



Why New Jersey said "no" to stem cell fund

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Scientists debate geoeengineering

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AIDS RESEARCH

Did Merck's Failed HIV Vaccine Cause Harm?

SEATTLE, WASHINGTON—A common cold virus has walloped the already ailing AIDS vaccine field.

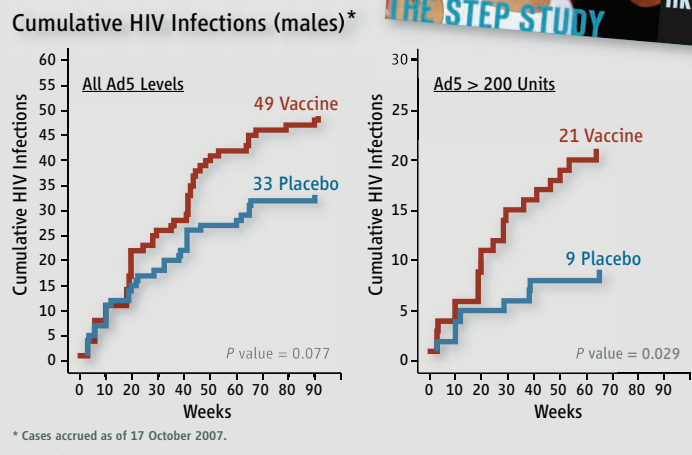
AIDS researchers, who are still staggering from the unexpected failure in September of the most promising vaccine candidate in clinical trials, met here last week to explore an even more alarming finding: The vaccine, made by Merck and Co., may actually have increased the risk of HIV infection in some study participants.

Working with the academic-based HIV Vaccine Trials Network (HVTN) and the U.S. National Institutes of Health (NIH) in Bethesda, Maryland, Merck researchers stopped the multicountry study after an interim analysis revealed that the vaccine did not work (*Science*, 5 October, p. 28). Now further analysis suggests that the vaccine may have helped HIV infect a subset of participants who at the trial's start had high levels of antibody to adenovirus 5 (Ad5), which causes the common cold and is also a component of the vaccine. "This is the worst possible outcome in a vaccine trial," said AIDS researcher Eric Hunter of Emory University in Atlanta, Georgia, one of the study sites.

The finding is as befuddling as it is frightening, and its implications are far-reaching. The data presented here to some 500 attendees at an HVTN meeting on 7 November found only a "trend" toward what's called "enhancement," leaving investigators wondering whether the elevated number of infections in vaccinees who had high Ad5 immunity was due to chance, behavior, or a vaccine-induced problem. Despite intensive investigations, no biological mechanism has emerged to explain how preexisting immunity to Ad5 could make vaccinated people more susceptible to HIV. "The data are very complex, and trying to

understand what they mean has required an enormous amount of work," said Merck's Michael Robertson, a co-chair of the study.

In the first full accounting of the trial results, Merck researchers and their partners reported that, as of 17 October, HIV had infected 83 people in the placebo-controlled



Double trouble. The vaccine clearly failed (*left*), but in men with high Ad5 antibodies (*right*), it may have increased their risk of infection. (Women were excluded from this analysis because only one became infected during the study.)

trial. Of these, 49 were vaccinated and 34 received saltwater injections. This difference clearly indicates that the vaccine does not protect against HIV, but the increased infections in vaccinees have no statistical import and likely are due to chance.

The discovery of possible enhancement in the so-called Step Study also owes something to chance. The vaccine contains three HIV genes stitched into a modified Ad5 vector that infects cells, creating HIV proteins that teach the immune system how to attack the real AIDS virus. From the outset, investigators worried that high levels of preexisting Ad5 antibodies might attack the vector and cripple the vaccine. So when Step began in December 2004, they enrolled 1500 people at high risk of

becoming infected with HIV who had low Ad5 antibody levels. When data then suggested that this concern had been overblown, they doubled the trial size in July 2005 to include people with high Ad5 immunity. Most participants were men who have sex with men, although 38% were women, many of whom were sex workers.

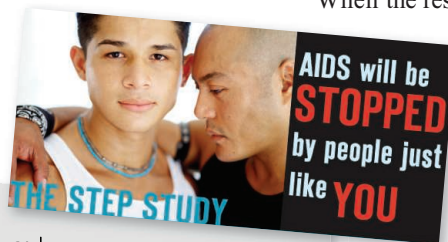
The interim analysis in September that revealed the vaccine wasn't working looked only at the low-Ad5-antibody group.

When the researchers subsequently examined the high-Ad5-antibody group, they were startled to find 21 infections in vaccinees versus nine in the placebo group.

The statistical analysis is ambiguous.

Typically, researchers deem a difference as significant if it has a 95% probability of not being due to chance—a *P* value of less than 0.05. By these standards, the finding, with a *P* value of 0.029, was significant. But Steven Self, HVTN's head statistician at the University of Washington (UW), Seattle, cautioned that this comparison merits a more stringent cutoff for significance, between 0.025 and 0.0025, because the study was not designed to assess potential harm, nor did investigators plan to evaluate a subset of the study population. Still, Self said this "trend" deserves close examination.

