Influenza (Flu)

How Flu Vaccine Effectiveness and Efficacy are Measured

Questions & Answers

Español

How do we measure how well influenza vaccines work?

Two general types of studies are used to determine how well influenza vaccines work: randomized controlled trials and observational studies. These study designs are described below.

Randomized controlled trials (RCTs)

The first type of study design is called randomized controlled trial (RCT). In a RCT, participants are randomly assigned to receive a vaccine or a control product (e.g., a shot of saline). Vaccine efficacy is measured by comparing the frequency of influenza illness in the vaccinated and the unvaccinated (placebo) groups. An RCT study design minimizes bias that could lead to invalid study results. Bias is an unintended systematic error in the way researchers select study participants, measure outcomes, or analyze data that can lead to inaccurate results. In a RCT, vaccine allocation is usually double-blinded, which means neither the participants nor the researchers know who has or has not received vaccine or placebo. Randomized controlled trials are required for Food and Drug Administration (FDA) in the United States, require RCTs to be conducted and to demonstrate protective benefit of a new vaccine before the vaccine is licensed for routine use. However, some vaccines are licensed based on RCTs that use antibody response to vaccine as a proxy for protection in laboratory, rather than decreases in influenza disease among people who were vaccinated.

Observational Studies

The second type of study design is an observational study. There are several types of observational studies, including cohort studies and case-control studies. Observational studies assess how influenza vaccines work by comparing the occurrence of influenza among people who have been vaccinated compared to people not vaccinated. Vaccine effectiveness is the percent reduction in the frequency of influenza illness among vaccinated people compared to unvaccinated people. Observational studies can also assess other factors (like presence of chronic medical conditions) that are related to both influenza illness and vaccination. (See below for details.)

Top of Page

How do vaccine effectiveness studies differ from vaccine efficacy studies?

Vaccine efficacy refers to vaccine protection measured in RCTs usually under optimal conditions where vaccine storage and delivery are monitored and participants are usually healthy. Vaccine effectiveness refers to vaccine protection measured in observational studies that include people with underlying medical conditions who have received vaccines by different health care providers under real-world conditions.

Data on influenza vaccine have been formed by FDA, recommendations are typically made by CDC's Advisory Committee for Immunization Practices (ACIP) for its routine use. For example, ACIP now recommends annual influenza vaccination for all U.S. residents aged six months and older. These universal vaccine recommendations are based on prior pre-licensure placebo-controlled RCTs because assigning people to a placebo group could place them at risk for serious complications from influenza. Also, observational studies have been used to compare vaccine effectiveness against less severe, less common influenza outcomes, such as hospitalization.

Top of Page

What factors can affect the results of influenza vaccine efficacy and effectiveness studies?

The measurement of influenza vaccine efficacy and effectiveness can be affected by virus and host factors as well as the study methodology used. Therefore, vaccine efficacy/effectiveness point estimates have varied among published studies.

Virus factors

The protective benefits of influenza vaccination are generally lower during flu seasons where the majority of circulating influenza viruses differ from the influenza viruses used to make the vaccine. Influenza viruses are continually changing through a natural process known as antigenic drift. (For more information, see How the flu virus can change: Drift and Shift.) However, the degree of antigenic drift can vary from season to season. Influenza viruses that are the most different from the three or four viruses included in the seasonal flu vaccine. So even when circulating influenza viruses are mildly or moderately drifted in comparison to the vaccine, it is possible that some of the circulating influenza viruses will be inactivated by vaccination, and if other circulating influenza viruses are well matched, the vaccine could still provide protective benefit overall.

Host factors

In addition to virus factors, host factors such as age, underlying medical conditions, history of prior infections and prior vaccinations can affect the benefits received from vaccination.

