

Proposition 'The new cell culture smallpox vaccine should be offered selectively to the general population'

For the proposition:

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Abbreviations

WHO	World Health Organisation
FSU	Former Soviet Union
VIG	Vaccinia immune globulin
NYCBH	New York City Board of Health strain
FDA	US Food and Drug Administration
NIAID	National Institute for Allergy and Infectious Diseases
MVA	Modified Vaccinia Ankara
IDF	Israeli Defense Force
CDC	Centers for Disease Control and Prevention
R ₀	Basic Reproductive Rate

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Summary

A series of major factors must be weighed in deciding whether or not, and to what extent, a particular country should consider pre-exposure vaccination for smallpox. These include the risk of a bioterrorist attack using smallpox, the risk of secondary spread from another country, the risks and benefits of vaccination, the effectiveness of vaccination pre- and post-exposure, the prevalence of immunocompromised persons, the capacity of the medical care delivery system and the wealth of a nation. We review here the issues and variables relevant for policy making, propose a framework for country-specific decision making and suggest the World Health Organization has a key role to play, particularly with regard to lower-income countries. In doing so, we support the proposition that the new cell culture smallpox vaccine should be selectively offered to the general population.

Introduction

Smallpox (*Variola Major*) is a deadly scourge with, at present, no known treatment other than supportive therapy. It has an overall mortality in the unvaccinated of 30%, leaves 60 to 80% of survivors permanently disfigured and has death rates in the very young and the elderly approaching 50% [1, 2, 3, 4, 5]. There is an extremely effective live virus vaccine available that very rarely results in death but somewhat more frequently causes severe complications [6, 7]. The last cases of smallpox occurred in 1977 and 1978, the US and Britain stopped routine vaccination in the early 1970s and the world was declared free of smallpox in 1980 by the World Health Organisation (WHO) [8, 9, 10]. The virus has been weaponized and weaponized virus may have leaked from the Former Soviet Union (FSU) and/or stocks of virus may not have been destroyed by some countries as called for by WHO in the late 1970s [11, 12]. The former deputy director of the Soviet biological weapons program considers it proven that North Korea possesses the smallpox virus and that Iraq is also a likely candidate to have the virus [13]. Vaccination of North Korean and Iraqi troops has also been reported [14].

Bioterrorism and smallpox became a pressing US and international issue after September 11, 2001. The US Government considered the threat sufficient to purchase vaccine and vaccinia immune globulin (VIG) for all Americans in preparation for a possible smallpox attack [15, 16]. Vaccinia immune globulin is a blood product derived from the plasma of humans who have recently been vaccinated. It is available in two forms, intramuscular and intravenous, and is in short supply in the US and almost certainly worldwide. 15,000 doses are currently being produced in the US with options for up to 100,000 total doses. VIG is substantially effective in controlling generalized vaccinia, and eczema vaccinatum. Its effectiveness in vaccinia necrosum is more problematic; it is not effective for post-vaccinal encephalitis and is contraindicated in vaccinia keratitis. The call for pre-exposure vaccination came quickly [17, 18, 19, 20]. The head of Russia's Vektor Institute urged widespread immunization against smallpox, the British Government bought enough vaccine for 50% of the population, Germany purchased 6 million doses and Israel began vaccinating first responders [12, 21, 22, 23]. The US initially considered very modest pre-exposure vaccination [17, 24]. Now, the White House appears to be on the verge of announcing a far more ambitious plan for pre-attack vaccination of first responders followed by voluntary vaccination of the general public [25].

The former WHO Director of Smallpox Eradication summarized the threat as early as 1999 [26]:

"Despite routine vaccination in Yugoslavia, the first case in the 1972 outbreak resulted in 11 others; those 11, on average, each infected 13 more. Other outbreaks in Europe from 1958 on showed that such explosive spread was not unusual during the seasonal period of high transmission.....One can only speculate on the probable rapidity of spread of the smallpox virus in a population where no one younger than 25 years of age has ever been vaccinated and older persons have little remaining residual immunity."

The Questions

The fundamental questions facing countries around the world are:

- 1 - What is the risk of being a target for a smallpox attack?
- 2 - What is the risk of secondary spread from an attacked country?
- 3 - What are the risks of vaccination?
- 4 - What is the feasibility of reducing the risk of vaccination?
- 5 - What are the direct and opportunity costs of pre-exposure vaccination in a particular country?
- 6 - What are the options for post-exposure control?

The answers to these questions will help illuminate the local policy options, which range from:

- 1 - Do nothing;
- 2 - Stockpile limited amounts of vaccine with or without vaccinia immune globulin;
- 3 - Vaccinate key personnel before any exposure;
- 4 - Vaccinate the general population voluntarily;
- 5 - Require mandatory pre-exposure vaccination of the general population.

Countries at high risk of attack face malicious dissemination by multiple terrorists in multiple geographic areas in the context of a mobile population with low immunity. Countries at low risk of attack but subject to secondary spread will face accidental dissemination and possibly far fewer disseminators. Countries will have a variable number of immunocompromized individuals, particularly due to HIV infection which may be unrecognised in many citizens. Further, without regard to the prevalence of AIDS, the capacity of a country's health system or the opportunity costs of pre-exposure vaccination, low-risk countries can reasonably consider less aggressive pre-exposure strategies. For some countries, when health care delivery capacity, opportunity costs and HIV/AIDS prevalence are considered, the case for modest or no pre-exposure action is strong.

