

Report SAGE consultation on smallpox vaccines

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Introduction

The last case of Smallpox, a disease with a case fatality rate of up to 30%, occurred in 1977. In 1980 the World Health Assembly declared this disease eradicated. Throughout the program a global stockpile of vaccines, had been held in Switzerland, created with donations from Member States. After eradication, a stockpile of vaccine was maintained in readiness for a potential reappearance of the disease. After some time had passed with no reappearance of smallpox, a small proportion of this vaccine stockpile was retained in Geneva, to be used for a proven re-emergence of the disease. In 2004 a WHO Ad-Hoc Orthopoxvirus Committee recommended that the emergency vaccine stockpile be enhanced and updated for use, should an outbreak of smallpox occur. The Committee recommended that the stockpile consist of 200 million doses of which at least 5 million doses would be held in Geneva for emergency use; the balance, representing a virtual stockpile would be retained in the donor countries ready for immediate shipment as necessary.

The WHO vaccine stockpile held in Switzerland includes both vaccines used during the eradication (animal lymph) and vaccines produced in tissue/cell culture. It consists of 600,000 doses (0.01ml/dose) of vaccine as used during the eradication program, which could be expanded to ~ 2.4 million doses, if the vaccine is administered by bifurcated needles plus 300,000 doses produced in tissue/cell culture. The entire virtual stockpile of vaccine held by WHO plus Member States currently consists of 31 million doses.

In order for WHO to make an informed decision (risk-benefit) on which vaccines to stock and to be able to give advice to countries on their own national stockpile, WHO has asked the Strategic Advisory Group of Experts (SAGE) for immunization to address this. In preparation for the annual SAGE meeting that will be held in November 2013, WHO organized a SAGE consultation on smallpox vaccine in September that would advise the SAGE Members. Specifically WHO would like the SAGE to address the following questions:

Question 1:

Which vaccine should be recommended to be used during an outbreak of smallpox? (vaccine used during the eradication (animal lymph), vaccine produced in tissue cell, or further attenuated vaccines).

- Composition of stockpile
- Size of stockpile
- Should we consider different scenarios of risk?

Question 2:

Once vaccination is decided in an outbreak, what other groups should be prioritized to be vaccinated while faced with limited vaccine supply?

- Age groups, risk factors/safety aspects, vulnerable populations, ethical considerations
- Which vaccine should be given?

Question 3:

Which vaccine should be recommended for preventive use?

What would be the immunization schedule? (First aid responders, army, police, health workers)

SAGE recommendation 1: Which vaccine should be recommended to be used during an outbreak of smallpox?

The development of smallpox vaccines has a long history extending back to 1796, the year Jenner discovered vaccination. Multiple strains developed over the years, and several different strains were used in vaccines during the eradication. As a requirement of the WHO eradication programme, all vaccines to be used had to meet established standards of potency, purity, and stability. Based on studies of adverse reactions post-

vaccination, especially post vaccinia encephalitis, two strains were most frequently used, the New York City Board of Health (NYCBH) strain and the Lister strain, although other strains were also used.

The WHO eradication program was also aided by the introduction of the bifurcated needle as a simple and effective way to do vaccinations. The bifurcated needle increased up to four times the number of vaccinations that could be done with a given volume of vaccine. WHO also recommended that vaccines be lyophilized so that they retained their potency during storage and shipment even in tropical areas and without having a cold chain to maintain their potency.

The vaccines used during the eradication program sometimes produced significant adverse reactions, some of which were occasionally fatal. These included post vaccinia encephalitis, progressive vaccinia, and eczema vaccinatum. Vaccinia was also occasionally transmitted from a vaccinee to close contacts, particularly those with open skin lesions. (F. Fenner, WHO, 1988 (ISBN: 92 4 156110 6). These led to an interest in producing safer vaccines, yet ones that still gave a robust immunity.

The vaccines used during the 1960s and 1970s were produced on the skin of live animals and yielded virus laden lymph that contained some bacterial contaminants. Accordingly, vaccines in recent years have been produced in cell culture. They are produced under current Good Manufacturing Practices (GMP) standard. These vaccines probably have the same risk of serious adverse events as they are produced with the same strain. The most well-developed of such vaccines is ACAM2000, which is derived from a single clone of the NYCBH vaccinia strain, and is licensed in the United States.

