

VACCINE SAFETY TRIALS AND PLACEBOS: AN EXPLAINER

Vaccines are one of the most effective ways to protect children against diseases like measles, pertussis (whooping cough), and polio, and rigorous testing has demonstrated that vaccines are very safe. The information contained in this document has been developed by experts to answer commonly asked questions about vaccine safety trials and the use of placebos.

Do vaccine safety trials use placebos?

While placebo-controlled trials are often considered the gold standard for evaluating medical interventions, the use of inert placebos (e.g., the injection of saline solution) is not always required for vaccine trials and in fact is sometimes unethical. Trials of new vaccines may instead use comparison groups that receive the current vaccine or another established vaccine so that children receive some benefit from participating, as it would be unethical to withhold an established vaccine with demonstrated effectiveness. For example, if a hypothetical new measles vaccine were being tested, it would be unethical to withhold established measles vaccines and leave children vulnerable to disease. In this case, one group of children would receive the new vaccine, while the comparison group would receive the current measles vaccine.

Other vaccine trials may involve the use of placebos that contain vaccine components, such as adjuvants or stabilizers, but not the target antigen. By including almost all the same ingredients as the vaccine, researchers can determine if potential side effects are due to the antigen itself or one of the other ingredients.

What are the limitations of placebo-controlled trials?

In addition to the ethical reasons for not using an inert placebo when evaluating vaccine safety, placebo-controlled trials are also unlikely to identify potential rare adverse outcomes, which requires studying very large numbers of people. For example, to detect a doubling of risk for an adverse event that occurs in 1 in 1,000 individuals, a clinical trial with at least 50,000 participants would be required. Even a study this large would not be able to detect rarer adverse events. Thus, rare adverse outcomes are more likely to be identified in post-licensure observational studies of vaccines and other vaccine safety surveillance systems such as the Vaccine Adverse Event Reporting System (VAERS), V-safe, the Vaccine Safety Datalink (VSD), and the Clinical Immunization Safety Assessment (CISA) Project.

Another limitation is that placebo-controlled trials sometimes exclude specific groups of people, such as pregnant women, children, or those who are immunocompromised, limiting the generalizability of the results.

Are annually updated influenza vaccines tested against placebos?

Vaccines that are updated each year, like those to protect children and adults against influenza, are not typically tested against placebos each year due to the ethical implications mentioned above – it would be unethical to leave individuals unprotected against the potentially serious complications of influenza. Because the safety of influenza vaccines is well established, annual vaccines updated with the currently circulating strains of influenza virus are not evaluated in clinical trials. Requiring annual placebo-controlled trials for updated versions of influenza or Covid vaccines would be an inefficient use of resources and would risk leaving individuals vulnerable to disease.

For more information on vaccine safety, visit vaccinesafety.edu.