We suggest a country-specific risk profile to illuminate the policy decision of whether or not to vaccinate before smallpox occurs. Depending on the risk profile of a country, options 1 through 4 are reasonable. We find no situation that merits option 5. However, before moving to country-specific policy decisions, it is necessary to consider how attack risk varies by country, the risks of vaccination and post-attack control methods.

The Risks of Direct Attack and Secondary Spread

We posit that the highest-risk countries are the US, Israel and the UK. Unfortunately, meaningful quantification of the risk is not possible, and others may wish to add to or delete from this list. The case for selective, progressive, voluntary pre-exposure vaccination of the entire population merits very serious consideration in the US. This has been proposed by one of us, and is being actively debated as this article is being written [17, 18, 19, 20, 24, 25].

All countries are at risk of secondary spread from an attacked country. However, that risk is greatest for geographically contiguous countries or countries where there is extensive travel from a country at high risk of attack. Thus, if the US is attacked, Canada will be at far higher risk of secondary exposure than Bhutan. In like manner, an attack on Israel places the West Bank and the Gaza Strip at much higher risk than Malaysia.

A country such as Zambia is very unlikely to be a direct target of smallpox bioterrorism and has only moderate risk of indirect spread. Further, it has a high HIV/AIDS prevalence, low expenditure on public health and medical care and many pressing unmet needs for health services [27, 28]. Countries with this type of profile may be well advised to do nothing at this stage.

A country such as Singapore presents a very different situation. The risk of attack is low but travel through Singapore from high-risk countries is high. HIV/AIDS prevalence is also low and the capacity to identify and protect the immunocompromized is high [27]. The health system functions well and the country could afford an investment in preventing a low-risk event that, should it occur, would have calamitous health and economic consequences [29]. Thus, Singapore could reasonably consider vaccinating first responders and stockpiling sufficient vaccine and VIG for its entire population.

A similar analysis can be done for any country. It is essential to emphasize that the analysis is going to be heavily influenced by value judgments that will vary greatly country by country. Thus it is possible that two somewhat similar jurisdictions, such as Singapore and Hong Kong, using the same analytic framework, might choose different policies.

Underlying these conclusions are assumptions about the risks of vaccination, the ability to identify and protect the immunocompromized and the ease or difficulty of containing an outbreak of smallpox. Resuming vaccination before smallpox recurs, if it ever does, requires an assessment of attack risk and a full understanding of the risk of vaccination by age, prior vaccination history, immunocompromized status, skin condition and possibly pregnancy. However, pregnancy may not be a contraindication [30, 31].

New Smallpox Vaccines and Vaccination Methods

A new cell culture derived vaccine, in full-scale production by Acambis, uses the same vaccinia strain (New York City Board of Health; NYCBH) as the older US product (Wyeth Dryvax). Licensure is anticipated as soon as manufacturing, control and clinical data are acceptable to the US Food and Drug Administration (FDA). This vaccine was designed to mimic the immunogenicity of the old product. The side effects are expected to be similar to the side effects of the Dryvax that was used widely until 1972 and intermittently to the present [32].

The US National Institute for Allergy and Infectious Diseases (NIAID) is encouraging the development of a smallpox vaccine using a non-replicating live vaccinia virus (Modified Vaccinia Ankara or MVA). The NIAID hopes to demonstrate that MVA will be safe for use in immunocompromized hosts, persons with atopic dermatitis, and the general population. If development and licensure proceed without difficulty, MVA could be licensed by the FDA in 2005 and available thereafter. Alternative live attenuated replicating vaccinia vaccines, e.g. the Japanese LC16m8, may have fewer side effects than the NYCBH strain and be a safer product for use in the general population, but probably not in the immunocompromized. FDA licensure of an attenuated replicating vaccine would be unlikely before 2005 [33,34]. Once Acambis has fulfilled its obligations to the US Government, its vaccine will be available for

purchase by other jurisdictions [32]. For planning purposes, until at least 2005, it is prudent to assume a vaccine risk profile based on historical data. If safer and effective vaccines become available, all other risks and benefits remaining constant, the case for more extensive pre-exposure vaccination would become stronger.

As a human challenge with smallpox to test the true protective effect of new vaccines is not possible, there may always be some doubt as to the efficacy of an attenuated or non-replicating vaccine. Fenner, has suggested, as have the Germans, that immunization with an attenuated or non-replicating vaccine might decrease side effects from a subsequent, known to be protective, immunization with the replicating NYBH strain [35].

A case can be made for the use of Jet Injectors, particularly in a post-exposure setting. However, even where maintenance is not a problem, there is concern that transmission of blood and blood borne disease is possible from vaccinee to vaccinee [36]. Thus, at his time, jet injectors are not the method of choice. CDC is contracting for the development of "a high-speed device which uses safe, disposable cartridges" [37]. If and as this is proven effective and safe, then it will be appropriate to reconsider a higher speed and more automated method for vaccination.

The Risks of Vaccination

The most relevant, recent experience, from US 1968 data on complications and deaths associated with 5,594,000 primary vaccinations and 8,547,000 revaccinations including complication and deaths in contacts of vaccinees is summarized below [6]:

Post-Vaccinal Encephalitis - 4 deaths/16 cases, no treatment.

Vaccinia Necrosum or Progressive Vaccinia - 4 deaths/11 cases - usually in immunocompromized - historically no effective treatment, VIG may be of some benefit.

