response to vaccination [1]. Our results highlight 3 key findings of relevance to the interpretation of rVE estimates. First, the additional benefits from a positive rVE in terms of averted disease are inversely proportional to the aVE of IIV. Thus, for a fixed rVE, the absolute benefits of eIV in terms of averted events vary widely depending on the aVE of comparator vaccine, IIV. Benefits of eIV can be greater in scenarios of lower vaccine protection with IIV. Thus, additional benefits of eIV are expected to be greatest in: (1) adults aged ≥ 65 years, who experience lower efficacy compared with younger age groups, (2) during seasons when the aVE of IIV is lower for varying reasons (eg, circulating viruses differ antigenically from vaccine components), and (3) when considering protection against viruses such as A(H3N2) against which aVE has been inferior compared with influenza A(H1N1) and B viruses, particularly among the elderly [22].

Second, when aVE is low against nonspecific outcomes, our averted burdens estimated for illustrative purposes showed that a lower rVE (eg, <5%) is likely to approximate more realistic estimates of what an eIV can achieve. In contrast to an rVE of 5%, rVE estimates of 18% generated unrealistic estimates of additional all-cause CV hospitalizations averted, a nonspecific endpoint for which aVE is expected to be much lower. For example, in comparison to IIV, where aVE is 33–67% against laboratory-confirmed influenza, the aVE of IIV is unlikely to exceed 5–10% for all-cause CV hospitalizations because influenza is just one of many causes of these events [1, 22]. With a low aVE of 1% for IIV, an rVE of 18% for the comparator eIV would translate to averting ~258 100 additional all-cause CV hospitalizations (~272 600 all-cause CV hospitalizations in total) annually among a fully vaccinated population of US adults ≥ 65 years (Table 2). These implausible estimates are more than two and a half times the ~100 000 influenza-specific hospitalizations that could be averted by IIV in the same population based on CDC estimates of influenza burden and an aVE for IIV of ~30%. In contrast, an eIV with rVE of 5% against all-cause CV hospitalizations when aVE of IIV is 1% would avert an additional ~72 500 all-cause CV hospitalizations (Supplementary Table 2) and ~87 000 all-cause CV hospitalizations in total, more realistic estimates that are less than the ~100 000 influenza-specific hospitalizations that would be averted from IIV with an aVE of ~30%. Due to the higher burden of nonspecific events such as all-cause death and cardiovascular hospitalizations compared with influenza-specific events, even small gains in relative efficacy of 5% can substantially increase the number of additional deaths and hospitalizations averted.

Third, our findings have sample size implications. As an example, a recent study [5] seeking to estimate the efficacy of a high-dose IIV against all-cause deaths and cardiopulmonary hospitalizations was terminated early because the rates of the primary composite endpoint of all-cause mortality or cardiopulmonary hospitalization, within season or across the 3-year study period, were not significantly different between recipients of the 2 vaccines. However, a meaningful difference between the 2 vaccines against all-cause cardiopulmonary outcomes might have been detected with increased sample size generated by higher enrollment. Investigators powered the study sample to detect a rVE of 18%, based on clinical trial findings of rVE of high-dose vs standard dose IIV against laboratory-confirmed influenza A viruses [5, 6, 10]. Our simulations show that a more realistic rVE of 5% is likely to still be quite meaningful in terms of averted disease burden. As compared with the 5260 participants enrolled in the clinical trial, rVE of 5% would require enrolling ~20 000 participants under the same study assumptions and event rates (~42–45% each year across 3 years). Lower event rates of 10–15% as originally estimated prior to the trial would further increase the sample size requirements. Precise

quantification of the effect size, including rVE estimates, is critically relevant for sample size considerations to ensure sufficient statistical power when assessing the comparative efficacy of vaccines against nonspecific outcomes.

