EDITORIAL

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Pre-event smallpox vaccination: Unresolved issues

AS THIS ARTICLE goes to press, the United States appears on the verge of implementing the first phase of a program of smallpox vaccination. After the President was revaccinated at the end of December 2002, the Bush administration asked health departments to vaccinate health care workers on a voluntary basis.

Specialists and local health departments are creating a coherent plan for vaccination

WHY VACCINATE NOW? THE PROS AND CONS

Americans would accept a great deal of risk from vaccination, were a case of smallpox to occur. It may be risky, however, to embark on a pre-event vaccination program for civilians in the absence of known disease, especially if the benefits are not tangible but the adverse events (real or perceived) are readily measurable. Public acceptance of smallpox vaccine could be jeopardized, creating a public health and military disaster should a need for mass immunization arise.

Despite these risks, launching a pre-event vaccination program now has several advantages.

- Vaccinees would provide a source of vaccinia immunoglobulin, which can be harvested from volunteers through plasmapheresis. The current US stockpile of vaccinia immunoglobulin is around 5,000 doses. At least 37,000 doses would need to be stockpiled to treat anticipated complications of vaccination if all Americans were vaccinated. This would require immunizing and performing plasmapheresis in at least 10,000 volunteers.
- The program would give us experience and a template for planning for mass immunization of the entire population, should the need arise. We should make it a priority to train and immunize enough volunteer vaccinators and to plan for sites and delivery of vaccine so that the entire population could be immunized within 5 days of a bioterrorist event.
- The program would show the public that the government is doing something about bioterrorism.
- It may deter terrorists from intentionally releasing smallpox as a bioweapon.

Failure to plan and act could have serious consequences should there be an intentional release of smallpox. Dark Winter, a tabletop exercise to assess the risk of a smallpox bioterrorist attack on the United States, estimated that 3 million people would contract smallpox and 1 million would die.

Many of us involved in the planning are working with local health departments to develop a coherent policy. In weighing the risks and benefits of smallpox vaccination before there is an actual bioterrorism event, the critical considerations are dynamic and include the level of disease risk and threat and the expected severe adverse reactions to vaccination.

HOW REAL IS THE THREAT?

The former Soviet Union worked hard at turning smallpox and other biologic agents into weapons of mass destruction.

In 1971, a Soviet field test of weaponized smallpox caused an outbreak in Aralsk, a port on the Aral Sea, when an ecological research ship sailed too close to a military smallpox test that sent out a deadly plume. Ten people contracted smallpox and three died; 50,000 people were vaccinated on an emergency basis and quarantine measures were imposed to

Excellent CDC smallpox resources online

Given the world situation, we physicians must begin to familiarize ourselves with smallpox and vaccinia (smallpox) vaccine. The best, most complete and authoritative information is available online at the Centers for Disease Control and Prevention web site at **www.bt.cdc.gov/agent/smallpox/index.asp.**

A particularly good index of materials for both patients and health care professionals is available at **www.bt.cdc.gov/agent/smallpox/reference/resource-kit.asp.**

control the outbreak.

Although only two countries, the United States and Russia, are known to possess smallpox strains, many analysts believe that other countries secretly have them as well. More ominously, the Central Intelligence Agency is investigating whether a former official of the Soviet Union's biological warfare program delivered a weaponized smallpox strain to Iraq.

We do not know if the US vaccine protects against the Aralsk strain or the more than 100 other militarized strains of Soviet smallpox.

New intelligence about the threat of a smallpox attack would clearly change the risk-benefit assessment for pre-event vaccination.

WHAT ARE THE RISKS OF SMALLPOX VACCINATION?

The incidence of reactions to the current Dryvax vaccine (the US live-attenuated virus vaccine) depends in large part on the population that is vaccinated.

At least two published reports addressed the adverse effects of smallpox vaccination: the experience of nationwide immunization in the Untied States in 1968,[1,2] and that of the Israeli Defense Force, which routinely immunized its recruits until 1995 (TABLE 1).[3]

In both programs, adverse events occurred in about 1 in 1,000 people vaccinated, but most were not life-threatening.

Notably, the overall rate of adverse reactions was higher in the Israeli program (4 in 1,000), perhaps in part because more of the Israeli recruits were receiving the vaccine for the first time (primary vaccination) than in the US cohort in 1968 (23% vs 7%). A few deaths (1 per million) and cases of encephalitis occurred in the US program, but not in the Israeli program; these complications occurred most often in children younger than 10 years, who were not included in the Israeli cohort.

Will these rates of complications be higher in a 2003 vaccination program? Encephalitis and deaths occur chiefly in children, so the death rate would not be expected to be as high in adult health care workers.

Nonetheless, the America of 2003 is much different from the America of 1968. There are now approximately 1 million people infected with human immunodeficiency virus (HIV), one third of whom have not been tested and do not know they are HIV-positive. Vaccination of HIV-positive patients may lead to disseminated vaccinia.[4] Millions of other Americans have relative contraindications to Dryvax vaccine due to increased risk of serious side effects (TABLE 2).

The America of 2003 is much different from the America of 1968

People who volunteer to receive the smallpox vaccine need to know the conditions that increase the risk of a serious complication and how to care for the smallpox vaccination site to avoid transmission of the vaccine virus to themselves or others—especially family or household members. Shedding from vaccinia inoculation may occur for probably 19 days (until scabbing), but the risk of transmission from a covered vaccine site is probably very small, assuming the person vaccinated does not pick at the site, follows good handwashing, and wears a shirt over the site. Patients need to be screened for atopic dermatitis, for pregnancy, and for HIV infection with history or testing or both.