Eczema Vaccinatum -1 death in a contact/58 cases in primary vaccinees, 8 cases in revaccinees and 60 cases in contacts - treatment with VIG very effective

Generalized Vaccinia - 0 deaths/143 cases - usually self-limited

All other complications - 0 deaths/276 cases, all minor

The risk in those who have been vaccinated previously is very small, with 14 severe complications, including 2 deaths (one under age 10) in 8,547,000 revaccinees. However, the primary vaccinee population older than 9 was comparatively small (694,000) and primary vaccinees over 14 number only 399,000. The two deaths in persons over 14, a primary vaccinee with aplastic anaemia and a revaccinee with chronic lymphocytic leukaemia, were in patients we would anticipate screening out in a pre-exposure scenario today

78% of deaths (7 of 9), 82% of very serious complications (Vaccinia Necrosum, Post-Vaccinal Encephalitis, Eczema Vaccinatum) and 81% of all complications occurred in children under ten. Six of nine deaths were in primary vaccinees, two in revaccinees (one child, one adult) and the one death in a contact was from Eczema Vaccinatum in an accidentally infected child. It is clear that primary vaccination is most risky in children under ten. If children under 10 and persons who could reasonably be expected to be screened out were eliminated from this data and, *pari passu*, 90% of the contact cases also eliminated, there would be a total of 8,973,000 vaccinations (4.4% primary) with 25 to 30 severe complications including 0 to 3 deaths.

Although there is additional experience with adult vaccination in the US military, the Israeli Defense Force (IDF), CDC in the 1980s and 1990s and Israeli first responders today, these are primarily if not exclusively revaccinations. We do know there were three US military vaccine-related deaths in WWII [38] and one case of disseminated vaccinia in an HIV-infected man. The man's disseminated vaccinia resolved with vaccinia immune globulin (VIG) therapy, healed in mid-Aug 1984, well before his death in Dec 1985 [39]. He was treated with amphotericin for cryptococcal meningitis until the time of his death. No autopsy was performed. No other causally attributable deaths due to smallpox vaccination among US military personnel have yet been identified [40]. The IDF reports no deaths but some complications [41]. CDC has vaccinated about 11,400 adults since the early 1980s with no known severe complications or deaths [42]. Currently, 9,000 first responders have been vaccinated in Israel with no serious complications or deaths [43]. These sources confirm that revaccination of adults is very safe but do not add to the adult primary vaccination experience.

Neff, et al comprehensively reviewed accidental transmission and report the vast majority of accidental vaccinations are from close contact with siblings, family members or playmates (138/143). Of the remaining cases, three featured close contact and 2 were children in day care centers with unknown contacts [7].

Since widespread vaccination stopped in the 1970s, HIV has become pandemic, with large numbers of immunocompromized persons in some countries and at least a small number in virtually all countries [27]. Organ transplant patients on long-term immunosuppressive therapy are also at increased risk. Some cancer patients may be immunosuppressed due to therapy, as may some patients on corticosteroids. In addition, at least in the US, the prevalence of eczema may have increased two or three fold and patients with eczema or a history of eczema are at a higher risk of dermal complications than the general population and are also at higher risk of accidental vaccination by close contact, usually a family member [6, 7].

Controlling the Risks of Vaccination

As we consider the risks of vaccination, particularly to the immunocompromized, it is well to remember that the immunocompromized are also at the highest risk of death from smallpox. Orderly and careful pre-exposure screening with counselling as to what to do in the case of an outbreak, along with increasing the immunity of the general population, all serve to protect the immunocompromized pre- and post-exposure. Pre-exposure vaccination should be unhurried, screening out individuals at higher risk of complications. Serious consideration should be given to either voluntary or mandatory HIV testing prior to vaccination if there is any question about HIV status.

Specific steps to decrease pre-exposure vaccination morbidity and mortality include:

- 1 - Use the double semi-permeable membrane dressing reported to reduce viral shedding by 97% or more. This will greatly decrease an already very low risk of accidentally vaccinating others [44, 45].
- 2 - Do not vaccinate children under 10 unless the risk of attack is judged to be high and imminent. This eliminates many cases of active eczema and historically would eliminate 80% of very severe complications and deaths from vaccination. In case of attack, children can be isolated and rapidly vaccinated.

3 - Carefully screen all adults with the expectation that those who have been vaccinated previously have a risk of death on the order of one in five million. The remaining population at highest risk of complications is older children and young unvaccinated adults (ages 10 to 33). In more developed countries this will be about 27% of the total population [46]. By observing the current Israeli experience and the US experience with vaccination of adult first responders, likely to begin very soon, other countries can determine the effectiveness of screening and the actual risk their population may face.

We note that, for those countries that continued routine vaccination after 1972, the proportion of the population at lower risk of vaccination side effects will be higher. Thus, in assessing the risks and benefits of vaccination, the percent of the population who have never been vaccinated and are 10 years old or older should be estimated for each country.

Careful screening, not vaccinating children and using the double semi-permeable membrane dressing should keep pre-exposure vaccination complications and deaths at or below historic levels. For countries with a high HIV/AIDS prevalence, limited capacity to determine who is actually immunocompromized and without sufficient resources to assure supplies of VIG and semi-permeable dressings, pre-exposure immunization is, almost certainly, contraindicated.

