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# Influenza Vaccine Effectiveness: New Insights and Challenges

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Methods for assessing influenza vaccine efficacy and effectiveness have evolved over six decades. Randomized trials remain the gold standard for licensure, but observational studies are needed for annual assessment of vaccine effectiveness (VE). The test-negative design (TND) has become the de facto standard for these field studies. Patients who seek medical care with acute respiratory illness are tested for influenza, and VE is estimated from the odds of vaccination among influenza cases versus test-negative controls. VE varies across seasons, populations, age groups, and products, but VE estimates are consistently higher for A(H1N1) pdm09 and type B compared with A(H3N2). VE studies are increasingly used in combination with molecular epidemiology to understand the viral and immune system factors that drive clinical efficacy and effectiveness. The emerging field of immunoepidemiology offers the potential to understand complex host–virus interactions that affect vaccine protection, and this knowledge will contribute to universal vaccine development.

One of the earliest clinical trials of influenza vaccine efficacy was conducted in United States Army personnel in 1943 (Commission on Influenza 1944). More than 11,000 previously unvaccinated young men/trainees received bivalent vaccine including influenza virus types A and B. With febrile illness as the clinical end point, the attack rate was 2.2% in the vaccine group and 7.1% in the placebo group (69% efficacy). This was perhaps the first clear-cut evidence that influenza vaccine offered significant protection against illness during seasonal epidemics. Subsequent military studies in the 1950s continued to show vaccine protection, although many relied on serologic measures of infection that yielded biased results (Stuart-Harris 1957). Widespread vaccine use in civilian populations began in 1960 when the U.S. Public Health Service (USPHS) recommended annual vaccination of adults aged ≥65 yr, pregnant women, and those with chronic illness (Burney 1960). The impact was disappointing, and 4 years later a review of the program by USPHS leaders concluded, "there is little evidence that recent vaccines have significantly prevented clinical illness, as well as equally little evidence to evaluate effects on mortality" (Langmuir et al. 1964).

We now have a deeper understanding of influenza immunology and vaccine response, but many questions remain regarding vaccine efficacy and factors that affect the magnitude and

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duration of protection. Over the past two decades, there has been a tremendous increase in the number of field studies assessing influenza vaccine effectiveness. These studies have yielded new insights into factors that influence the magnitude and duration of vaccine protection. In this work, we review recent advances in methodology to assess influenza vaccine effectiveness and discuss key factors that influence vaccine effectiveness.

## EVALUATING INFLUENZA VACCINE EFFICACY AND EFFECTIVENESS

Influenza vaccine protection can be assessed by randomized controlled trials (efficacy) and observational field studies (effectiveness).

### Randomized Controlled Trials

Influenza vaccines are licensed based on demonstrated vaccine safety and efficacy from randomized controlled trials (RCTs). RCTs measure vaccine protection, or efficacy, under ideal circumstances. Vaccine allocation is usually double-blinded with placebo, and randomization minimizes bias. However, RCTs are expensive, not practical to conduct every season, and generally enroll healthy individuals. Additionally, placebo-controlled trials are considered unethical in populations for whom vaccine is recommended.

In a meta-analysis of RCTs using virus-confirmed laboratory end points from 1967 to 2011, pooled vaccine efficacy against any virus-confirmed influenza was 59% in adults aged 18–64 yr (Osterholm et al. 2012).

### Observational Studies

After licensure, field studies are used to provide information on vaccine effectiveness (VE) in real-world settings. VE is typically measured using nonrandomized observational studies in the community. Several observational study designs, including cohort and case–control studies, can be used (World Health Organization 2017).

### Study End Points

For any study design, the choice of the end point is important. Many twentieth century vaccine trials used the hemagglutination inhibition (HAI) test as a serologic marker to identify influenza infections. However, British investigators warned in 1955 that HAI yielded a biased estimate of vaccine protection because of an antibody ceiling effect: Vaccinated persons have a muted serologic response after influenza infection compared with unvaccinated persons (McDonald and Andrews 1955). This bias was confirmed decades later in a RCT that included both serologic and molecular diagnostic tests; only 23% of vaccinated participants with laboratory-confirmed influenza infections seroconverted versus 90% of placebo recipients (Petrie et al. 2011).

