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Smallpox Immunity May Persist From Childhood

Israelis trying to develop skin test to confirm

HEALTH CARE WORKERS WHO WERE VACCINATED AS CHILDREN MAY BE PROTECTED AGAINST FATAL SMALLPOX infection even if they declined to participate in recent immunization efforts, according to a recent study.

Researchers report that more than 90% of volunteers vaccinated 25-75 years ago still maintain substantial humoral and/or cellular immunity against vaccinia, the virus used to vaccinate against smallpox.[1] Antiviral antibody responses remained stable between 1-75 years after vaccination, whereas antiviral T-cell responses declined slowly, with a half-life of 8-15 years.

"If these levels of immunity are considered to be at least partially protective, then the morbidity and mortality associated with an intentional smallpox outbreak would be substantially reduced because of pre-existing immunity in a large number of previously vaccinated individuals," the researchers concluded.

However, even if those previously immunized only were infected mildly during a smallpox attack, they still could spread the disease, so health care workers would need to be immunized to protect patients. Still, the historical smallpox literature indicates those who have less severe smallpox infection due to previous vaccination are four times less likely to transmit the disease to their contacts, says lead researcher Mark Slifka, PhD, director of the Oregon Health & Science University Vaccine and Gene Therapy Institute in Beaverton.

"If you're on a smallpox task force team, you would still want to be vaccinated as an obvious precautionary measure, but for the average person—no," he says.

More importantly, the study by Slifka and colleagues raises the possibility that roughly half of the country—those immunized before the national program was dropped in 1972—have some level of immunity. But the traditional wisdom among smallpox experts has been that immunity fades after 5-10 years post-vaccination.

The Centers for Disease Control and Prevention states on its smallpox web site that, "Smallpox vaccination provides high level immunity for 3-5 years and decreasing immunity thereafter. . . . It is important to note, however, that at the time when the smallpox vaccine was used to eradicate the disease, testing was not as advanced or precise as it is today, so there may still be things to learn about the vaccine and its effectiveness and length of protection."

Since smallpox has been eradicated as a natural-occurring disease, it is difficult to know the nature of persistent immunity in the previously vaccinated. Some in the scientific community remain unconvinced that the issue has any major relevance for smallpox preparedness.

"It's a nice thought," says Brian L. Strom, MD, MPH, chairman of the Institute of Medicine smallpox panel and director of the Center for Clinical Epidemiology and Biostatistics at the University of Pennsylvania School of Medicine in Philadelphia.

Good News, Bad News

"The good news is there are these serological measures that suggest immunity last longer. The bad news is that we have no idea whether those serologic measures are of any clinical importance whatsoever," he explains.

"Those measures weren't available when we had disease and now that we have those measures, we don't have disease. The available data when there was disease would argue that [these findings] are probably not important because they are probably not correct. The people who got vaccinated seemed to get disease after a few years—milder disease—but they seemed to be subject to still getting sick," Strom adds.

But that is precisely the point, Slifka argues—those previously immunized would be considerably less vulnerable to smallpox infection. "It depends on your definition of protection," he says.

"It's interesting because the same arguments keep coming up over and over again. Even if you got vaccinated six months or six days before you were exposed, there is no guarantee that you won't contract smallpox.

"But it will be mild. If you knew you were going to have a high probability of exposures, you would probably want

to get vaccinated. But for the average person, long-term immunity is probably going to provide that protection," Slifka explains.

Thus it seems the primary implications will arise when and if the public is ever offered smallpox vaccine, which was to occur in the third phase of the national smallpox plan that is now in limbo.

"The historical data on this are really pretty solid," Slifka says. "Obviously, the largest numbers come from back in the days when smallpox was endemic, but a paper published in 1913 shows really quite well that immunity against lethal disease lasts for life."

He also points out that Edward Jenner—who made the connection between cowpox (vaccinia) and smallpox (variola)—was working with farm families that had very good health records kept at churches.

Jenner found that people were protected against smallpox as long as 53 years after cowpox infection, Slifka explains.

"Some 60% to 70% of unvaccinated people, when exposed, get smallpox," he explains. "In contrast, only 4% of vaccinated people get smallpox. Of those [vaccinated people] who get smallpox, mortality is 7% or less. Even if we are conservative and say there is a 10% attack rate instead of the 4% and 10% mortality instead of 7%, 10% of 10% equals 1%. That means that 99% of vaccinated people are protected from lethal infection."