Given the safety profiles of vaccines used during the eradication programme and the vaccine produced in tissue cells, major efforts have been made in recent years to produce vaccines that are genetically modified – i.e. are less reactogenic but retain the ability to produce protection against smallpox. There are two major problems to develop such a vaccine. First, there are no established laboratory markers that are known to have perfect correlation with protection from smallpox, and there is no animal model that accurately mimics smallpox. Thus, it is difficult to judge the comparative efficacy/effectiveness of newer vaccines. Second, since the serious adverse effects produced by vaccines used during the eradication programme, occur in rates of a few per 1 million vaccinees, trials to establish the comparative safety of the newer vaccines are difficult if not impossible.

Vaccine candidates that are genetically modified to be less reactogenic and lower rate of adverse reactions to humans either by serial passage of a vaccinia strain on various cell substrates, or by intentional manipulation of the genome using modern genetic techniques, and may be further attenuated or non-replicating vaccines. While many such strains have been produced, very few are sufficiently well developed so that they can be thought of as potential vaccines. Two, LC16m8, a replicating live vaccine produced in Japan from the Lister strain of vaccinia, and Modified Vaccinia Ankara-Bavarian Nordic (Imvanex also designated as MVA-BN or Imvamune), a live but non-replicating vaccine derived from the Ankara strain of vaccinia, have advanced to human trials and are licensed in Japan and in the 28 Member States of the European Union, Iceland, Liechtenstein and Norway respectively.

Ideally, any vaccine proposed for actual use against smallpox should be lyophilized so that it will retain potency for extended periods at room temperature, be administered via bifurcated needles so that syringes and needles for injection are not required, and if possible produce a visible major cutaneous reaction (i.e. “take”) that is a marker of successful vaccination.

LC16m8 produces a major cutaneous reaction very similar to that produced by vaccines used during the eradication programme, such as the NYCBH vaccine, is administered by the bifurcated needle, is lyophilized, and meets WHO/TRS No 926, 2004 standards of purity, potency, and stability. Japan has a production facility that is actively producing the vaccine, and indeed is the only facility in the world currently producing a replication competent smallpox vaccine. (SAGE consultation review paper, H. Meyer, Paul Ehrlich Institute for WHO, 2013).

Imvanex is produced as a liquid, requires a cold chain for use, must be given intramuscularly or subcutaneously with a syringe and needle, does not replicate in human tissues, and does not produce a major cutaneous reaction. The approved human vaccination regimen comprises of two doses given four weeks apart to ensure high seroconversion rates. Moreover, although it is believed to be at least as safe as the replicating vaccines, little is known about the likelihood of it producing serious adverse reactions in some vaccinees, as fewer than 7000 persons have been vaccinated with MVA-BN in modern clinical trials. It is therefore not a good candidate for first-line use to control an outbreak.

In controlling an outbreak, countries should use any smallpox vaccine on hand that meets WHO/TRS No 926, 2004 standards of potency, purity, and stability. If no such vaccine is on hand, ACAM2000 or LC16m8 should be sought (which meet WHO/TRS No 926, 2004 standards).

From the WHO stockpile, first, licensed vaccines ACAM2000 (or LC16m8 if donated) should be used as well as other vaccines, based on the current stockpile composition that were used during the eradication. Vaccines used during the eradication should meet WHO recommendations (TRSN° 926, 2004).

What vaccines should be sought for the WHO stockpile?

A 2004 Ad-Hoc Orthopoxvirus Committee recommended, as a target, a stockpile of 200 million doses of which at least 5 million would be kept in Geneva for emergency use and the balance specifically pledged by countries but held in national stockpiles, ready for emergency shipment as might be required. They also recommended that there be at least two standby facilities that could rapidly produce substantial additional vaccine if needed. The 2004 WHO Smallpox Ad Hoc Committee recognized that the quantities noted might be insufficient should multiple outbreaks appear in different locations. However, given national and international constraints on resources, it simply proposed that the previously stated targets be retained and periodically reviewed as circumstances changed.

Today, smallpox vaccine that meets WHO /TRS No. 926, 2004 standards is in very short supply as has been the case for the past decade. (Therefore no vaccine should be discarded if it is believed to meet WHO/TRS No. 926, 2004 standards). Furthermore there are very few companies capable of large scale production on short notice. Kaketsuken in Japan, is the only facility that currently is producing vaccine. It has a capacity to produce approximately 40 to 80 million doses a year. Sanofi Pasteur has a facility in Massachusetts (USA) that has been under development for some 4 years. It is expected to be in full operation by the end of 2014. Its capacity is expected to be 50 million doses per year.