Nonlaboratory, syndrome-based end points such as administrative diagnosis codes, influenza-like illness (ILI), hospitalization, and mortality have also been used to estimate VE. However, use of nonspecific end points can magnify the effect of bias and confounding. For example, a 2002 meta-analysis concluded that influenza vaccine reduced all-cause mortality by 50% in older adults (Vu et al. 2002). This effect was implausible because influenza accounts for <10% of all-cause winter mortality in the elderly (Simonsen et al. 2007). Later studies showed that this apparent mortality benefit was the result of residual confounding and selection bias. Unvaccinated older adults were more frail and more likely to die compared with vaccinated older adults (Jackson et al. 2006; Simonsen et al. 2007; Baxter et al. 2010). VE against all-cause mortality was 4.6% in a later analysis that accounted for this selection bias (Fireman et al. 2009).

Over the past two decades, use of reverse-transcription polymerase chain reaction (RT-PCR) to detect influenza nucleic acids in respiratory samples has revolutionized influenza vaccine trials and field studies. RT-PCR detects specific nucleic acid sequences for each influenza type, subtype, and lineage with high sensitivity and specificity (Merckx et al. 2017). Studies using RT-PCR are less susceptible to bias com-

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pared with studies using nonspecific or serologic measures for case detection.

## Test-Negative Design

The availability of RT-PCR for laboratory confirmation of influenza stimulated novel approaches for evaluating VE. In 2005, Canadian investigators conducted a pilot VE study that was similar to a case–control design (Skowronski et al. 2005). This approach was used in 1980 to assess VE of pneumococcal vaccine (Broome et al. 1980). In the Canadian study, patients seeking care for ILI at sentinel surveillance sites were enrolled and respiratory swabs were tested for influenza by RT-PCR and viral culture. "Cases" were patients who tested positive for influenza, and "controls" were patients with a negative test result (noninfluenza respiratory illness). By calculating the age-adjusted odds ratio (aOR) for vaccination among influenza cases versus test-negative controls, they estimated VE to be 70% against influenza A.

Since that initial report, the test-negative design (TND) has become the de facto standard for routine assessment of influenza VE in North America, Europe, Australia, and elsewhere. Most TND studies have been conducted in outpatient settings, although studies have also addressed influenza-associated hospitalizations. VE estimates can be generalized to the entire study population as long as VE does not vary by health-care-seeking behavior (Jackson and Nelson 2013). However, VE against medically attended influenza may overestimate VE against symptomatic influenza if vaccination reduces both influenza severity and the probability of seeking care for ILI (Ainslie et al. 2017).

The target population for enrollment in TND studies includes patients who seek medical care for a prespecified set of symptoms representing acute respiratory illness. Selection bias can be introduced when testing criteria are based on clinician preference rather than study protocol or standard clinical criteria. Screening based on specific symptom criteria is essential to minimize potential bias due to differences in severity between vaccinated and unvaccinated individuals. The specific criteria vary across studies. Screening occurs in a variety of outpatient settings and may be performed by sentinel providers or dedicated research staff. Respiratory samples should include a midturbinate nasal swab, and some studies combine this with a throat swab for increased sensitivity of influenza detection (de la Tabla et al. 2010).

Vaccination status is a critical exposure variable for TND studies, and misclassification can lead to biased estimates. Misclassification of vaccination status is likely to be nondifferential. The TND avoids differential recall bias of vaccination status between influenza cases and controls because case status is unknown at the time of recruitment. Methods for ascertaining vaccination status vary widely, but vaccine receipt and dates should be confirmed by medical records whenever possible. Self-report is generally accurate and can be used for adult patients when records are not accessible (Laurence et al. 2016; King et al. 2018). Most studies exclude patients who were vaccinated <14 d before enrollment (or illness onset) because the antibody response is incomplete during that period. Patients vaccinated <14 d before enrollment should not be included as unvaccinated because they may have partial protection from an evolving antibody response.

VE is calculated in a regression model using the aOR for vaccination among influenza cases versus test-negative controls:

$$\mathrm{VE} = 100\% \times (1 - \mathrm{aOR}).$$

All models should adjust for age a priori, because both influenza risk and probability of vaccination vary across age groups. Other model covariates vary substantially across studies, but age, high-risk status, and calendar time should be routinely collected and assessed (Sullivan et al. 2016). The World Health Organization (WHO) recommends a "change in estimate" approach to identify confounders for inclusion in the model (World Health Organization 2017). With this approach, a covariate is included in the final model if it changes the unadjusted VE by a prespecified amount (typically 10%).