The argument for long-term immunity is borne out by other live virus vaccines, he adds. "This is a live viral vaccine, and it is an acute or short-term infection," Slifka says.

"So this is not unique to vaccinia. If you take a look at measles, mumps, rubella, polio, and yellow fever—those are five other viruses—all of those are short-term infections that induce lifelong immunity. It is not surprising that vaccinia does the same," he adds.

Researchers Seeking Smallpox Skin Test

But even if immunity does persist overall, is there any reliable way to detect it in an individual?

Researchers in Israel are trying to answer that question and develop a simple skin test to determine whether someone has persistent immunity. The skin test is applied to the forearm using the same technique as the tuberculin skin test used for the diagnosis of latent TB infection.

"It is well known that some people who were vaccinated many years ago are well protected against smallpox," says Eli Somekh, MD, head of pediatric infectious diseases and immunology at Wolfson Medical Center in Holon, Israel.

"The problem is how to identify these people. We hope that this skin test will be proved as a simple and reliable method for this purpose," he points out.

In data recently presented recently in Chicago at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy, Somekh described the quest for a skin test.[2]

A skin test solution was prepared from vials of smallpox vaccine, which was inactivated by exposure of the vials to temperature of 600°C for one hour.

Inactivation was confirmed by the lack of growth in virus culture. The solution was then diluted in a ratio of 1:20 with normal saline.

The material was injected superficially in the forearm to 77 healthy subjects ages 17 to 55. Twenty patients had been immunized for smallpox within three months before skin testing (group 1).

Thirty-seven patients had their smallpox vaccination in the past, at least 20 years before skin test application (group 2), while 20 patients had never been vaccinated for smallpox (group 3).

Tests were read at 48 hours and were considered as positive when the diameter of swelling was 5 mm or larger. Blood samples were drawn prior to skin testing and kept at –700°C until analyzed for neutralizing antibody assay. Titers of 1:64 or greater were considered as protective.

The skin test reliably differentiated between people who had not been vaccinated for smallpox and those who were vaccinated recently or in past.

In addition, a positive skin test reaction in a person who was vaccinated for smallpox recently or remotely was associated with protective level of antibodies against vaccinia virus.

There was a significant difference in induration (swelling) size of patients from the different groups of patients (mean induration was 7.9 mm, 5.3 mm, and 0 mm for patients from group 1, group 2, and group 3, respectively).

There was a significant correlation of skin test results with serologic results. The specificity and sensitivity of the skin test as compared to the serologic results were 83.3% and 92.3% respectively.

Simple and Cheap Method

Except for the expected local redness and swelling (which was considered as positive reaction to the skin test), there were no other local or generalized manifestations. The results suggest that a vaccinia skin test prepared in a simple and cheap method is a safe and a potentially useful tool by which to assess immunity.

"Skin test reactions represent memory of T Lymphocytes from a previous encounter with a specific antigen/pathogen," Somekh said.

"Positive reaction does not always suggest an existing immunity; however, in our study, skin test reactivity was significantly correlated with protective levels of antibodies to vaccinia. Our results are still preliminary, and we do not suggest avoiding vaccination of people with posi-

tive skin test reactions until these results can be further studied and confirmed," he adds. ■

References

1. Hammerlund E, et al. *Nat Med*. 2003;9(9):1131-1137.
2. Somekh E,et al. Abstract G-1087. Presented at the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago; September 2003.

Why Has the Smallpox Program Stalled Out?

Three critical errors in thinking

ANALYSTS CITE THREE "MUTUALLY REINFORCING errors" that have dogged and delayed the government's national smallpox immunization campaign:

1. Not distinguishing between the risk of vaccination in healthy, well-screened adults and the risk to children and high-risk adults.
2. Not adequately recognizing the difference between naturally occurring disease and disease introduced by bioterrorism. For example, no one has epidemic-control experience with smallpox in a nominee, highly mobile population where exposure will be malicious rather than benign. The relevance of lessons from the eradication experience (characterized by very different circumstances) is limited.
3. Not sufficiently appreciating that the decision to undertake pre-exposure vaccination is far more than a medical decision about the risks of vaccination. Of equal or greater importance, it involves social, economic, and national security considerations.[1] ■

Reference

1. Bicknell WJ, Bloem KD. *Smallpox and Bioterrorism: Why the Plan to Protect the Nation Is Stalled and What to Do*. Paper No. 85. Washington, DC: Cato Institute; Sept. 5, 2003.

