22

facing failure on the way towards success: lessons learned from the VaxGen trial

RICHARD JEFFERYS

IN FEBRUARY 2003, the long-awaited results from the world's first AIDS vaccine ***efficacy*** trial were announced. The trial (dubbed VAX004) tested whether a vaccine called *AIDSVAX* could prevent HIV infection in people with a high risk of sexual exposure—most of them gay men, plus a small number of women. The results were disappointing: there was no protection in the overall study group *(**cohort**)*.

But the announcement also included a confusing and controversial claim by the vaccine's manufacturer, a California-based company called VaxGen, Inc. According to VaxGen, AIDSVAX *did* show protection of participants from certain racial minorities—namely those categorized as Black, Asian or Other—even though it failed to protect White or Hispanic participants.

More thorough review of the data in the following weeks and months found the claim to be wrong, the result of a statistical error related to the very small number of non-White participants.

But despite its disappointing outcome and controversial ending, the trial nevertheless offered some valuable insights into conducting vaccine efficacy trials among high-risk populations—an undertaking that some scientists had worried would be very hard to pull off. What follows is a discussions of the main lessons learned, in particular:

Although the vaccine showed no efficacy, the trial nevertheless offered valuable insights into conducting efficacy trials among high-risk populations.

- The trial was able to enroll roughly 5,400 high-risk volunteers, and over 85% of them stayed with it for the full three years.
- The infection rate during the trial (2.8% per year for the men; 1.5% for the women) shows that HIV ***incidence*** is significant in these high-risk groups, and that efficacy trials can be done in certain populations in the US.
- The trial gave clear answers to the questions of whether the vaccine could protect against HIV infection or slow progression of infections that occurred after vaccination. (Progression was measured by following changes in ***CD4+ T-cell*** count and ***viral load*** over time.) This may not sound like a major accomplishment, since the vaccine didn't work, but it is; a variety of scenarios could have led to an ambiguous outcome about the vaccine's efficacy.
- Risk behavior among participants didn't appear to increase as a result of being in the trial—another early fear that proved to be unfounded.
- Confusion over the results in racial subgroups drove home the importance of doing efficacy trials in diverse study populations of both men and women. It also emphasized the dangers of publicly releasing results from the trial without careful review to ensure absolute accuracy.

a brief history of the trial

The AIDSVAX vaccine was originally designed well over a decade ago. The formulation tested in VAX004 contains two versions *(genetic variants)* of the HIV outer ***envelope protein***, called ***gp120***. The hope was that the vaccine would trigger production of ***antibodies*** which would bind to the ***virus*** if a vaccinated person was exposed to HIV and prevent it from infecting cells in the body. (This is called ***neutralizing*** an infection.) Many scientists were skeptical about the potential of AIDSVAX because the antibodies it induces neutralize gp120 only from HIV ***strains*** grown in the lab, not from HIV ***isolated*** directly from infected people. What's more, gp120 ***proteins*** are notorious for constantly ***mutating*** and changing shape, making them a difficult (and moving) target for antibodies.

Altogether the VAX004 trial enrolled 5,417 HIV-negative volunteers at 61 sites in the US, Puerto Rico, Canada and the Netherlands, beginning in 1998 (see Table 3.4 for a breakdown by gender and demographics). Each volunteer received seven vaccinations over a 30-month period. At each study visit, they also received HIV pre-test counseling and then had blood drawn to test whether they'd remained HIV-negative and to measure their ***immune responses*** (i.e., level of antibodies) to the vaccine.

Table 3.4 Race, gender and the VAX004 trial volunteers

Group (average age 36)	Number of volunteers	Percent of volunteers
Male	5,095	94%
Female	308	6%
White	4,489	83%
Hispanic	367	7%
Black	349	7%
Asian	77	2%
Other	121	2%

the results

The trial data clearly showed that AIDSVAX failed to prevent HIV infection in the study cohort as a whole (see Table 3.5, below), since there was roughly the same rate of infection among study participants who received the vaccine and those who got a ***placebo***. Nor did the vaccine show any effect on CD4+ T-cell counts or viral load levels in vaccinated volunteers who later became infected.

But VaxGen initially claimed that the vaccine *did* reduce infection rates by about two-thirds (66–67%) in participants whose race was categorized (by the participants themselves) as Black, Asian or Other.

Even major newspapers were uncertain how to report VaxGen's claims. Some focused on the overall results and wrote that AIDSVAX had failed. At least one paper wrote that the vaccine "appears to work." Understandably, many groups representing Black and Asian communities were concerned that the apparent success of the vaccine in these subgroups was being ignored or downplayed because it hadn't worked among whites.

Table 3.5 VAX004 trial results: infection rates in vaccine and placebo groups

Group	Number infected	Percent infected, vaccinees	Percent infected, placebo	Percent vaccine efficacy*
Overall	368	6.7%	7.0%	6%
White/Non-Hispanic	309	7.1%	6.6%	–7%
All non-white	59	5.0%	9.4%	47%
Hispanic	23	5.9%	7.0%	15%
Black/Hispanic	15	2.6%	7.8%	67%
Asian/Pacific Islander	6	5.4%	14.3%	66%
Other	15	9.2%	17.8%	50%

*Vaccine efficacy is the percent reduction in infection rate due to the vaccine (compared with the rate in the placebo group).