Residual Immunity

Unfortunately there is no clear and unambiguous answer to the duration of immunity. Most would agree that it is substantial for 10 years and wanes thereafter. Mack in his review of European outbreaks from 1950 to 1971 presents figures which suggest that vaccination from 0 to 10 years before exposure has a case mortality rate of 1.4%, between 11 and 20 years 7% and after 20 years the mortality rises to 11% [5]. The data from a smallpox outbreak in Liverpool in 1902-03 suggest that immunity may be greater, with case death rates between 5% and 10% 30 to 60 years after vaccination. [47, 48]. In fact, we do not know the degree of residual immunity, only that it wanes over time and in 2002 will probably decrease deaths but cannot be counted on for protection against disease.

Infectivity of Smallpox

In determining the risks associated with either attack or accidental spread to another country, it is important to consider how many persons a terrorist might infect (the first generation of transmission) versus how many persons will be infected by cases in the second and subsequent generations of transmission. Or, how will the basic reproductive rate (R_0) vary by generation? A terrorist could spread smallpox either as an infected person or by using an aerosol. Aerosol spread would likely be more effective. Consider the case of a single infected terrorist who travels to the country being attacked just after being infected. There is no way to screen for the disease in the prodrome. Once in the country the terrorist need only go to a hotel, assure a supply of food and fluids and watch his temperature curve. As the prodrome ends and his temperature drops, he will have no visible rash, be feeling better but not well and have 2 to 4 days to move about in crowded venues before showing the characteristic rash of smallpox. In these few days it is plausible, even likely, that one terrorist could infect a hundred or more persons. An outbreak reported by Wanklyn in 1913 and cited by Dixon is chilling and prescient [49]:

"One person with smallpox arriving in the country travelled by train....he was apparently in the initial phase of the disease, as nobody noticed a rash on his face...Almost everyone who travelled with him in the compartment from Queensborough to Manchester contracted

smallpox, the ticket collector...and those who travelled with him to Stalybridge in another train, something like a hundred people being infected from one single case."

Malicious dissemination, by multiple terrorists in a high-risk country that has a mobile, low-immunity population, could have devastating consequences. Our modelling suggests that 5 terrorists in the US could easily infect 200 persons leading to 114,000 cases and 28,500 deaths in over 600 cities and towns by days 40 to 45 [50]. Second and subsequent generations of cases with public information and awareness, isolation, limits on travel, and the implementation of vaccination would soon reduce the intergenerational transmission rates and the outbreak would be controlled. If post-exposure vaccination is not instituted rapidly, control will take longer. Our second and subsequent transmission rates are consistent with the findings of Gani and Leach, who have analyzed a number of outbreaks and conclude [51]:

"For contemporary outbreaks in industrialized countries, which now have low levels of herd immunity an R_0 value of 4 to 6 would probably apply for community-acquired infections, but might transiently be higher (for example, 10 to 12) before the disease was correctly recognized and appropriate hospital infection controls implemented. These values differ from recently applied values. The higher values from 10 to 20 have been estimated from atypical outbreaks with unusually high transmission rates, whereas the lower estimates of around 2 appear to have neglected concurrent herd immunity..... significant epidemics could result, particularly if there were delays in detecting the first cases or in setting up effective public health interventions."

The situation is different for the person who, infected by a terrorist in an attacked country, travels to another country. This infected person is likely to infect others but without malicious intent and the initial R_0 will be smaller, perhaps 10 to 12, quite possibly less.

The Ephemeral Post-Exposure Window of Opportunity for Vaccination

A widespread belief that vaccination within 4 days of exposure will protect against smallpox is buttressed by seemingly authoritative statements [52]. However, hard data is scant. Dixon, reporting on the 1946 Tripoli outbreak noted 21 persons with no history of vaccination who were vaccinated within 5 days of exposure. All 21 came down with smallpox and none died. He concluded [53]:

"Successful vaccination, even done as soon after contact as this, therefore, is no guarantee of complete protection although there may be a guarantee against death."

This conclusion is consistent with much earlier data from Liverpool reported by Hannah as cited by Baxby reporting no subsequent disease in an unvaccinated contact vaccinated on the day of exposure and a second unvaccinated contact vaccinated 2 days after exposure [48]. However, 2 others vaccinated on day 2 developed mild cases of smallpox and all persons vaccinated on days 3, and thereafter developed smallpox. McVail's somewhat weaker data as reported by Mortimer also support a conclusion of limited benefit from early post-exposure vaccination [54].

Those with experience of smallpox eradication report anecdotally that vaccination shortly after exposure decreases the severity of disease [55]. However, Mack, in his review of European outbreaks, reported 70 persons vaccinated after exposure with 20 deaths or 29% mortality but does not report the interval between exposure and vaccination [5, 56]. Clearly, the post-exposure window is more hope than reality and, at best, provides very little opportunity for outbreak control.

Controlling an Outbreak of Smallpox

Smallpox is most contagious as soon as lesions appear in the mouth and throat. At this point the prodrome of 5 to 11 days ends, fever typically drops and the patient is very infectious. The rash in the mouth and throat is not visible and when the rash first appears on the skin it is easily overlooked in the first day or two and is not usually classic in appearance until day 3, or more likely day 4 or even 5 [2, 3, 4]. From a control perspective this means that there is ample opportunity for person-to-person spread before any case can be diagnosed and quarantined. Kaplan, Craft and Wein have demonstrated that ring vaccination is a prescription for failure in the face of a serious bioterrorism attack, negating the overly optimistic assumptions in the CDC modelling by Meltzer, et al [57, 58]. Kaplan and Wein have also demonstrated that the reported effectiveness of ring vaccination in smallpox eradication in West and Central Africa reported by Foege, et al can be explained solely on the basis of growing population immunity [59, 60]. Isolation and quarantine are an integral part of the ring vaccination strategy. However, enforcing widespread quarantine and isolation in most societies, and certainly the US, is unlikely to work [61].