Data from different studies may be pooled in some circumstances to provide a larger sample

size and more precise effect estimates. However, pooling data from different studies and seasons poses serious challenges because of differences in population characteristics, vaccine coverage, enrollment criteria, vaccine composition, and product types, among other factors.

In simulation studies, the TND yields a valid VE estimate in most scenarios (Orenstein et al. 2007; Foppa et al. 2013; Jackson and Nelson 2013; Haber et al. 2015). A major advantage of the TND over other observational study designs is the reduced misclassification of influenza infection status and reduced confounding caused by differences in health-care-seeking behavior. The validity of the TND design relies on the assumption that influenza vaccination does not modify the risk of noninfluenza respiratory illness. The vaccine antibody response is specific to influenza, and VE estimates are not biased by selection of "influenza negative" versus "other virus positive" patients as the comparison group (Sundaram et al. 2013; Pierse et al. 2016; Feng et al. 2018). This assumption was further supported by reanalysis of a randomized, placebo-controlled trial of live attenuated influenza vaccine (LAIV). The original trial results were compared with the TND approach and found to be nearly identical with similar precision (De Serres et al. 2013).

Bias can occur if disease or symptom severity is associated with vaccination status, and symptom severity is different for influenza cases and test-negative participants (Ainslie et al. 2017; Lewnard et al. 2018). The TND has other potential sources of bias that may be important. One such bias occurs if those most susceptible (i.e., unvaccinated) will be infected sooner than those with some protection from vaccination (Lipsitch et al. 2016; Lewnard et al. 2018). This effect becomes more pronounced as the season progresses. As a result, VE estimates obtained early to midseason may be less susceptible to this bias. Additional sources of bias in estimating VE using TND studies have been discussed in depth elsewhere (Lipsitch et al. 2016; Sullivan et al. 2016; Lewnard et al. 2018).

Despite its limitations, TND studies provide new and timely information on influenza vaccine protection in different populations and seasons. Results have been used by health-care providers, national vaccine programs, and policymakers. Annual VE estimates contribute to models that assess the impact of vaccination on disease burden (e.g., cases averted) and health-care expenditures.

## ESTIMATES OF VE BY INFLUENZA TYPES AND SUBTYPES

There is substantial variation in VE across influenza subtypes and lineages. A meta-analysis of TND studies published between 2004 and early 2015 found highest VE against A(H1N1)pdm09 and type B and lowest against A(H3N2) (Belongia et al. 2016).

### VE against A(H1N1)

Pooled VE against A(H1N1)pdm09 was 67% with low heterogeneity between estimates between 2009 and 2015 (Belongia et al. 2016). However, VE against A(H1N1)pdm09 in Canada, Europe, and the United States was low (43%, 33%, and 45%, respectively) in 2015–2016 compared with prior postpandemic seasons in each region (Jackson et al. 2017; Skowronski et al. 2017b; Kissling et al. 2018). The lower VE against A(H1N1)pdm09 was attributed to emergence of a genetic variant (6B.1), and this led to an update of the A(H1N1) vaccine component for the first time since the pandemic virus emerged (see who.int/influenza/vaccines/virus/recommendations/2017_south/en/). During 2018–2019, the observed 44% VE against A(H1N1)pdm09 in the United States was lower than the pooled estimate from the meta-analysis (67%) (Flannery et al. 2019b), whereas the 69% VE observed in Canada was similar to previous estimates (see bccdc.ca/health-info/diseases-conditions/influenza/sentinel-network-spsn).

### VE against A(H3N2)

VE against A(H3N2) is consistently lower than A(H1N1)pdm09 and type B, with high heterogeneity across populations and seasons. Pooled VE against A(H3N2) was 33% in TND studies published before early 2015, and only slightly

lower in seasons in which the predominant circulating A(H3N2) viruses were considered antigenically distinct (23%) versus antigenically similar (33%) from the vaccine strain (Belongia et al. 2016). More recently, the ability to rapidly sequence influenza viruses has allowed VE estimates by genetic group. Clade-specific VE estimates have shown differences based on genetic similarity to the A(H3N2) vaccine strain. In 2014–2015, studies in North America found that seasonal vaccines were moderately effective against the antigenically similar A(H3N2) clade 3C.3b viruses (VE 44% and 52%), but not against infections caused by clade 3C.2a viruses (1% and −13%) (Flannery et al. 2016; Skowronski et al. 2016). The same pattern was seen again in the United States during 2018–2019; VE against infections caused by the vaccine clade (3C.2a1) virus was 46%, but only 5% against clade 3C.3a viruses (Flannery et al. 2019b).