At first glance, the results in the table *do* seem to suggest some protection in these two subgroups. But the suggestion rests on a very small number of infections (15 and 6, respectively)—which is where the complicated science of statistics comes into play.

One of the most important things to remember when looking at results from any ***clinical trial*** is that small numbers of events (in this case, HIV infections) increase the possibility that apparently positive results will occur purely by chance. Think of flipping a coin five times. It is quite possible—although unlikely—that the coin could come up heads five times in a row. If you flip a coin 100 times, it's much more likely that heads and tails will come up roughly equal numbers of times. If the coin came up heads 100 times in a row you would think that there must be a cause (like the coin having more weight on one side).

When it comes to clinical trial results, the purpose of statistics is to decide whether a result happened by chance, or if it was caused by the medicine or vaccine being tested. After VaxGen's announcement, an in-depth statistical analysis of the data (done by experts from the US Centers for Disease Control, the National Institutes of Health, the HIV Vaccine Trials Network and VaxGen) found that the subgroup results were almost certainly a result of chance due to the small numbers involved, like a coin randomly coming up heads several times in a row. It turned out that VaxGen had not used the proper statistical tools to correct for the small numbers of minority volunteers, or for the total number of subgroups analyzed.

risk behavior among trial participants

ONE OF THE MOST IMPORTANT questions surrounding this (and future) efficacy trials is whether high-risk participants may increase their risk behavior based on a false sense of being protected. Behavior was therefore closely monitored throughout the trial, and at each study visit participants were counseled on how to reduce their risk of infection and reminded not to assume they're protected. They were also asked about any instances of unprotected sex with any partner, or with a partner known to be HIV-positive (for gay men, specifically about unprotected anal sex; for women, vaginal sex).

The results showed a significant drop in the number of gay male participants reporting unprotected anal sex with any partner during the first six months of the study (from just under 60% of the men to around 50%). From then on, the reported frequency stayed low, despite a small increase over time. The incidence of unprotected anal sex with a known HIV-positive partner also declined initially (from roughly 20% of participants to about 10%), and this decline was maintained. The rate of new infections among the men stayed at around 3% per year throughout the trial.

Results for women were not as statistically robust since there were so few female participants. But the overall pattern was similar: Unprotected vaginal sex declined somewhat at the beginning, and then remained near the baseline level for most of the study (with about 50% of women reporting this risk behavior). Unprotected vaginal sex with a known HIV-positive partner declined from just over 10% at baseline to around 5% at month 36.

Overall, these results are encouraging. But the researchers involved have pointed out several limitations. First, the trial population was primarily gay white men, so it's not clear whether these findings would apply to a broader cross-section of high-risk populations. Second, these studies didn't prove beyond any doubt that there was no "vaccine optimism" (false sense of security) affecting the volunteers' risk behavior. Rigorous proof would require comparing VAX004 volunteers to a similar high-risk population that got the same regular risk-reduction counseling and medical care. And when researcher Susan Buchbinder from the University of California at San Francisco did this type of comparison (using a non-vaccine cohort recruited two years after VAX004 began) she found that risk behavior did decline more in the non-vaccine group than in the VAX004 volunteers—and so did HIV infection rates (slightly). So, while once again the results don't give 100% proof (since these two groups were not studied in parallel), they may hint at a small effect of "vaccine optimism."

moving ahead

One of the most important lessons to take away from VAX004 is that future trials must assemble racially diverse study cohorts of both women and men so that possible differences in vaccine effects can be detected. To put the issue in perspective, so far there are no examples of licensed vaccines known to work better or worse among different racial groups. But there is a fascinating (and surprising) example based on gender: the still-experimental vaccine against genital ***herpes*** (see chapter 30) seems to work only in women—a finding that researchers are now attempting to confirm in a new study. So, while it will usually not be feasible for a single efficacy trial to give ***statistically significant*** results on every subgroup of participants (since this would require huge numbers of volunteers), it's essential that trials are designed to detect hints of any differences, which could then be tested through follow-up studies.

The controversy surrounding VaxGen's initial claims of efficacy among racial subgroups also shows how important it is for trial results to be rigorously evaluated before they are made public. It can be tempting for commercial companies to give a positive spin to their products, as a way to help ensure corporate survival. But plain errors, spin or anything else that oversells the promise of an AIDS vaccine will undermine public confidence. It would also be helpful for community activists to work together in the future to quickly sort through the meaning of uncertain results if such a confusing situation ever arises again.

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Future efficacy trials will also need to remain vigilant about monitoring risk behavior, since each trial will involve a different study population. It will also be important to compare risk behavior among trial participants to risk a similar cohort that isn't taking part in the trial but gets the same level of counseling, to fully assess the possible effect of "vaccine optimism."

resources

http://avac.org.phtemp.com/pdf/UnderstandingAIDSVAX.pdf
Understanding the Results of the AIDSVAX trial. AVAC website. This document discusses the confusing findings, and the follow-up work done to clarify the confusion, in simple language. Available in English, French and Spanish.