Study Design Factors

Experts consider RCTs to be the best study design because they are less susceptible to biases. However, as stated above, these studies cannot be conducted when vaccination is recommended in a population and their results may not be easily applied to conduct for more severe outcomes that are less common. There are several observational study designs, but many programs currently use the test-negative, case-control study design to measure vaccine effectiveness against medically-attended acute respiratory illness are enrolled at ambulatory care settings (such as outpatient clinics, urgent care clinics, and emergency departments) and are tested for influenza virus infection using molecular assays. Participants with illness who are tested for influenza using a highly specific and sensitive assay for influenza virus infection, such as reverse transcription polymerase chain reaction (RT-PCR), are tested for vaccinated to unvaccinated persons (i.e., the odds of influenza vaccination is then compared for patients with and without laboratory-confirmed influenza). Vaccine effectiveness design remains selection bias due to health-care seeking behaviors. In addition to the test-negative design, there are additional observational study designs that have been used to estimate vaccine effectiveness.

Factors Related to Measuring Specific versus Non-Specific Outcomes

For both RCTs and observational studies, the specificity of the outcome measured in the study is important. Non-specific outcomes, such as pneumonia hospitalizations or all-cause illness (ILI) can be associated with influenza virus infections as well as infections with other viruses and bacteria. Vaccine efficacy/effectiveness estimates against non-specific outcomes are generally lower, depending on what proportion of the non-specific outcome is caused by influenza. For example, a study among healthy adults found that the inactivated influenza vaccine (i.e., the flu shot) was 86% effective against laboratory-confirmed influenza, but only 10% effective against all-cause respiratory illness in the same population and season.[1] Laboratory-confirmed influenza virus infections, by RT-PCR or viral culture, are generally the specific outcomes for vaccine efficacy/effectiveness studies.

Serologic assays to detect influenza infection (i.e., which require a four-fold rise in antibody titers against influenza viruses between blood samples taken 21 days apart) are not specific for influenza virus infection because they require two blood tests, such as RT-PCR, becoming widely available. The problem with this method is that even if a four-fold rise in influenza infection, is that vaccination elevates antibody levels, similar to infection. New influenza infections could be missed or is vaccinated person since antibodies are already high and a four-fold increase doesn't develop. Therefore, serologic testing methods can result in biased VE estimates that inflate VE.

Top of Page

Can you describe biases that are important to consider for observational studies measuring vaccine effectiveness?

Observational studies are subject to various forms of bias (see glossary for definition) more so than RCT studies. Therefore, it is important that bias be minimized and the study design or adjusted for in the analysis. Observational studies of influenza vaccine effectiveness can be subject to three forms of bias: confounding, selection bias, and information bias.

Confounding occurs when the probability of the risk of the outcome being measured (e.g., influenza-related hospitalizations confirmed by RT-PCR) is distorted by another factor associated both with vaccination (the exposure) and the outcome. In RCTs, confounding factors are expected to be evenly distributed between vaccine and control groups. This is not true of observational studies. For example, chronic medical conditions can confound the association between influenza vaccination and influenza in observational studies. Chronic medical conditions increase the risk of influenza-related hospitalization and vaccination coverage often is higher among people with chronic medical conditions. Thus, chronic medical conditions are associated with both influenza vaccination and the confounding factor that should be considered in study design or in the analysis. For example if chronic medical conditions increase the risk of influenza-related hospitalizations and vaccination coverage is higher among people with chronic medical conditions, and therefore, they are more likely to be vaccinated, a chronic medical condition is related to the outcome and adjusting for confounders could bias the vaccine effectiveness estimate away from the true estimate. In the example given, the specific outcome for vaccine efficacy would be biased lower, or toward the null.

Selection bias occurs when people with the outcome being measured by the study (i.e., influenza infection) differ from people who do not have the outcome. In observational studies of influenza vaccine effectiveness, people who are sick without influenza may have different likelihoods of being vaccinated, and this can bias the estimate of vaccine effectiveness. For example, people who visit their health care provider in outpatient clinics, urgent care clinics, and urgent care are more likely to be vaccinated than people who do not go to a provider for care. If controls are selected from a different population than the cases (e.g., people who are free of influenza from the community rather than people who have been seeking behaviors, selection bias related to health care seeking (and the likelihood to be vaccinated) may be introduced. For example, if people who are more likely to be vaccinated are also more likely to seek care for influenza, and controls are selected for a respiratory illness. This study design is only truly valid if controls are selected from the same population that produced vaccine effectiveness.