### VE against Type B

In the meta-analysis, pooled VE against type B was 54% and estimates were generally similar across studies (Belongia et al. 2016). Lineage-specific VE estimates were infrequently reported before 2015, and it was not possible to assess lineage-specific protection. However, an eight-season analysis of lineage-specific data from Canada's Sentinel Practitioner Surveillance Network found VE against type B exceeded 50% regardless of vaccine lineage match with circulating viruses, except when the type B vaccine strain was unchanged from the previous season (Skowronski et al. 2019a). Cross-lineage protection has been observed in multiple studies, but it is not consistent in all seasons and the magnitude of cross-lineage protection varied (Skowronski et al. 2014; McLean et al. 2015; Flannery et al. 2019a).

## VIRUS FACTORS THAT INFLUENCE VE

### Mismatch between Vaccine Strain and Circulating Viruses

Antigenic drift is a well-documented factor that reduces vaccine protection, and contributes to VE variation across and within virus subtypes and lineages. This is a particular concern for A(H3N2) viruses, which have a higher rate of antigenic evolution compared with A(H1N1) or B (Neher et al. 2016). When circulating viruses do not match the vaccine strain, vaccination provides little to no protection (Flannery et al. 2016, 2019b; Skowronski et al. 2016). Optimal vaccine strain selection is challenging because the decision must be made 6–8 mo in advance of vaccine distribution. Recently developed phylodynamic prediction models using global surveillance data have the potential to improve strain selection (and subsequently VE) by identifying virus clades likely to predominate in the future (Morris et al. 2018). VE estimates by genetic clade are becoming more common, and will enhance our understanding of virus genetic evolution and clinical protection.

### Egg-Induced Mutations in Vaccine Strains

Influenza vaccine strains have been grown in embryonated chicken eggs since the 1940s, and most inactivated influenza vaccines (IIVs) are still manufactured in eggs. In recent years, evidence has emerged that egg passage generates strong selection pressure for antigenically important mutations in A(H3N2) viruses (Chen et al. 2019). During 2012–2013, low VE in Canada was attributed to specific egg-induced mutations in the A(H3N2) vaccine strain (Skowronski et al. 2014). During 2016–2017, the egg-adapted A(H3N2) vaccine strain lost a glycosylation site that contributed to low VE against A(H3N2) in the United States (Zost et al. 2017; Flannery et al. 2019a). Further evidence for a link between egg adaptation and reduced VE is provided by an ecologic analysis showing a significant negative correlation between vaccine virus egg adaptation and A(H3N2) VE from 2010–2015 (Chen et al. 2019).

## HOST FACTORS THAT INFLUENCE VE

### Repeated Vaccination Effects

The effect of prior influenza vaccination history on influenza VE was first noted during a series of outbreaks at a British boarding school in the

1970s. Cumulative attack rates across three outbreaks were similar among boys vaccinated before each outbreak and boys who were unvaccinated throughout the study period, suggesting repeat vaccination did not provide any long-term advantage (Hoskins et al. 1979). In the 1980s, a five-season clinical trial found no consistent patterns with regard to repeat vaccination and VE (Keitel et al. 1997; Beyer et al. 1999). However, this study has been criticized because some repeat vaccinees were not randomized, and the primary clinical end point included serologic measures of infection, a recognized source of bias (Belongia et al. 2017). During the 1987–1988 study season, virus-confirmed infections were more likely with increasing number of vaccine doses received. During the same season, the postvaccination A(H3N2) antibody titers were inversely related to the number of prior vaccines received. These findings supported a negative effect from repeated vaccination during that season even though the five-season analysis did not identify repeat vaccination effects.

The antigenic distance hypothesis was first proposed in 1999 to explain the mechanism of repeat vaccination effects on VE (Smith et al. 1999). It was derived from a simulation model showing that VE is influenced by the antigenic relationships between past vaccine strain, current vaccine strain, and circulating strains. The model predicts negative interference (or negative antigenic interaction) between current and prior season vaccination when the antigenic distance between sequential vaccine strains is small. However, the model predicts how VE varies based on these antigenic relationships, but it does not predict absolute vaccine efficacy. It does not account for age cohort effects, prior influenza infections, or vaccinations received over multiple prior seasons.

