BIOTERRORISM

Smallpox Vaccinations: How Much Protection Remains?

Immunity from smallpox vaccination is widely assumed to decline rapidly, but studies suggest that some protection may persist for decades

If one of the worst nightmares of biowarfare experts is realized with the release of smallpox in a major city, the virus would have a field day. The disease would sweep through an entirely unprotected population: Anybody born after the early 1970s—when most countries stopped vaccinating against smallpox—would be completely vulnerable, and the vaccinations given to older people would by now offer no protection. That, at least, is the conventional wisdom. But some experts believe this picture is excessively bleak.

There's no question that unvaccinated people are especially vulnerable: The virus kills about 30% of those who have no immunity. But just how much protection decades-old vaccinations still provide has become a matter of debate. The U.S. Centers for Disease Control and Prevention (CDC) echoes a widely held assumption: "Most estimates suggest immunity from the vaccination lasts 3 to 5 years," it says on a new public Web site devoted to smallpox. But a handful of researchers who have examined the scientific literature, including century-old studies as well as state-of-the-art explorations of immunologic memory, believe protection may be far more durable.

At first glance, the debate may seem irrelevant. A smallpox outbreak would still be horrific: In the United States alone, roughly 120 million of the 275 million people in the country were born after routine vaccination ended, and no public health official would risk not revaccinating those who received a smallpox shot 30 years or more ago. But if a substantial fraction of the population does have significant immunity, the disease might not spread as fast, and the epidemic would not be as deadly as many fear. And that knowledge could shape decisions about who should receive vaccines first if an outbreak occurs when supplies are still limited. "It should influence the discussion, and this should prompt doing some studies," says Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases.

Frank Fenner, a leading smallpox authority based at the John Curtin School of Medical Research in Canberra, Australia, is among those who believe vaccine-induced immunity to variola, the smallpox-causing virus, is quite long-lasting. Fenner, who co-authored *Smallpox and Its Eradication*, the seminal book about the disease, points to a study first published in 1913, "Studies in small-pox and vaccination," a monograph by William Hanna. In that work, researchers analyzed an outbreak of smallpox in Liverpool, England, in 1902–1903. At that time, notes Fenner, Great Britain immunized people only once, during infancy. The study looked at severity of disease in 1163 people, comparing the vaccinated to the unvaccinated in different age groups. The data show that immunity did wane over time, leading to the idea that booster shots were needed at least every 10 years. But 93% of the people 50 or older who had received the vaccine escaped severe disease and death; in contrast, six of 12 unvaccinated people in that age bracket came down with a serious case of smallpox and all of them died (see table).

During the past 11 years, two studies of the immune systems of vaccinated people also found evidence of long-lasting immunity. One arm of the immune system produces antibodies in response to foreign "antigens," preventing invaders from infecting cells, while another marshals T cells to find and destroy infected cells. A study conducted by Israeli researchers found that antibody levels declined in the first 3 years after vaccination, but after that initial drop, this type of immunity "remains stable for at least 30 years after the last revaccination," Baruch El-Ad and his colleagues reported in the *Journal of Infectious Diseases* in 1990.

In 1996, Francis Ennis and co-workers at the University of Massachusetts Medical School in Worcester reported in the *Journal of Virology* that T cell immunity in response to the smallpox vaccine also remains intact for decades. The researchers stimulated white blood cells from vaccinated people with vaccinia, the virus that serves as the smallpox vaccine and found "striking" responses. "The data presented here are perhaps the first clear evidence that virus-specific T cell memory can persist for up to 50 years in humans in the presumed absence of antigen," they concluded.

Rolf Zinkernagel, an immunologist at the University of Zürich in Switzerland who won the Nobel Prize for his discoveries about the role of T cells in immunity, cautions that these measures don't necessarily correlate with protection. Still, Zinkernagel believes that substantial immunity to smallpox does exist in the U.S. population. If a smallpox attack occurs, he says, "it will not be as bad as the epidemics in the Middle Ages." Immunologist Rafi Ahmed of Emory University in Atlanta, Georgia, agrees. The U.S. population probably has much more immunity to smallpox than many people realize, he says. "We're probably not as badly off as we have thought." But coming up with a better sense of how much protection exists remains conjecture, as even Ahmed and Zinkernagel have strikingly different perspectives about what triggers immunologic memory and how it persists.

James Leduc, the leading smallpox authority at the CDC, says, "we're now looking very closely at the historical data" on the durability of immunity. And Leduc, who says CDC hopes to update its Web site next week with scientifically based information about these questions, stresses that many uncertainties will remain: "We have a disease and a scientific database that really stopped progressing 20 years ago."

—JON COHEN

SMALLPOX CASES IN LIVERPOOL, ENGLAND, 1902–1903

Age group	Vaccination in infancy	SEVERITY Mild	Moderate	Severe	Number of deaths	TOTAL Number of cases	Fatality rate (%)
0–4	+	7	0	0	0	7	0
	-	6	24	25	25	55	45.0
5–14	+	85	11	0	0	96	0
	-	15	34	8	6	57	10.5
15–29	+	338	91	7	3	436	0.7
	-	12	41	19	10	72	13.9
30–49	+	226	101	22	13	349	3.7
	-	1	8	15	13	24	54.2
>50	+	30	21	4	3	55	5.5
	-	3	3	6	6	12	50.0
All ages	+	686	224	33	28	943	3.0
	-	37	110	73	60	220	27.2
TOTAL		**723**	**334**	**106**	**88**	**1163**	**7.6**

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