Increasingly, studies are showing enhanced immune responses after second-generation eIVs with potential for commensurate improvements in influenza vaccine protection as compared with standard dose IIVs [23]. In persons aged ≥ 65 years, high-dose vaccines have been estimated to have rVE of 5–9% against confirmed influenza or influenza-like illness [24, 25], 7% for all-cause hospitalization [26], 18–27% against hospitalization for influenza [9, 26], and 40% against hospitalization for pneumonia [26]. Other types of eIVs have also been reported to provide additional protection against influenza and influenza-like illness, including cell-cultured/cell-propagated (3–11%) [6, 8, 27], adjuvanted egg-based (8%) [6], and recombinant (13%) [28]vaccine. However, interpreting rVE also requires knowledge of the influenza season and specific vaccine virus type/subtype for which rVE was estimated because aVE of any vaccine can vary substantially based on these factors. For example, a meta-analysis of high-dose eIV efficacy in populations aged ≥ 65 years based on studies conducted during 2004–2015 found that aVE of the eIV was higher against A(H1N1)pdm09 (67%) compared with A(H3N2) viruses that were antigenically matched (33%) and for viruses mismatched to the vaccine virus (23%) [1]. A study with similar parameters conducted during the 2015–2019 influenza seasons, however, found not only that that aVE of the eIV was against A(H1N1)pdm09 (30%) was not substantially different from that against A(H3N2) (31%) [23] but also that the comparator aVE values for the IIV (40% and 19%, respectively) differed to the extent that rVE was negative for A(H1N1)pdm09 and positive for A(H3N2) viruses [25].

In terms of reporting, studies evaluating enhanced influenza vaccines should make clear their limitations to generalizability and acknowledge that reporting rVE of enhanced vaccines needs to carefully employ contextual data on the season(s) during which the rVE of eIV was measured, and the population and endpoint against which eIV was evaluated. When a control or a placebo group is used, reporting of aVE and rVE for both an enhanced vaccine and the comparator vaccine should be reported, as done in the 2015–2019 study [25], to reinforce the comparative, incremental nature of rVE. As another reporting option, a 2017–2018 study [6], like the scenarios demonstrated in this report, puts rVE estimates in context by deriving estimates of absolute VE for the enhanced vaccine based on several possible values for the comparator vaccine during that influenza season. In the scenarios provided in this report, an extra metric of additional absolute VE benefit (ie, difference between aVE of IIV and aVE of eIV) has been provided to show the gain in VE offered by eIV. Additional reporting improvements could allow for a more accurate comparison of similar enhanced vaccine products across studies. For example, future studies estimating rVE of an eIV could also calculate aVE for eIV based on a pooled aVE estimate for IIV or on a range of aVE estimates appropriate for the population and clinical endpoint evaluated. These pooled estimates could be based on meta-analyses or other studies from that season [1, 29]. Studies could also report the averted disease burden estimates under both the scenario evaluated and hypothetical scenarios under using different aVE for IIV.

Finally, we limited our simulation to strictly address conceptual issues of interpreting rVE with true changes in aVE, unrelated to biases. Potential biases in the estimation of aVE for eIV, from which rVE is derived, might also affect rVE. For example, aVE for eIV could be overestimated or underestimated depending on factors such as differential healthcare seeking behaviors between vaccinated and unvaccinated persons, or differential access to eIVs across populations with varying risk of influenza [30, 31]. For example, aVE for eIV could be underestimated if eIV is given preferentially to patients with potentially weaker immune response (eg, transplant patients, immunocompromised patients) and these differences in chronic medical conditions and immunocompromised status are not accounted for across the IIV and eIV comparator groups.

We showed that rVE is difficult to interpret when reported without contextual information and on its own is a potentially insufficient metric to measure and compare the benefits of eIVs. At the same time, rVE provides a useful way to quickly gauge the additional preventive benefit of an enhanced vaccine vs a standard one when no unvaccinated or placebo cohorts are available. Clinicians and public health agencies must take these limitations into account when interpreting studies, designing adequately powered clinical trials, and reporting study findings. With a decade of data on enhanced influenza vaccines to leverage, accurate interpretation of influenza vaccine effectiveness will be an important first step in capturing the public health potential of enhanced influenza vaccines.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

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