

## is it safe?

PAT FAST

---

**IS IT SAFE?** This is the question all of us want answered before we enter a *clinical trial*. The level of risk varies from trial to trial, but as long as a vaccine is investigational (which means that it is being studied to see if it should be licensed), the only honest answer to this question is “we aren’t sure it will be safe for you.” This is a hard answer to hear, but no one should enter a clinical trial until he or she has understood and accepted it. The degree of risk can be estimated from previous experience with the vaccine (and similar ones) in humans, and from the results of tests in animals. But no one knows for sure what will happen to you.

We expect a lot from vaccines. As children, we got vaccines and Mom said they were good for us. She was right. And almost no one suffers serious harm from childhood vaccines. For example: The rates of serious *adverse events* related to two childhood vaccines—Measles, Mumps and Rubella (called MMR), and Diphtheria Toxin, Pertussis (or DTP)—are about one per million or less. These events are so rare that sometimes it’s not really clear if the vaccine causes them or not. And diseases that killed, maimed or paralyzed earlier generations

have been virtually eliminated by these vaccines.

But investigational vaccines could be different. In vaccine clinical trials, one of the goals is to estimate the risk. This means investigators are trying to see how people respond to the vaccine. They ask questions such as: Do people get a fever after getting vaccinated? Do they get a sore arm? Confidence that a vaccine is safe increases as more and more people receive it without harm.

---

## regulation and review of vaccine trials

Before a single person is given an experimental vaccine, it has gone through rigorous laboratory and animal tests to show that it is safe and induces *immune responses*. These data, along with information on the process used to manufacture the vaccine and the procedures being proposed for the clinical trial (called the trial *protocol*), have also been extensively reviewed by a series of expert committees. These include:

### *National Regulatory Authorities*

The US Food and Drug Administration (FDA), the South African Medicines Control Council or the Drugs Controller General of India are examples. Sometimes other national bodies (such as an ethics review committee) or international group (e.g., the HIV Vaccine Advisory Committee of the World Health Organization/UNAIDS) also conduct reviews.

### *Institutional Review Boards (IRBs) and ethics committees*

Every group or institution that enrolls volunteers in clinical trials must have an independent committee that reviews the trial protocol, *informed consent* documents and any advertisements or other recruitment materials, to be sure that they contain the appropriate information, are not misleading, and do not promise things that would make individuals enroll without regard to any risks they may be taking. Although not strictly required, community advisory groups often review specific studies as well.

---

“no evidence of harm”—what does that mean?

When an investigational vaccine enters *Phase I* testing, you might be only the fifth person to receive it. So alongside animal safety tests, the data could be something like this: “We gave this vaccine to four people last week and so far they are okay.” Later, in *Phase III*, the data might be: “We have given this vaccine and very similar ones to 600 people over 10 years, and there is no evidence that it is harmful.” When a vaccine is finally licensed, the evidence is more like: “We have given the vaccine to over 10,000 people, and FDA scientists plus an advisory panel of medical experts consider it safe and effective.” Even with licensed vaccines, there remains a very small uncertainty about whether they will be safe for every single recipient, but the benefit to individuals and to society as a whole is usually judged to outweigh an extremely low risk.

But evaluating risk is often not simple. People in vaccine trials get hurt, get sick and die from the same things as people who are not in trials. In large trials there may be accidental deaths, murders, suicides, heart attacks or cancer in both the *immunized* group and the *controls* (those who got the *placebo*, or “blank”). Each serious event is evaluated immediately, and later all serious and non-serious events are re-evaluated to look for a pattern that suggests harm. Common sense tells us that murder is not a vaccine effect, but most decisions are not so obvious. Let’s go through this process in detail.

Bad things that happen after vaccination are called adverse events. The official definition of an adverse event is any unfavorable change in the body or worsening of a pre-existing problem shortly after being given the vaccine, whether or not the investigator thinks it is caused by the vaccine. As mentioned above, many of these are unrelated to vaccination. Sometimes a list of predicted adverse events (such as a sore arm after an injection) is included in the trial protocol and informed consent documents, so that trial participants understand what might happen and explicitly agree to take the chance of putting up with these side effects. The protocol should say how severe these events are likely to be (if it is known). Two days

of tenderness in the arm might be considered okay, whereas severe swelling which prevents the use of the arm might not. Still, a few very sore arms might be accepted if the vaccine prevents a fatal disease.

Mild adverse reactions like a few very sore arms might be accepted if the vaccine prevents a fatal disease.

Adverse events can also include symptoms such as a body-wide rash or sore joints, although these may turn out to be unrelated to the vaccination. But to be on the safe side, *everything* bad is reported, even automobile accidents. This is to prevent human error in overlooking events that don't seem related but actually might be.

The numbers and types of adverse events in the placebo and immunized groups are then compared, to see if there is a pattern suggesting that the vaccine is to blame.