There are three options for post-exposure control:

- 1 - National post-exposure vaccination;
- 2 - Local, wide-spread mass vaccination;
- 3 - Identification of contacts and ring vaccination with isolation and quarantine.

As Kaplan, et al and one of us (WB) have pointed out, all post-exposure control strategies work faster when more people are vaccinated before an attack as it is harder for the disease to spread and there are fewer people to vaccinate [57, 17].

The Intervention Options

The points of intervention can be considered linearly from pre-exposure to post-exposure along with the effectiveness and risk of each intervention.

Pre-Attack:

- 1 - Prevent Attack by confiscating supplies. This is arguably desirable but highly speculative as the locations of possible stocks of smallpox are not known and are very difficult to determine.
- 2 - Mandatory pre-exposure vaccination of all persons without contraindications to vaccination - Possible only in societies with strong central governments capable of enforcing a mandatory order. The feasibility of mandatory pre-exposure vaccination in most countries is speculative, nor is there need, as other less draconian options are sufficient.
- 3 - Voluntary pre-exposure vaccination of all persons without contraindications to vaccination - Feasible in any wealthy country and, if the numbers accepting vaccination are as predicted in the US (about 60% of adults), post-exposure control would be far simpler [62].
- 4 - Pre-exposure vaccination of persons without contraindications to vaccination necessary to maintain the functions of civil society- This option in the US would require vaccinating an estimated 2% to 3% of the entire population. D.A. Henderson at the Advisory Committee on

Immunization Practices meeting May 8, 2002 at CDC suggested 10 million as a possible number. We arrive at the same number as follows: all medical personnel in the US number about 5.5 million, others necessary to maintain civil society, at least another 5 million (also estimated by Dr. Henderson). An upper bound of 5% to 7% of the total population or between 15 and 20 million people seems generous and of these one could expect 40% to either decline or be ineligible for vaccination for a final total of 2 to 3% of the population or up to 10 million broadly defined first responders.

5 - Pre-exposure vaccination of first medical responders without contraindications to vaccination. Limiting first responders to medical and public health personnel drops the number to 5.5 million and, assuming 40% opt out or are ineligible, the final number is 2.2 million or about 0.8% of the US population.

6 - Pre-exposure vaccination of a small number of public health laboratory and epidemiologic investigatory personnel and a limited number of first responders all without contraindications to vaccination sufficient to operate laboratories and initiate outbreak investigations and post-attack vaccination. Initial CDC estimates of this number were around 20,000 persons nationwide or about .0001% of the population [17, 24].

7 – No pre-exposure activity beyond a minimal, country-specific, risk assessment.

As the US health care delivery system is generously staffed in comparison to many other countries, the proportion of the population who would need to be immunized to satisfy options 4 and 5 in other countries would likely be no higher and probably lower than in the US.

Post-Attack Including Secondary Spread:

1 - Mass vaccination of the entire population. Depending on national preference, this could be voluntary or mandatory with few if any exemptions for known or suspected smallpox contacts and limited exemptions linked to isolation for persons with underlying diseases (e.g. the immunocompromised) not believed to be direct contacts;

2 - Local mass vaccination in the geographic areas where cases occur with the same caveats as in 1 just above;

3 - Ring vaccination, isolation of contacts and quarantine of cases.

Depending on national geography, population distribution and intensity of attack or secondary exposure, option 2 may be preferable to option 1. Options 1 and 2 would, if feasible, include quarantine of cases and isolation of contacts. The CDC revised guidelines (September 23, 2002) describing "voluntary, large-scale, postevent smallpox vaccination" broadly endorse approaches 1 and 2 [63].

Overall, for a high-risk country pre-attack option 3 plus post-attack option 1 provides the highest level of protection of the general population and can be expected to control an attack very rapidly with minimal cases and deaths [17, 57, 64]. Alternatively, pre-attack option 4 plus post-attack option 1 can well be argued as equally desirable. The side effects of vaccination would be less and the number of additional cases of smallpox post attack would be small.

If smallpox ever appears in another country, it is reasonable to consider imposing travel restrictions on entrants from that country and from other countries at high risk of secondary spread. Further, a country at high risk of post-attack secondary spread might also move rapidly to pre-emptive voluntary mass vaccination.

The weakness of pre-attack option 5 is that it ignores essential functions such as supplying urban populations with food, operating the electric power grid, public safety, maintaining communications, including an effective media, and similar functions. Pre-attack option 6, although reasonable in many countries, quite correctly appears to be rapidly moving off the agenda in the US. Option 7 is reasonable for countries with special risks (see below).

Countries by Risk Group

If the countries at highest risk of attack are the US, Israel and the UK, then the countries at high risk of secondary spread are Canada, Mexico, Ireland, the Occupied Territories, Lebanon and possibly Syria, Jordan and Egypt. Countries at moderate risk of secondary infection would include most European countries, many Caribbean countries that are tourist destinations, Singapore, Hong Kong and Japan. Other countries would qualify as being at lower risk of infection. To move from a provisional to a final classification requires a quantitative assessment of travel from high risk of attack countries to other countries.

