AIDS VACCINES

Will Media Reports KO Upcoming Real-Life Trials?

The paucity of medical weapons for fighting AIDS poses agonizing choices for researchers. Among the most painful: Should officials at the National Institutes of Health (NIH) press ahead with large, expensive clinical trials of HIV vaccines, which currently show only marginal promise? Or should they wait until vaccines show more promising results in preliminary trials—knowing that infected people are dying every day? The research community is deeply divided on this point, but recently the scales seemed to be tilting toward launching trials of two vaccines (*Science*, 20 May, p. 1072). Now they have swung back, however, tipped by new information about volunteers in small AIDS vaccine trials who became infected after being vaccinated.

Most researchers believe the new information has little scientific import and has been blown out of proportion by the media. But in the charged atmosphere surrounding AIDS vaccine trials, perceptions can carry as much weight as science. And so, when the *Chicago Tribune* reported on 29 May that five people who had received AIDS vaccines in small trials had become infected with HIV, that story colored the debate about whether to launch large AIDS vaccine trials.

The media jumped on the story, upsetting some AIDS vaccine researchers. Mary Lou Clements, head of the Center for Immunization Research at Johns Hopkins University in Baltimore, says she is "appalled by this feeding frenzy with half-baked data." Clements is particularly concerned that some stories implied that the vaccines are useless or, worse, that they caused the infections. And she worries that large-scale efficacy trials could be put on hold. "Perception is part of the decision tree, and the way this has been distorted puts a very negative perception on this," says Clements. Barney Graham, who runs AIDS vaccine trials at Vanderbilt University in Nashville, Tennessee, has similar worries. "I'm sure it's influenced the political side of the equation, because political decisions are mixed up with emotions," says Graham. "But emotions don't necessarily line up with the data."

Most of the emotions in this case center on the two vaccines being considered for large-scale trials—one by Biocine, the other by Genentech. Four of the five infections reported in the *Tribune* were in people who had received one of those two preparations. But *Science* has learned that that's only part of the story: At least 10 people vaccinated in various trials, and two people who received dummy placebo shots, have become infected. These infections occurred among people who received one of at least five different experimental vaccines. And six of them became infected before receiving the minimum three injections typically needed for a vaccine to work. "If they don't get all the shots, you can't expect a vaccine to work," says Clements.

INFECTIONS AFTER AIDS VACCINES

Case/Vaccine	# of Vaccinations
1. MicroGeneSys gp160	1
2. MicroGeneSys gp160	1
3. MicroGeneSys gp160	4
4. Bristol-Myers HIVAC-1e + gp160 boost	At least 4
5. Genentech gp120/QS-21 or gp120/alum adjuvant*	2
6. Either Genentech gp120 or Biocine gp120*	0–1**
7. Either Genentech gp120 or Biocine gp120*	2**
8. Either Genentech gp120 or Biocine gp120*	2–3**
9. Biocine gp120	4
10. Viral Technologies HGP-30	3

* Data from these trials are still blinded.
** Preliminary data.

Even if the vaccines had failed in those cases, 10 infections out of more than 1600 volunteers vaccinated in trials doesn't mean the vaccine search is headed in the wrong direction. "It tells you for sure you aren't looking at a 100% effective vaccine," says Anthony Fauci, director of the National Institutes of Allergy and Infectious Diseases (NIAID). But, he adds, "it doesn't tell you anything that has statistical significance or is even approaching statistical significance."

Aside from the lack of statistical significance in these few cases (and the fact that these trials were preliminary tests of safety and immune-stimulating power, not efficacy), AIDS researchers say they are concerned about what Graham brands the "twisted" media accounts of vaccine risks. The misconception that most worries Graham is the notion that these vaccines actually transmitted HIV. This is impossible because the vaccines contain only a protein from HIV's surface, gp120, and not HIV itself. A more plausible fear raised in the press is that HIV vaccines could make a person more susceptible to infection by HIV. No evidence suggests that this happened, but investigators are exploring the possibility.

Some media accounts also focused on the risk that vaccinations might somehow accelerate the disease process in people who subsequently became infected. Again, there is little evidence that this has happened, although one of the 10 people infected has shown a rapid loss of CD4 cells, the key white blood cells that typically decline slowly in HIV-infected people. Though normally people have 800 to 1200 CD4s per cubic milliliter of blood, this person dropped to fewer than 200 within 15 months. "It frightens people to see this," says NIAID's Patricia Fast, who has been tracking these infections. Yet Fast notes that studies show that within a year, 3% to 10% of infected, unvaccinated people drop below 300.

Although the information gleaned from these infections has little bearing on the safety or efficacy of these vaccines, Fauci says "that doesn't mean I feel this is irrelevant." Indeed, Fauci concedes that the infection story "absolutely tilts the political framework" for deciding whether NIH should soon launch large trials—which just a few weeks ago appeared likely.

In April, an influential AIDS vaccine "working group" organized by NIAID concluded that staging large tests with the Genentech and Biocine vaccines made sense. But that recommendation was made with many reservations—and the picture may now be changing. On 24 May, before the *Tribune* story broke, NIAID's AIDS Vaccine Data Safety and Monitoring Board (DSMB) discussed the case of the person whose CD4 count dropped quickly. According to NIAID documents, the DSMB concluded that the data "do not materially alter the perceived risk of accelerated CD4 loss," yet it recommended that the informed consent forms for the trials be changed to include "a clearer warning" about risks. NIH officials urge researchers to weigh the infection cases carefully. "Our hope is that these events will be put in their proper context and be weighed as one of many factors in a complicated decision," says Jack Killen, head of NIAID's Division of AIDS.

Whether the infections will tip the scales should become clear during the next step in the decision-making process, a meeting slated for 17 June of the AIDS Research Advisory Committee (ARAC), which will debate the issue and make its recommendation to Fauci. "Many people on the committee have been hoping to find positive data," says ARAC member Nancy Haigwood. "This isn't positive." The recent spate of news certainly hasn't helped, but the final call will be made by Fauci. He plans to make a decision shortly after the ARAC meeting.

–Jon Cohen