The consultation group recommended that additional vaccine donations should be considered, as well as funds that could be used to manage the stockpile and purchase additional vaccine. Countries donating vaccine to WHO stockpile should provide the same vaccine as they have in country stockpiles. However, WHO

should not jeopardize other programs or donations by placing the needs for additional smallpox vaccine ahead of other programmatic priorities.

For new vaccine donations for virtual as well as for on-hand storage, both licensed ACAM2000 and LC16m8 should be accepted, as well vaccine used during the eradication, meeting WHO/TRS No. 926, 2004 standards. Vaccine should be bundled with bifurcated needles, lyophilized, and produce a major cutaneous reaction after administration with the bifurcated needles.

The participants recognized that in order to advise on the number of doses for the WHO stockpile, it would be necessary to consider different scenarios. The acceptable range of doses will depend on the type or likelihood of occurrence of the various scenarios considered. Factors that could be considered include, but are not limited to, the cause of re-emergence (natural, bioterrorism), the location of initial emergence (urban, rural, mass-gathering event...), population density and movement and vaccine production capacity. Therefore further work is needed to come up with a meaningful estimate.

SAGE recommendation 2 Who should be vaccinated during an outbreak?

The epidemiology and transmission dynamics of smallpox are well established. Transmission generally required face-to-face contact with a visibly ill individual with rash. Patients are not infectious during the febrile prodrome, which is usually severe enough to require the patient to go to bed and not be mobile. Once the rash appears virus is shed from the upper respiratory tract and the patient becomes infectious. The eradication of smallpox was greatly facilitated by this pattern of transmission, with patients rarely spreading the disease to more than 3 contacts. Strict isolation of patients, coupled with vaccination of the small numbers of contacts who attended the patient during the infectious period, quickly eliminated outbreaks. Primary vaccination within 3-4 days of contact generally prevented development of the disease, whereas revaccination of previously vaccinated individuals within one week post-exposure was largely protective. (Mortimer Clin Infect Dis 2003)

Given these facts, and coupled with the occasional serious adverse events following smallpox vaccination, only vaccination of immediate contacts is recommended. Medical personnel who care for patients can be vaccinated immediately after their initial contact. First responders who have direct contact with symptomatic patients such as interviewing them, escorting them to hospital or other care facilities, feeding them etc. should be considered contacts and vaccinated.

Regarding risk factors, for those individuals with bona fide close direct contact, there are no contraindications for vaccination, and thus the risk/benefit ratio favors vaccination.

Contacts of contacts, the so-called “second ring of contacts”, should not be vaccinated. They should be identified, and communications established so that they can be vaccinated if the first ring contact actually develops smallpox or symptoms possibly suggesting smallpox.

Laboratory or other health care personnel who collect diagnostic specimens from patients, or who handle or process such specimens, should be vaccinated.

Vaccine used should meet WHO/TRS No. 926, 2004 standards for potency and stability, and be capable of producing a major cutaneous reaction following a single dose administration, preferably with a bifurcated

needle. Vaccine available locally similar to those used during the eradication campaign are acceptable, as are ACAM2000 and LC16m8.

SAGE recommendation 3: What other groups should be given preventive vaccination?

For preventive use, smallpox vaccination should not be recommended for any groups.

Countries may consider vaccinating laboratory workers in labs working with orthopoxviruses. If a biosafety assessment of such laboratories suggests some risk, workers should be vaccinated with ACAM2000 or LC16m8 or a locally available well-established vaccine that meets WHO/TRS NO 926, 2004 standards.

Regarding vaccination schedule, there is insufficient data on the length of time that optimal protection lasts, although some serologic markers of immunity persist for several decades. Thus the group considered there is not enough scientific evidence to provide any recommendation on the need and frequency of booster immunizations. Since frequent vaccinations decrease the likelihood of adverse events., most labs use a frequency of revaccination with an interval of 2 to 6 years.

Concerning to recently licensed Imvanex (MVA-BN/Imvamune) by EMA, based on the evidence provided for this review and consultation, the group recommended that more clinical data on its efficacy and safety should be produced before any recommendation can be given, even for preventive use. However, in countries where the vaccine is licensed, for individuals who refuse to be vaccinated with replicating live vaccines or have been designated as “high risk” (ie first responders, lab workers in orthopox virus laboratories, etc), and have been medically excluded from receiving standard replicating vaccine because of pre-existing immune deficiencies, immunosuppression, atopic dermatitis, etc. the MVA-BN is likely to be safer than replicating vaccines.