Several researchers described their recent efforts to make sense of the trial's results. UW's Juliana McElrath, an immunologist who directs HVTN's lab program, explored what many consider the most likely explanation: that people in the high-Ad5-antibody group were more vulnerable to HIV because of "immune activation." Specifically, HIV establishes an infection by attaching to T cells that have surface receptors known as CD4 and CCR5. Natural infection with Ad5 creates memory banks of these very T cells, which expand and direct an attack if Ad5 shows up again. Theoretically, the vaccine vector could have activated these memory cells in the





same way, creating more targets for HIV. But McElrath's preliminary work found no evidence for this scenario.

Behavioral changes don't seem to provide an explanation: Study co-chair Susan Buchbinder of the San Francisco Department of Public Health said risk behaviors had decreased across the board and more so in the high-Ad5-antibody group. Buchbinder said investigators still are sorting out many variables related to HIV transmission, including circumcision, coinfection with other sexually transmitted diseases, and genetic factors.

One thing is clear: The monkey studies that suggested that the vaccine could thwart the AIDS virus, fueling much excitement, misled Merck researchers. "Mice lie, monkey sometimes lie, and humans never lie," said Peggy

Johnston, head of NIH's AIDS vaccine program. "Some monkeys have lied to us this time." Other attendees stressed that Merck relied on a wimpy strain of the AIDS virus to "challenge" vaccinated monkeys and that challenges with stronger strains predicted that the vaccine would fail.

Although the mechanism remains elusive, researchers struggled with whether to tell trial participants if they received the vaccine or the placebo. A more recently launched study of the same vaccine in South Africa was stopped and quickly "unblinded" after learning the Step results, notifying everyone of their vaccine status (*Science*, 2 November, p. 729). After much debate here, Step's scientific steering committee recommended unblinding, and an oversight committee con-

curred on 13 November.

The specter of enhancement also affects the AIDS vaccine field's next-best hope. This NIH-made vaccine uses a similar Ad5 vector and was slated to enter a \$130 million trial this fall without screening people for Ad5 immunity. "Step's results demand that we reexamine and redesign our study," said principal investigator and Step collaborator Scott Hammer of Columbia University.

Merck's Mark Feinberg warned colleagues that "the whole field will come apart at the seams" if it doesn't properly investigate and respond to the Step results. "I've never seen more complicated data to emerge from a study," Feinberg said. "And this one focuses on as important a question as I've ever known."

—JON COHEN

EPIDEMIOLOGY

Privacy Policies Take a Toll on Research, Survey Finds

A federal rule aimed at protecting patient data is hindering epidemiology research, adding costs and delays without enhancing confidentiality, according to a study this week in the *Journal of the American Medical Association (JAMA)*. The survey responses from 1500 epidemiologists reflect the first systematic analysis of privacy rules that researchers have complained about for 4 years.

The problems stem from the Health Insurance Portability and Accountability Act (HIPAA), passed by Congress 11 years ago to make it easier for people to transfer their health insurance. A so-called Privacy Rule that took effect in April 2003 requiring health care providers to protect the privacy of medical records also affects research. Investigators must get permission to use a patient's medical data, even to identify potential participants. If that is not possible, the researchers can try to get by with a data set stripped of identifiers, such as name and address, or they can seek a waiver from an institutional ethics board.

These requirements have had a major impact on population-based health research, according to the survey, headed by epidemiologist Roberta Ness of the University of Pittsburgh in Pennsylvania. Survey invitations were e-mailed to more than 10,000 members of 13 epidemiology societies, and

1537 of them completed a Web survey. About 68% said the Privacy Rule has made research a great deal more difficult; half reported major delays; and nearly 40% faced much higher costs (see table). Only one-quarter said the rule has greatly improved confidentiality. Of those who modified a

heart disease care by mail rather than by phone, resulting in a drop in the response rate from 96% to 34% and a bias toward older, healthier, married participants. Ness's survey also suggests that U.S. surveillance of infectious diseases may be suffering because hospitals aren't sure what they can report.

Epidemiologists' Views on the Privacy Rule			
	None	Some	A great deal
Made research more difficult	9%	16%	68%
Enhanced confidentiality	47%	20%	26%
Added cost	22%	21%	39%
Delayed time to study completion	21%	19%	51%

Note: Based on 1527 responses. Results total less than 100% because they do not include responses of "don't know."

Overprotected? A rule meant to ensure the privacy of medical data is hampering research, according to survey of epidemiologists.

protocol to comply with HIPAA, two-thirds said it was much harder to recruit subjects.

The results support anecdotal evidence that the Privacy Rule has slowed enrollment and threatened some studies, says Ness (*Science*, 9 July 2004, p. 168; 17 March 2006, p. 1547). For example, at the University of Michigan, researchers were required to obtain consent for a survey of patients with

Three years ago, an advisory panel urged the Department of Health and Human Services (HHS), which administers the Privacy Rule, to ease the burden on researchers by revamping the rule. The agency never formally responded. But HHS and other organizations commissioned the U.S. National Academies' Institute of Medicine (IOM) to examine the issue broadly; one of the results is the *JAMA* survey. Researchers in other disciplines have told the panel of difficulties,

too. For instance, clinical oncologist Richard Schilsky of the University of Chicago Medical Center says HIPAA has been "a huge problem" for studies involving tissue samples, among others. Ness says she and her colleagues "really are hoping" that the IOM panel will devise recommendations that produce action. Its report is due by early 2009.

—JOCELYN KAISER