Information bias occurs if inaccurate or outcome information is used from different sources of information for people with and without the disease of interest. For example, if researchers obtain information on vaccination for children with influenza from immunization records but are unable to obtain information if the child was vaccinated, this difference in data collection procedures could bias the results of the study.

Top of Page

How well do influenza vaccines work during seasons in which the flu vaccine is not well matched to circulating influenza viruses?

As described above, when the virus components of the flu vaccine are not well matched with circulating influenza viruses, the benefit of influenza vaccination may be reduced. However, the degree of antigenic drift between circulating influenza viruses and the proportion of circulating drifted viruses can vary. As a result, even when circulating influenza viruses are mildly or moderately drifted in comparison to the vaccine, it is possible that some of the circulating influenza viruses will be inactivated from influenza vaccination. In addition, even when some circulating influenza viruses are significantly drifted, it is possible for other influenza viruses to circulate in the community to be well matched to the vaccine. It is possible to have both a mismatch and circulating strains that are matched in advance of the influenza season, nor is it possible to predict how this match may affect vaccine effectiveness.

Top of Page

What is the evidence that influenza vaccines work?

Adults 65 years or older

Among older adults, virus-inactivated vaccination was recommended based on the high burden of influenza-related complications and hospitalizations among older adults. One RCT of adults aged 60 years and older relied on serology for confirmation of influenza and reported a vaccine efficacy of 58% against influenza-like illness (ILI).[2] However, it is unknown if infections were missed by serology among the study participants that were vaccinated (and if the vaccine efficacy estimate is biased upwards – see previous discussion of how bias can occur in VE studies that use tests for influenza using serology). A meta-analysis of observational studies that used the test-negative design provided VE estimates for adults aged >65 years against RT-PCR confirmed influenza infection. This meta-analysis reported vaccine effectiveness of 52% (95% CI: 41-61) during seasons when the vaccine and circulating viruses were well matched and 30% (95% CI: 19-39) when the vaccine and circulating viruses were poorly matched, reported VE was 36% (95% CI: 29-42) overall.[3]

An RCT that compared a high-dose, inactivated influenza vaccine (containing four times the standard amount of influenza antigen) to standard dose vaccine in persons aged 65 years or older during the 2011-12 and 2012-13 influenza seasons found the high-dose vaccine was more effective than the standard dose (RR = 0.76; 95% CI: 0.70-0.83) among participants who received the vaccine compared to standard dose influenza vaccine, indicating that high-dose vaccine provided 24% better protection against influenza than standard dose vaccine in the trial.[4]

Several observational studies have reported significant vaccine effectiveness against RT-PCR confirmed influenza-related hospitalizations among adults aged 65 years and older. One test-negative, case-control study among Canadian adults aged 65 years and older reported VE against influenza-related hospitalizations of 52% (95% CI: 41-61) in an analysis of two additional seasons, including 2010-11 and 2011-2012 (excluding 2009-10). VE was 58% (95% CI: 8-81) against RT-PCR confirmed influenza-associated hospitalizations for persons <50 years of age for the five seasons combined.[5]

Adults

Several RCTs have been done in healthy adults aged <65 years[6,7,8,9,10,11,12]. These studies have reported vaccine efficacy estimates ranging from 16% -79%. VE was reported during a season when the vaccine and circulating influenza A(H1N1) virus in South Africa among HIV infected adults reported vaccine efficacy of 74% (95 CI: 9-96).[13] A meta-analysis that included data from RCTs of licensed inactivated influenza vaccine in healthy adults reported a pooled estimate of 59% (95 CI: 51-67) against influenza confirmed by RT-PCR or viral culture.[14] In addition, RCTs of cell-based inactivated influenza vaccines (IIVs) and recombinant influenza HA protein vaccine have been performed among healthy adults aged <65 years. Pooled estimates for these types of vaccines are similar to other inactivated influenza vaccines that are egg-based.[15,16,17]