The antigenic distance hypothesis provides a simple and useful framework to understand antigenic interactions, but model predictions have not been consistently supported by VE studies that evaluated current and prior season vaccination. Results from meta-analyses and subsequent analyses of data from multiple seasons have shown substantial heterogeneity in repeat vaccination effects by season and subtype (Belongia et al. 2017; Cheng et al. 2017; Martínez-Baz et al. 2017; Saito et al. 2017; Skowronski et al. 2017a; Valenciano et al. 2018; Nichols et al. 2019; Ramsay et al. 2019).

The effect of prior vaccination history is most pronounced (and variable) for VE against A(H3N2). In general, VE against A(H3N2) is highest among those vaccinated in the current season only and lower among those vaccinated in both the current and prior seasons, although this pattern is not consistent (Belongia et al. 2017; Skowronski et al. 2017a; Valenciano et al. 2018; Nichols et al. 2019; Ramsay et al. 2019). For A(H1N1)pdm09 and type B infections, VE is generally similar regardless of prior season vaccination status. In some seasons, residual protection from prior season vaccination has been observed for type B.

It is difficult to measure individual vaccination patterns over multiple seasons, and relatively few studies have examined the effect of historical vaccination patterns on current season vaccine response. These studies suggest an inverse relationship between number of prior doses and VE (McLean et al. 2014; Skowronski et al. 2016; Martínez-Baz et al. 2017; Saito et al. 2018). This is consistent with immunogenicity studies that also show an inverse relationship between prior vaccine doses and A(H3N2) vaccine response (Mosterín Hopping et al. 2016; Thompson et al. 2016).

Studies of prior vaccination history are likely influenced by bias. Individuals who are repeatedly vaccinated are different from those who habitually never get vaccinated or receive vaccine only sporadically. This can introduce bias that is difficult to measure and adjust for in the analysis. These differences and changes in vaccination habit may be correlated with risk of acquiring influenza. Standard methods used to estimate VE in TND may be inadequate to control the bias associated with prior exposure history (Sullivan et al. 2016). Vaccination history is increasingly captured in VE studies, but prior history of infection is also important but extremely difficult to ascertain. The effect of prior infection history within a given season may be small but could potentially be significant over

several seasons (Cheng et al. 2017). Finally, pooling of data across seasons to increase sample size may mask important variability and magnitude of the effects of repeat vaccination (Belongia et al. 2017; Skowronski and Chambers 2017).

### Imprinting and Cohort Effects

VE studies on prior vaccination history highlight the importance of past influenza exposure on VE. The impact of the first influenza infection on subsequent VE is an area of growing interest and may explain variations in age-specific VE estimates. The concept that the first influenza infection "imprints" itself on subsequent immune responses to influenza exposure was first described as "original antigenic sin" in 1960 (Francis 1960). The doctrine described differences in patterns of antibody response across age groups, with vaccine response biased toward viruses encountered early in childhood (Francis 1960; Monto et al. 2017). More recently, differences in birth year–specific risk of infection during seasonal influenza epidemics and pandemics have been attributed to "immune imprinting," defined as the effects of early influenza virus infection on immune responses to influenza viruses encountered later in life (Gostic et al. 2019).

It is challenging to study imprinting effects in the context of TND VE studies. Most VE studies are not large enough to estimate age-specific VE by subtype/lineage in every season and most have limited power to distinguish differences in VE across age groups and birth cohorts. Birth cohort effects are difficult to assess because birth year is an imprecise surrogate for imprinting subtype and epitope specificity.

Studies of imprinting effects on VE are limited, but some have reported differences in VE across birth cohorts. During 2015–2016, when the A(H1N1)pdm09 genetic group 6B.1 emerged in North America, analysis by birth year suggested that VE could be modified by early life exposure to specific influenza viruses (Skowronski et al. 2017b; Flannery et al. 2018). Although 6B.1 viruses were antigenically similar to the A/California/07/2009 reference virus based on HAI, the addition of a glycosylation site may have reduced or blocked antibody binding, resulting in reduced VE among groups with dominant antibody responses to the specific binding site (Flannery et al. 2018). Separate analyses of data from surveillance and VE studies suggests that risk of seasonal subtype-specific infection is shaped by differences in childhood imprinting at the subtype level (Arevalo et al. 2019; Gostic et al. 2019). A model of medically attended influenza patterns in the Marshfield Clinic VE study population found that primary infection in childhood appears to reduce the risk of medically attended illness with the same subtype throughout life (Arevalo et al. 2019). The effect was stronger for A(H1N1) compared with A(H3N2), and VE was influenced by both age and birth year in this model. However, the effects are complex- and strain- (vs. subtype-) specific (Arevalo et al. 2019). In addition, relatively little is known about the cumulative effect of lifetime exposures on adaptive immunity (e.g., antibody landscape) (Lessler et al. 2012; Fonville et al. 2014). Finally, one study has suggested that imprinting could have contributed to negative VE for A(H3N2) (i.e., increased risk in vaccinated individuals) among adults aged 35–54 yr during 2018–2019 in Canada, but this remains controversial (Skowronski et al. 2019b). The immunologic mechanism for increased influenza risk after vaccination remains unexplained, and the age-stratified VE estimates had low precision because of the small number of cases. It will be important to validate these findings in other VE studies.