In July 2002, Israel started to vaccinate 18,000 people (0.3% of a population of 6 million), including military personnel, health care workers, and first responders. The experience, reported in detail by Leonard Marcus of

the Harvard School of Public Health,[5] may provide insights for the US program.

The incidence of adverse events was very low. Five percent of vaccinees reported fevers, muscle pain, or malaise, and there were only two serious sequelae (no deaths), including a documented case of secondary transmission from a vaccinee to his immunocompromised spouse following an infection control breach regarding the vaccine site.

The careful selection process that the Israelis followed explains this low rate of adverse effects. *All vaccine recipients were volunteers and all had received smallpox vaccine before*. The incidence of vaccine complications is reduced if primary immunizations are not done and children are not immunized.

Moreover, the Israeli smallpox vaccine uses the Lister strain of vaccinia, which is less virulent than the one used in the US vaccine.

WHAT ABOUT LIABILITY?

The Federal government currently owns all of the smallpox vaccine in the United States, which includes various versions of vaccinia, and only a small portion is licensed by the Food and Drug Administration.

The Homeland Security Act is not clear where liability and compensation will fall, and this must be clarified to satisfy hospitals, third party payers, and clinicians who will be participating in the smallpox vaccination program.

HOW WILL WE MONITOR FOR AND TREAT SIDE EFFECTS?

The trickiest and most critical part of any vaccination program, even a very limited one, is monitoring vaccine safety.

The Centers for Disease Control and Prevention (CDC) is working on a system to provide real-time monitoring for adverse events. The states will set up 24- hour hotlines to answer questions and receive reports of possible adverse events in vaccine recipients and their contacts, and rapidly assess and report clinically significant or unexpected adverse events to the CDC along with requests for vaccinia immunoglobulin or the antiviral drug cidofovir.

TABLE 1

Complication rates of smallpox vaccine

COMPLICATION	ISRAELI DEFENSE RECRUITS (1991–1996)	US NATIONAL SURVEY (1968)
Primary vaccinees	23%	7%
Complications (per 10,000)		
Encephalitis	0	0.0018
Eczema vaccinatum	0.15	0.02
Total complications	0.40	0.12
Deaths	0	9 deaths*

*7 in children younger than 10 years

TABLE 2

Prevalence of contraindications to smallpox vaccination

CONDITION	ESTIMATED NO. (MILLIONS)
Active eczema	15.0
Rheumatoid arthritis	2.1
Lupus	1.4
Pregnancy	5.3*
HIV infection	0.9
Organ transplants	0.2
Incident cases of cancer	1.3

*4 million live births and 1.3 million legal abortions per year

We also need a "24/7" system to ensure that people who are immunized get timely and professional care, whether the adverse event is real or perceived. Vaccinees will demand quick assistance for themselves and their contacts.

Resources will have to be allocated by local health departments, and the likelihood of getting extra federal money is unclear. Right now hospitals will "take care of their own," which may entail great cost depending on how many people are immunized.

WHO SHOULD BE VACCINATED?

Approximately 500,000 health care workers are targeted for the initial phase, comprising

"smallpox teams" of 100 health care workers per team in 5,100 acute care hospitals. These are the people who would care for the first cases of smallpox should there be a bioterrorist attack. This number might expand to as many as 10 million, however.

For the pre-event program, we would probably want to pass over health care workers who routinely take care of severely immunocompromised patients such as transplant recipients. HIV is less of an issue for hospital patients, as far fewer patients with HIV are hospitalized today thanks to highly active antiretroviral therapy. Notably, the recent Israeli program did not furlough health care workers who were immunized.

No one is advocating immunization of the entire population, but FDA-approved vaccine will probably be available to everyone by 2004.

WILL VACCINATION ALONE CONTAIN OUTBREAKS?

FDA-approved vaccine may be available to everyone by 2004

To eradicate smallpox in Africa in the 1970s, the World Health Organization used a "ring" vaccination strategy, in which close contacts of infected persons were identified and vaccinated. Whether this strategy would contain an outbreak in an urban and mobile population is unclear.

In addition, without antismallpox chemotherapy, many immunocompromised people may be excluded from prophylaxis or treatment in an outbreak. Researchers are trying to develop safer vaccines and antiviral agents to treat smallpox.

At least two attenuated live-virus smallpox vaccines that are approved for use in Japan and Germany have excellent safety profiles in children. Notably, one of them has been given to immunocompromised patients (including HIV-infected patients) without serious side effects. Phase 1 studies in HIV-infected persons in the United States are to begin in February 2003.

WHAT IF THERE IS A CASE OF SMALLPOX?

If a case of smallpox is identified anywhere in the world, we would have to assume it was the result of bioterrorism and anticipate a global quarantine, cessation of international commerce, and mass smallpox immunizations.

Old stockpiles of Dryvax have been shown to induce immunity in primary vaccinees at a 1:10 dilution, which would extend the current US supply to approximately 150 million doses. Production of new vaccine for all Americans is ongoing, and is anticipated to be completed by the end of 2004.

This scenario raises an interesting question: will there be a struggle between the vaccine "haves" and "have-nots"? Would the United States give up some of its stockpile of smallpox vaccine to quell an outbreak in Korea or in Sweden? Before September 11, I would have said yes. Today, I'm not so sure.

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