Children

In a four-year RCT of inactivated vaccine among children aged 1-15 years, vaccine efficacy was estimated at 73% against influenza A (H3N2) and 91% against influenza A (H1N1) virus infection.[18] An RCT of children aged 6-24 months reported vaccine efficacy of 66% against laboratory-confirmed influenza in 1999-2000 but no protection in 2000-2001 when the strain was little antigenically drifted.[19] During 2010-11, the vaccine efficacy of a quadrivalent inactivated vaccine against influenza A (H1N1), A (H3N2), B/Yamagata, and B/Victoria was 59% against laboratory-confirmed influenza in children 6 months to 8 years. Among children aged 6 months -11 years with high-risk medical conditions, vaccine efficacy was 57% (95% CI: 18-77) against influenza A (H1N1) and 69% (95% CI: 19-89) against influenza A (H3N2), including a 58% reduction (95% CI: 5-81) in confirmed influenza A (H3N2) among those who received the vaccine and the "indirect" effect of influenza vaccination on prevention on disease transmission.[21]

Several RCTs of live attenuated influenza vaccine among young children have demonstrated vaccine efficacy against laboratory-confirmed influenza with estimates ranging from 74%-94%.[22,23,24,25]. A study conducted among children aged 12 through 36 months living in Asia during consecutive influenza seasons reported efficacy for live attenuated influenza vaccine of 64%-79%.[26].

Pregnant women

An RCT conducted among pregnant women in South Africa during 2011 and 2012 reported vaccine efficacy against RT-PCR confirmed influenza of 50% among HIV-negative women and 58% among HIV-positive women vaccinated during the third trimester.[27]. In addition, the trial showed that maternal immunization provided evidence of laboratory-confirmed influenza among infants born to HIV-negative women by 69%. the study was unable to assess vaccine efficacy among infants of HIV infected women. An observational study in the United States during 2010-11 and 2011-12 using a test-negative design reported vaccine effectiveness of 64% (95% CI: 5 to 67) against influenza among pregnant women[28].

A randomized trial in Bangladesh found that the offer of flu shots to mothers vaccinated during pregnancy and breastfed inactivated influenza vaccines were significantly less likely to be born small for gestational age and weighed an average of 200g more than babies born to unvaccinated mothers[29]. No effect on maternal hemoglobin concentration or anemia was reported in the South African trial described above. Some observational studies evaluating the association and developing countries have found lower risk of preterm birth and low birth weight in babies born to vaccinated mothers, but the effect has not been consistently demonstrated[31,32,33,34,35].

Top of Page

How well does the live attenuated influenza vaccine (LAIV) work compared to inactivated influenza vaccine (IIV)?

Children

Three randomized clinical trials comparing live attenuated influenza vaccine to trivalent inactivated influenza vaccine in young children, 2-8 years of age, have reported live influenza vaccine had superior efficacy compared to inactivated influenza vaccine[36,37,38]. Recently, several observational studies suggested that LAIV did not consistently provide protection against influenza-associated medical encounters in children aged 2-17 years during 2013-14 and 2014-15 seasons[39,40,41]. However, a school-based study in Canada reported a significant protective benefit of confirmed influenza among students vaccinated with live-attenuated vaccine compared to students vaccinated with inactivated influenza vaccine, as well as decreased influenza transmission among family members of students vaccinated with live-attenuated influenza vaccine[42].

Adults

Clinical trials during 2005-06, 2005-06, and 2007-08 that compared inactivated influenza vaccines and live attenuated influenza vaccines to no vaccine among adults suggested that inactivated influenza vaccines provided better protection against influenza than live attenuated influenza vaccines in adults.[43]

Top of Page

How does CDC monitor vaccine effectiveness?

CDC monitors vaccine effectiveness annually through the Influenza Vaccine Effectiveness (VE) Network, a collaboration with participating institutions in five geographic locations. These institutions enroll patients with respiratory symptoms at ambulatory clinics and test for influenza by RT-PCR. Vaccine effectiveness is estimated using the test negative design, comparing proportions (odds) of influenza-vaccinated patients with and without laboratory-confirmed influenza. Results are used to account for differences in age, race and underlying medical conditions that might influence vaccine effectiveness. Estimates are reported annually, and data from the network have contributed to studies of the relative risk of illness between circulating and vaccine viruses is not known during the season, annual estimates of vaccine effectiveness give a real-world look at how well the vaccine protects against influenza caused by circulating viruses each season.

Top of Page

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Top of Page