Syndromic Surveillance Picks up Terror 'Signals'

Establish thresholds, investigate anomalies

THE WAVE OF THE FUTURE IN BIOTERRORISM SURveillance is computer-based systems for syndromic reports that can serve as an early tripwire if an attack is under way.

Comparing selected clinical indicators against baseline thresholds, syndromic surveillance systems are increasingly being applied in health care systems and offered in the private sector.

But surveillance is nothing new to infection control professionals. The increasingly sophisticated syndromic systems don't replace time-honored gumshoe epidemiology, said Adi Gundlapalli, MD, PhD, an epidemiologist at University of Utah Medical Center in Salt Lake City.

"Computer-based surveillance systems are not really new, they are just novel applications," he said recently in San Antonio at the annual conference of the Association for Professionals in Infection Control and Epidemiology. "There are many surveillance systems we use almost everyday for hospital-acquired infections. It can be as simple as flagging resistant organisms [in lab reports]."

Gundlapalli helped develop and monitor a syndrome-based surveillance system to detect bioterrorism incidents during the 2002 Winter Olympics in Salt Lake City. "As professionals in infection control and hospital epidemiology, we have a unique expertise. We actually liaison between the hospital and public health," he said. "That turns out to be very important, especially when there is an event. You have to have pre-established relationships."

Held in February 2002, the Winter Olympics was one of the first major international events held in the wake of 9/11 and in the shadow of the anthrax attacks. "There was a week or two in Salt Lake City that people were not even sure if the games were going to be held," Gundlapalli said. "Bioterrorism had become a reality. There was no question that this had changed from the academic papers."

Deciding What to Track

To meet the threat, Gundlapalli and colleagues developed the Advanced Logic for Event Detection in Real Time (Alert) system. The system monitored patients seen in the University Hospital's emergency department, outpatient clinics, and a special clinic at the Olympic Village. "What we get out of it, for lack of a better word, are signals," he said. "Each data element is like a signal to us. The first question was what would be of interest to infection control personnel. The answer, of course, was everything. But you have to be able to handle it, so we sat down and talked about specific signals."

The surveillance indicators selected include emergency department admissions and orders for cultures, X-rays, and diagnostic tests. As specific clinical indicators were winnowed out, the clinicians also set threshold levels based on baseline data. "At the University of Utah hospital, we do

30 X-rays a day for various reasons," Gundlapalli said. "So on any day, if you are doing 60, then you know that there is something else going on. It may indicate that somebody is worried about something going on in the lungs."

By the same token, baseline levels and thresholds for response were set for blood cultures, stool cultures, and orders for diagnostic tests for specific diseases. "If someone orders a nasal swab for anthrax, you want to know about it," he said. "Even one—you want to know about." Other tracked indicators were patient's primary complaint, prescription of antibiotics, and use of any antidotes. "This is an attempt to look at patterns, to try and infer diseases or syndromes. I stress the point 'infer' because I don't think we can ever be sure just putting together syndromes," he added.

In the Alert system, patients are categorized on a 1 to 5 scale indicating severity of illness. The number increases as additional indicators are added to a patient's record. "We have a user interface that can be navigated," Gundlapalli told APIC attendees. "We are able to drill down. If I have a patient who comes up positive as an infectious pneumonia signal, then I could click on that and review their electronic medical record."

Beginning Feb. 1, 2002, the system was monitored via computer three or four times a day for four weeks. "It took about 30 to 45 minutes per session," he said. "You can imagine if I pulled up the grid and saw infectious pneumonia for five Level 4 or 5 patients, I would then go to the electronic medical records for each patient." The medical records were so complete, Gundlapalli only made two follow-up phone calls during the period to the physicians treating the actual patients. "We saw that most signals were within thresholds. The ER visits increased, on occasion, hospital admissions increased, and a lot of blood cultures were ordered during that time, which worried me a little bit. But really, no specific pattern was detected."

On one occasion, when the 75-patient threshold for daily emergency department visits hit 115, a surveillance colleague actually went to the hospital to get a first hand look at the situation, he said. "It was just a bad day for the ER. There was nothing specific. It shows you the power of this, but it also shows that you do need someone continuously monitoring this. You cannot have the computer make the decision."

The only real signal of a sharp disease increase was for influenza, which struck the Olympic Village and surrounding areas, he noted. Syndromic surveillance can be done without such elaborate measures, he said, urging ICPs to be, above all, "smart observers." Use the resources you have and the triggers you can read within the limits of your program, Gundlapalli advised. ■

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