National Policy Options

We propose the following for worldwide public and professional debate:

1 - Countries at high risk of attack:

Minimum package: Voluntary vaccination of eligible medical and public health first responders. Stockpile vaccine sufficient for the entire population and stockpile VIG sufficient to manage probable vaccine complications.

Maximum package: Minimum package plus voluntary vaccination of all remaining first responders. Make the vaccine available on a voluntary basis to the general public.

2 - Countries at high risk of secondary spread:

Minimum package: Stockpile vaccine sufficient for 50% to 100% of the population. Stockpile VIG sufficient to manage probable vaccine complications.

Maximum package: Minimum package plus vaccinate medical and public health first responders.

3 - Countries at moderate risk of secondary spread:

Minimum package: Stockpile sufficient vaccine and VIG to initiate but not complete widespread vaccination with a vaccine and VIG stockpile sufficient for 10% to 25% of the national population.

Maximum package: Minimum package plus vaccinate a limited number of medical and public health first responders.

4 - Countries at lower risk of secondary infection:

Minimum Package: Assure rapid availability of vaccine and VIG from sources in country or abroad.

Maximum package: Stockpile vaccine and VIG sufficient for 10% of the population. Vaccinate a limited number of medical and public health first responders.

5 - Countries with special risks:

If a country has a severely under-funded health system and/or has a high prevalence of AIDS, as is the case in much of eastern and southern Africa, then the combination of risks to the immunocompromized and the opportunity costs of immunizing against smallpox are sufficiently great to merit doing no more than assuring the rapid availability of vaccine and VIG should smallpox occur.

The definition of first responder or persons likely to come in contact with an infected person will vary from country to country. A high-volume transit country such as Singapore, for example, might include airport passenger service workers and hotel staff.

Some countries in categories 1, 2 and 3 just above, particularly smaller, wealthier countries with good medical and public health systems might choose voluntary pre-exposure mass vaccination to avoid economic and social disruption and, for all practical purposes, eliminate the risk of smallpox.

The Role of WHO

As many countries have constrained supplies of human and financial resources, WHO should consider the following:

1 - In consultation with lower-income member countries assist with developing country-specific smallpox strategies;

2 - In anticipation of a major bioterrorist use of smallpox, purchase and stockpile smallpox vaccine, bifurcated needles and VIG in sufficient quantities to control the accidental but predictable spread of smallpox to lower-income countries that cannot and should not purchase or stockpile their own supplies;

3 - Acting on behalf of all member nations consider contracting with one or more suppliers of semi-permeable membrane dressings. Richer countries could pay but could use the contract to obtain advantageous pricing. In the case of poorer countries with an interest in pre-exposure vaccination, WHO should consider purchasing and providing the dressings.

4 - Identify, train and vaccinate regional rapid response teams to assist in identifying cases and implementing national responses.

5 - Identify and, as needed, assist in strengthening regional laboratories for the definitive diagnosis of smallpox.

Conclusions

The case for pre-exposure vaccination varies country by country and requires a country-specific assessment of risk factors prior to making a policy choice. The few countries at highest risk of attack should consider substantial pre-exposure immunization as Israel and the US are doing. Other countries can reasonably do less and some countries with weak health-care delivery systems, limited human and financial resources and a high prevalence of HIV/AIDS should consider taking no anticipatory action. WHO has a key role to play in

assisting lower-income countries in developing country-specific risk assessments, stockpiling smallpox vaccine, bifurcated needles and VIG for use in lower income countries, arranging for the purchase and/or supply of semi-permeable membrane dressings, organizing regional rapid response teams and assuring the diagnostic capacity of regional laboratories.

References

1. LeDuc JW, Damon I, Meegan JM, Relman DA, Huggins J, Jahrling PB. Smallpox research activities: U.S. interagency collaboration, 2001. *Emerg Infect Dis* 2002; Vol. 8, No. 7 July, <http://www.cdc.gov/ncidod/EID/vol8no7/02-0032.htm> accessed 9/21/02.
2. Breman JG, Henderson DA. Diagnosis and management of smallpox. *N Engl J Med* 2002; 346:1300-1308.
3. Henderson DA, Inglesby TV, Bartlett JG, et al. Smallpox as a biological weapon: medical and public health management. *JAMA* 1999;281:2127-37.
4. Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi ID. *Smallpox and its eradication*. Geneva: World Health Organization, 1988. <http://www.who.int/emc/diseases/smallpox/Smallpoxeradication.html> accessed 9/21/02.
5. Mack, TM, Smallpox in Europe, 1950-1971, *Journal of Infectious Diseases*, 1972, Vol. 125, No. 2, February, pages 161-169. It is noteworthy that Mack found that young adult unvaccinated hospital workers had a smallpox mortality of 70%, with 14 deaths in 20 cases.
6. Lane JM, Ruben FL, Neff JM, Millar JD, Complications of smallpox, national surveillance in the United States 1968. *N Engl J Med*, 1969; 281, 1201-1208, November 27.
7. Neff, JM, Lane JM, Fulginiti VA, Henderson DA, Risk of transmission of vaccinia virus to contacts. *JAMA* 2002; 288: 1901-04.
8. World Health Organization declares smallpox eradicated 1980. <http://www.pbs.org/wgbh/aso/databank/entries/dm79sp.html> accessed 9/14/02.
9. Kemper AR, Davis MM, Free GL. Expected adverse events in a mass smallpox vaccination campaign. *Effective Clinical Practice* 2002; March/April, pages 84-90. <http://www.acponline.org/journals/ecp/marapr02/kemper.htm> accessed 9/21/02
10. BBC News. Smallpox Immunity Waning., 2002; May 29. <http://news.bbc.co.uk/1/hi/health/2014513.stm>, accessed 9/21/02
11. Alibek K. *Biohazard* Random House, Inc. 1999.
12. Picard A. Experts raise smallpox alert: global vaccination campaign urged by scientists fearing bioterror threat. *Globe and Mail (Canada)* 2001; November 6, page 1.
13. Alibek K. Testimony before a special US congressional hearing "Combating Terrorism: Assessing the Threat of a Biological Weapons Attack." October 22, 2001. <http://www.newsmax.com/archives/articles/2001/10/21/204923.shtml> accessed 9/24/01.
14. Personal communication with Dr. Jonathan Tucker, Director of the Chemical and Biological Weapons Nonproliferation Program of the Monterey Institute, Washington DC. He stated declassified Defense Intelligence Agency documents noted evidence of recent vaccination of North Korean troops and Vaccination of Iraqi troops at an unspecified time, June 4, 2002.