## WANING

Waning of vaccine protection during a single season has been reported in multiple studies. A meta-analysis of TND studies conducted before July 2017 found VE was significantly lower 91–180 d versus 15–90 d after vaccination, with the magnitude of decline more pronounced for A(H3N2) and B than A(H1N1) (Young et al. 2018). During the 2007–2008 season, increased risk of A(H3N2) infection with increasing time since vaccination was only seen in young children and older adults (Belongia et al. 2015).

There was moderate decline in VE during the same season when data from a RCT of healthy working-aged adults were reanalyzed by time since vaccination (Petrie et al. 2016). In this trial that directly compared clinical efficacy and HAI titers over one season, the rate of VE waning was generally consistent with the rate of antibody decay (Petrie et al. 2016). For A(H1N1)pdm09, antibody decay increased with repeated vaccination, although the antibody half-life exceeded the length of a typical influenza season among persons with repeated vaccination (Zelner et al. 2019).

When waning is observed in observational studies, it is difficult to determine how much is attributable to artifact versus a real decline in vaccine protection. Multiple other factors may contribute to apparent waning. For example, VE may be lower later in the season as a result of virus evolution and antigenic drift. Changes in the at-risk population between early and late season can also provide the appearance of waning in the absence of a true effect. VE estimates decline over time because of misclassification of immune status; unvaccinated individuals become infected and exit the "at-risk" population at a higher rate than vaccinated individuals. This is an expected source of bias from a "leaky" vaccine, and the effect increases as the season progresses (Farrington 1992; Lipsitch 2019). This bias is amplified by low VE, as is often the case for A(H3N2) (Lewnard et al. 2018). Finally, differences in VE across subgroups (such as age groups) may contribute to time-varying VE for the entire population because the most susceptible individuals will have a higher likelihood of early infection (Durham et al. 1998).

Interpretation of waning effects is complicated by variation in timing of vaccination from year to year, host susceptibility differences between individuals who choose to get vaccinated early versus late, and variation in virus strains within and between seasons. Some of these challenges were addressed in a seven-season retrospective study at Kaiser Permanente Northern California (Ray et al. 2019). In an analysis of vaccinated members who had a subsequent RT-PCR test for influenza and RSV, the odds of testing positive for influenza increased by ~16% for each additional 28 d since vaccination. Time since vaccination was not associated with RSV positivity. However, these results could still represent a "leaky vaccine" (i.e., conferring partial protection) effect rather than true waning of protection (Ferdinands et al. 2019).

## ASSESSING VE FOR SPECIFIC VACCINE PRODUCTS

The number of different types of influenza vaccines have increased significantly in recent years, including enhanced vaccines, which are designed to increase immune response, and cell-based vaccines. Product-specific efficacy has been reported from prelicensure trials, including trials using standard IIV as a comparison group. However, few studies have performed head-to-head comparisons or relative efficacy/effectiveness of one product versus another. Most comparison studies are limited by use of nonspecific outcomes rather than laboratory-confirmed outcomes.

### Adjuvanted IIV

Several observational studies have reported greater effectiveness of MF59-adjuvanted IIV compared with standard IIV (Domnich et al. 2017). In Italy, relative effectiveness of adjuvanted vaccine among adults aged ≥65 yr was 25% for preventing hospitalization due to pneumonia and influenza during three seasons (2006–2007 through 2008–2009) (Mannino et al. 2012), whereas relative effectiveness in Canada was 63% against laboratory-confirmed influenza in 2011–2012 (Van Buynder et al. 2013).

