

# Causality assessment and vaccine safety

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The poor understanding of the science of causality assessment by healthcare professionals and the general public contributes to false assumptions of causal relationships and disruption of immunization programs. Although many adverse events are identified in prelicensure controlled clinical trials, causal relationships are determined from uncommon or rare adverse events through postlicensure studies. Establishing or ruling out causal associations in postlicensure studies is more difficult. If a vaccine increases the risk of an adverse event we usually consider the vaccine to be a causal factor. However, most adverse events have multiple causes and vaccines usually are only one of several contributing factors. Rarely, a vaccine may be a sufficient cause, or a necessary and sufficient cause. Establishing causality usually requires epidemiologic evidence of an increased risk of the adverse event in vaccinated versus unvaccinated populations, or evidence that affected individuals were more likely to have received the vaccine in defined time windows than matched controls. These methods can be difficult in settings where almost all individuals are vaccinated. Newer methods of assessing rare risks of serious adverse events have utilized large healthcare systems where both vaccines and all health outcomes are recorded in electronic databases. In such settings, case only approaches for assessing temporal clustering of adverse events within specific time windows have proven to be extremely valuable for providing evidence for or against causal relationships.

In rare situations causal associations may be determined from in-depth laboratory and other studies of individual cases. For example, the live attenuated yellow fever vaccine has been shown to cause disseminated disease based upon identifying genetic sequence documented vaccine viruses in affected tissues, histopathology consistent with yellow fever virus associated disease, and temporal relationships. However, caution is needed when assessing individual cases of new syndromes because of concurrent illnesses, coincidental presence of vaccine viruses in tissue affected by other diseases, contamination, and other problems as has been evidenced from many false conclusions based on individual case reports.

Consistency of findings from different studies in different populations is the most valuable factor for assessing causal relationships.