To see how this works in practice, let's take an example of an HIV vaccine trial that starts in the winter, with several participants reporting high fever, muscle aches and coughs. These symptoms might be an effect of the vaccine, or they could reflect a seasonal influenza outbreak. Comparing the numbers of immunized people and placebo recipients who showed these symptoms will help: if only immunized people have them, the investigator will suspect that the vaccine is at least partly responsible. But if the symptoms occur equally in vaccine and placebo recipients, they will be judged unrelated. If the investigator detects influenza *virus* on throat swabs from the volunteers who are sick, this provides even better evidence that the vaccine is not the culprit.

Of course, one small trial can't prove that a vaccine won't have rare, serious side effects later on. A "serious adverse event" (SAE) is defined as one which is life-threatening or leads to death, permanent disability or hospitalization, or to a congenital anomaly in an infant of a treated person (usually a woman). SAEs must be reported and analyzed for a possible relationship to the vaccine, although careful investigations have generally shown that most are unrelated.

Other factors can help decide about cause and effect. If five immunized people in a large trial get a rash—one right after vaccination, another two weeks later, and the others after 6 to 12 months—it is much less suspicious than if all five rashes

occurred within a week of vaccination. Most trials have an initial period (usually 4–6 weeks) during which *all* events are captured, while SAE's are recorded throughout the entire study.

The job of deciding whether an adverse event is related to the vaccine falls first to the physicians running the trial, since they have firsthand knowledge of the events and the participants. Physicians who work for the trial sponsors (usually the vaccine manufacturer and/or government) then review these decisions. All initial decisions are made *before* the doctors know whether the person received vaccine or placebo. The sponsor cannot take away the primary physician's judgment that an event is vaccine related, but might see a pattern across several trials, or several centers conducting one trial, that suggests a relationship not recognized by the doctor at a single study site. Usually there is a grading scale: definitely related, probably, possibly, probably not, and definitely not.

The scale reflects how hard it is to be certain. SAEs that are judged "related" (even "possibly related") must be reported to the FDA (or other national regulatory authority) within a few days and to the trial site's institutional review board or ethics committee for review.

Finally, the international standard on *Good Clinical Practice* (a set of guidelines on how best to conduct clinical research) requires that trial participants be given any information that might affect their decision to remain in the study. This applies primarily to trials in which the drug or vaccine is given repeatedly over time. If a vaccine is only given once or twice at the beginning of the trial, then "remaining in the study" after this point means only returning for checkups and blood tests; withdrawal from the trial will not affect risk once no further vaccinations are involved. The requirement to inform volunteers still applies, though, so if a vaccine is shown to be harmful, all trial participants will be notified. This would not apply to sore arms or other minor problems described in the informed consent document, because participants already know about those risks.

The system is a bit confusing, because lots of events that have nothing to do with vaccination are reported and listed. Why make it so hard? The reason is simple. The system of

checks and balances is designed to avoid a natural human tendency to see what we want to believe. Vaccine companies have a motivation to want adverse events to be unrelated. (On the other hand, it is bad business to sell a dangerous product. So if their vaccine really is harmful, they want to find this out and avoid future losses.) Investigators in charge of trials at academic centers won't have investments riding on these decisions, but they do have their sense of expectation, achievement and professionalism. These people do not want to harm anyone.

The system of checks and balances is designed to avoid a natural human tendency to see what we want to believe.

Therefore, all the data are collected and reviewed not only by the trial physicians and company scientists, but also by statisticians (often part of an independent group), the university IRB and the FDA. Many large trials also have a specially appointed “data and

safety monitoring board” of independent statisticians, scientist physicians, and ethics specialists, who review the data on a regular basis. It is their job to decide if a trial should stop early because of safety problems. They also might halt a trial either because it has already succeeded in proving that the vaccine works or because, due to changed circumstances (such as slow recruitment or a very small effect of the vaccine), the trial will be unable to clearly prove whether the vaccine works.

Once a vaccine is licensed and marketed, a different adverse event reporting system comes into play in the US. This system relies on physicians who suspect a link between vaccination and adverse events to submit a report, so it invariably misses some events that should be captured. Because there is no control group, it is especially difficult to assess cause and effect, and many events can be listed that have no relationship to the vaccine.

These data are sometimes misunderstood. A recent article by an opponent of childhood vaccination simply quoted the number of “adverse events” in the database. Without further analysis, such as determining how many people were vaccinated and attempting to relate specific events to specific vaccines, this number is meaningless.

A more sophisticated system for monitoring post-marketing safety is Vaccine DataLink ([www.vaers.org](http://www.vaers.org)). Here, four large US health maintenance organization databases are checked to see how frequently certain events occur without vaccination compared to the period just after vaccination.

**LET'S HOPE** that someday we will have an HIV vaccine and epidemiologists will be trying to determine how many side effects occur per million vaccinations—while we all watch the epidemic dwindle to nothing.