15. The Council on Foreign Affairs in cooperation with the Markle foundation. Terrorism: Questions and Answers. <http://www.terrorismanswers.com/weapons/smallpox3.html> accessed 9/14/02).
16. Personal communication with John Becher CDC 7/24/02 and 8/12/02. The US government has also contracted for the production of sufficient Vaccinia Immune globulin (VIG) to manage the side effects of vaccination for the entire population. Also <http://micro.newswire.ca/releases/August2002/12/c1906.html/6128-0> accessed 9/21/02.
17. Bicknell WJ. The case for voluntary smallpox vaccination. *N Engl J Med* 2002; 346:1323-25.
18. Editorial (unsigned). The Public Health Priesthood. 2002; *The Wall Street Journal* June 19.
19. Editorial (unsigned). How to Prepare for a Smallpox Attack, *The New York Times* June 23, 2002.
20. Editorial, Senator Bill Frist. Deciding Who is Protected Against Smallpox. *New York Times*, 2002; Late Edition, Final, Section A; Page 15; August 9.
21. BBC. Smallpox Threat, <http://www.bbc.co.uk/science/hottopics/smallpox/vaccine.shtml?tl3> accessed 9/14/02.
22. Paul-Ehrlich and Robert-Koch Institutes. http://www.pei.de/english/pm/2001/13_2001_e.htm accessed 9/14/02.
23. Brennan P. Israel preparing for worst: Begins smallpox vaccinations. *NewsMax.com* 2002; Aug. 19. <http://www.newsmax.com/archives/articles/2002/8/17/165828.shtml> accessed 9/14/02.
24. CDC Telebriefing Transcript, Smallpox vaccine, June 20, 2002, Briefers: Drs. Gerberding and Modlin, <http://www.cdc.gov/od/oc/media/transcripts/t020620.htm> accessed 9/14/02.
25. Altman LK, Stolberg SG. Smallpox Vaccine Backed for Public. *The New York Times*, October 5, 2002 citing Dr. Fauci, Dr. Gerberding and Mr. Hauer.
26. Henderson DA. Smallpox: Clinical and epidemiologic features. *Emerg Infect Dis* 1999; 5(4):537-9, Jul-Aug..
27. UNAIDS, Epidemiological fact sheets by country. http://www.unaids.org/hivaidsinfo/statistics/fact_sheets/index_en.htm accessed 9/21/02.
28. World Health Organization, *World Health Report 2001*. Annex Table 5, page 166. <http://www.who.int/whr/2001/main/en/annex/annex5.htm> accessed 9/24/02.
29. World Health Organization, *World Health Report 2001*. Annex Table 5, page 165. <http://www.who.int/whr/2001/main/en/annex/annex5.htm> accessed 9/24/02.
30. Levine MM. Live-virus vaccines in pregnancy. Risks and recommendations. *Lancet* 1974; 2(7871):34-8, Jul 6.
31. Saxon L, Cantell K, Hakama M. Relation between smallpox vaccination and outcome of pregnancy. *American Journal of Public Health & the Nation's Health* 1968; 58(10): 1910-21, Oct.
32. Personal communication Thomas P. Monath, MD, Chief Scientific Officer Acambis Inc., 38 Sidney Street, Cambridge MA 02139, USA, 9/21/02.
33. Personal communication Dr. Pamela McInnes, Deputy Director, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services, Executive Branch, US Government, 9/24/02.