### High-Dose IIV

There is a large body of evidence supporting greater effectiveness of high-dose versus standard IIV in older adults, particularly those aged ≥85 yr (Richardson et al. 2015; Lee et al. 2018; Lu et al. 2019). However, the magnitude of this benefit varies across seasons, age groups, and clinical end points. In a large RCT, relative efficacy of high-dose versus standard IIV against

laboratory-confirmed influenza was 24% during two A(H3N2) predominant seasons (2011–2012 and 2012–2013) (DiazGranados et al. 2014). Against influenza-related hospitalizations, relative effectiveness ranged from a non-significant 5% to significant 25% (Richardson et al. 2015; Young-Xu et al. 2018; Lu et al. 2019). In a pragmatic cluster-randomized trial, nursing home facilities that received high-dose IIV had fewer respiratory-related hospitalizations in 2013–2014 than facilities that received standard dose (relative VE 12%, 95% CI 2–22) (Gravenstein et al. 2017). Additionally, a retrospective study comparing high-dose versus adjuvanted vaccine in older adults using claims data found relative VE of 12% for the 2016–2017 and 2017–2018 seasons (van Aalst et al. 2019).

### Recombinant Influenza Vaccine (RIV)

Relative efficacy of RIV versus standard IIV has been assessed in one RCT. Relative efficacy against laboratory-confirmed influenza A was 36% among those aged ≥50 yr during 2014–2015 (Dunkle et al. 2017). Although antigenic testing was not conducted, the 2014–2015 season was characterized as an A(H3N2)-dominated season, in which the majority of A(H3N2) viruses were considered antigenically drifted from the vaccine virus in the United States (Flannery et al. 2016).

### Cell-Culture-Based IIVs

In 2017–2018, a study using Medicare administrative data found cell-culture-based IIV (ccIIV) was modestly more effective against influenza-related office visits (relative VE 11%, 95% confidence interval [CI] 8%–14%) and influenza-related hospitalizations (relative VE 10%, 95% CI 7%–13%) than standard IIV among adults aged ≥65 yr (Izurieta et al. 2019). In contrast, two other studies conducted during the same season that included both children and adults did not find significant benefit of ccIIV over standard IIV against laboratory-confirmed influenza or influenza-related hospitalization (Bruxvoort et al. 2019; DeMarcus et al. 2019). Differences across studies are likely due to differences in study designs and populations.

### Challenges of Conducting Studies of Relative Effectiveness

The number of vaccine products limits the number of direct comparisons that can be performed. The increasing number of enhanced vaccines creates challenges for determining which product(s), if any, should be preferentially recommended for use. Large sample sizes are needed to detect significant differences between products, and observational studies are uninformative if products of interest are not used in the target population. As use increases, there will be additional challenges in generalizability as vaccine formulations (trivalent to quadrivalent, egg-based to cell culture-based virus, etc.), circulating viruses, and types available continue to change each year and/or differ by populations. New sources of bias and error may occur in comparative VE studies. For example, confounding by indication may occur if vaccine product selection is related to the risk of outpatient or hospitalized influenza. Alternative study designs, such as cluster-randomized trials, may be needed to assess VE when there is great potential for bias and confounding. Evidence to inform policy decisions will depend on multiple studies in different populations, with consistent results, over several seasons (Flannery and Fry 2019).

## CONCLUSIONS

Influenza vaccines have been in use for more than 60 years. Methods for assessing vaccine efficacy and effectiveness have evolved and improved during that time, but challenges remain. Unlike other vaccines, influenza VE is a moving target. Influenza viruses continue to evolve, vaccine strains are routinely updated, the immune profile of the population changes, and new vaccine products are being developed with the potential to generate enhanced protection. The use of TND to estimate influenza VE has allowed systematic assessment of VE each season in several regions. This has highlighted important dif-

ferences across subtypes and increased our understanding of VE variation across time and in different populations. The TND will continue to serve as a key strategy for annual VE assessment in different populations, and there will be increasing need for studies that compare the relative effectiveness of different products as the science evolves. These studies will generate valuable information for policy-makers, public health agencies, and vaccine manufacturers.

VE studies also contribute to the emerging field of immunoepidemiology. Multiple approaches, including prospective cohort studies and clinical trials, are needed to understand the complex host–virus interactions that influence vaccine protection. This knowledge will contribute to more effective seasonal vaccines with the ultimate goal of a universal influenza vaccine.

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