34. Rosenthal SR, Merchlinsky M, Kleppinger C, Goldenthal KL. Developing new smallpox vaccines. *Emerg Infect Dis* 2001; 7:920-6. Also available at <http://www.cdc.gov/ncidod/EID/vol7no6/rosenthal.htm> accessed 9/21/02.
35. Personal communication Dr. Frank Fenner, Professor, The John Curtin School of Medical Research, Australian National University, Canberra, Australia, 10/18/02.
36. Weniger, BG. Bifurcated needles vs. high-speed jet injectors for smallpox vaccination. Draft prepared for the Advisory Committee on Immunization Practices, CDC, 1/9/02.
37. Personal communication Dr. Bruce Weniger, Assistant Chief for Vaccine Development, CDC, 10/2/02.
38. Coates JB Jr., Hoff EC. *Medical Department, United States Army, in World War II—Preventive Medicine in World War II, Volume III: Personal Health Measures and Immunization*. Washington, DC: Department of the Army, 1955, pages 280-287.
39. Redfield RR, Wright DC, James WD, Jones TS, Brown C, Burke DS. Disseminated vaccinia in a military recruit with human immunodeficiency virus (HIV) disease. *N Engl J Med*. 316(11):673-6, 1987 Mar 12.
40. Personal Communication with Lt. Col John Grabenstein, Office of the Surgeon General, US Army, 8/7/02.
41. Haim M, Gdalevich M, Mimouni D, Askenazi I, Shemer J, Adverse reactions to smallpox vaccine: The Israel Defense Force experience, 1991 to 1996. *Military Medicine* 2000; 165(4): 287-9, Apr.
42. Personal Communications with Joel Kuritsky, CDC, late April, 2002 and Michael Osterholm, Bioterrorism Adviser to the Secretary of HHS and CDC, May 2, 2002. CDC vaccinated 10,454 laboratory workers since the early 1980s. Adding the approximately 200 workers vaccinated for smallpox epidemic control and the 740 subjects in the dilution studies (*N Engl J Med* April 25, 2002), the total is 11,400 adults, with most likely to be revaccinees. Detailed data for complications is lacking. However, it is a near certainty that a severe complication or death would be known.
43. Personal communication Professor Edward H. Kaplan, Yale University, New Haven, Connecticut, USA, 10/18/02.
44. Frey SE, Couch RB, Tacket CO, et al. Clinical response to undiluted and diluted smallpox vaccine. *N Engl J Med* 2002; 346, April 25.
45. Belshe RB. Presentation at CDC, May 8, 2002 reporting no detectable viral shedding when a double thickness semi-permeable membrane was used over a folded gauze pad.
46. *World Population Profile: 1998*, Bureau of the Census, US Department of Commerce.
47. Cohen J. Bioterrorism: smallpox vaccinations: how much protection remains? *Science* 2001; 294:985.
48. Baxby D. Studies in smallpox and vaccination. *Rev. Med. Virol.* 2002; 12:201-209.

49. Dixon CW, *Smallpox*, J & A Churchill Ltd., London, 1962; page 311.
50. Bicknell W. Modeling a smallpox bioterrorist attack – an Excel model. The detailed assumptions are: A mortality rate of 25% with 5 terrorists each starting in different cities and traveling to 2 additional cities (all mutually exclusive) come within 6 feet of 200 persons in each city and infect 20% of close contacts for a total of 200 persons initially infected. We further assume that 8% of initially infected persons travel to yet different cities and towns. Each 1st round case infects 9 others, 2nd round cases infect 5 others and 3rd round cases infect 3 others. Only 2% of person infected after the round travel to different cities. This is a straightforward model in Excel and available on request to either wbicknel@bu.edu or kenjames@bu.edu.
51. Gani R, Leach S. Transmission potential of smallpox in contemporary situations. *Nature* 2001; Volume 414, 13, 748-751 December and a correction, *Nature*, 2002 Vol. 415, 28, 1056 February.
52. Facts about Smallpox, Centers for Disease Control and Prevention web site <http://www.bt.cdc.gov/documentsapp/FactSheet/SmallPox/About.asp> accessed 10/20/02.
53. Dixon. CW. Smallpox in Tripolitania, 1946: An epidemiological and clinical study of 500 Cases, including trials of penicillin treatment. *Journal of Hygiene* 1948; Vol 46, No. 4: 351-377.
54. Mortimer PP. (Review of McVail JC) Smallpox in Glasgow, 1900-1902. *Rev. Med. Virol.* 2002; 12: 267-278.
55. Personal communications with Kenneth D. Bloem, Senior Fellow, Johns Hopkins Center for Civilian BioDefense Studies and a former US Peace Corps smallpox eradication worker with experience in Malawi, Zaire and Bangladesh, Summer 2002.
56. Personal communication with Dr. Mack. He stated the data was not sufficient to allow any statement about the interval between exposure and vaccination, 9/16/02.
57. Kaplan EH, Craft DL, Wein LM, Emergency response to a smallpox attack: The case for mass vaccination. *Proc. Natl. Acad. Sci. USA*, Published online before print July 12, 2002 available at <http://www.pnas.org/cgi/reprint/162282799v1> accessed 9/21/02.
58. Meltzer MI, Damon I, LeDuc JW, Millar JD. Modeling potential responses to smallpox as a bioterrorist weapon. *Emerg Infect Dis* 2001; 7:959-69. (Also available at <http://www.cdc.gov/ncidod/EID/vol7no6/meltzer.htm>.)
59. Presentation by Edward H Kaplan at CDC August 9, 2002 and *Epidemiology*, in press.
60. Foege WH, Millar JD, Henderson DA. Smallpox eradication in West and Central Africa. *Bulletin of the World Health Organization* 1975; 52(2): 209-22.

61. Barbera J, Macintyre A, Gostin L, et al. Large-scale quarantine following biological terrorism in the United States: scientific examination, logistic and legal limits, and possible consequences. *JAMA* 2001;286:2711-7.
62. Study no. Q946. Media, Pa.: International Communications Research, November 2001.
63. CDC Interim Smallpox Response Plan and Guidelines, September 23, 2002
<http://www.bt.cdc.gov/agent/smallpox/response-plan/index.asp> accessed 9/23/02.
64. Bicknell W. Smallpox: Terrorism, science, values, choice. The US health system faces uncertainty. Presented at the Cato Institute, Washington, DC, June 4,2002,
<http://www.cato.org/events/020604pf.html> accessed 9/22/02.