proved to have a heavy bacterial contamination after reconstitution. This has not been observed for any other vials of the IRP in either this study or in the original collaborative study and the origin of the contaminant(s) remains unclear.

Table 3.

Mean titres of samples exposed at 37°C for 28 and 96 days. The mean activity loss is also shown i.e. titre of untreated – treated.

Treatment	Sample	Untreated $\log_{10}$ pfu/ml (SD)	Treated $\log_{10}$ pfu/ml (SD)	Mean Activity Loss $\log_{10}$ pfu/ml
37°C 28 days	IRP	7.92 (0.06)	8.01 (0.03)	-0.09
	Candidate #1	8.64 (0.03)	8.32 (0.02)	0.32
	Candidate #2	8.15 (0.07)	7.77 (0.03)	0.38
37°C 96 days	IRP	7.71 (0.08)	ND	ND
	Candidate #1	8.79 (0.01)	7.98 (0.04)	0.81
	Candidate #2	8.18 (0.02)	7.30 (0.14)	0.88

Table 4.

Mean titres of untreated (-20°C) and treated samples exposed at 4°C for periods of up to 342 days. The mean activity loss is shown i.e. titre of untreated – treated.

Treatment	Sample	Untreated $\log_{10}$ pfu/ml (SD)	Treated $\log_{10}$ pfu/ml (SD)	Mean Activity Loss $\log_{10}$ pfu/ml
4°C 62 days	IRP	7.98 (0.10)	7.78 (0.02)	0.20
	Candidate #1	8.75 (0.03)	8.49 (0.25)	0.26
	Candidate #2	8.23 (0.09)	7.97 (0.31)	0.26
4°C 183 days	IRP	7.78 (0.32)	7.76 (0.45)	0.02
	Candidate #2	8.15 (0.05)	7.86 (0.23)	0.29
4°C 280 days[1]	Candidate #1	8.58 (0.08)	8.44 (0.13)	0.14
4°C 342 days[1]	IRP	7.78 (0.19)	7.61 (0.17)	0.17
	Candidate #2	7.97 (0.15)	7.43 (0.18)	0.54

[1] These assays were conducted in parallel in June 2004.

Treatment at 4°C

Samples were exposed at 4°C for various periods of time (see Table 1). However, because of the unavailability of samples of Candidate #1 when the study was being set-up the timing of

samples at later time points are asynchronous i.e. samples of Candidate #1 assayed after 280 days exposure were actually assayed alongside those of the IRP and Candidate #2 exposed for 342 days (See Table 4). The results for exposures at 4°C are shown in Table 4 and summarized in Figure 2.

The data gathered thus far indicate that short term exposure (up to 280 days) at 4°C does not lead to any significant loss of activity for any of the samples tested in the current study. However, it is worth noting that there is some loss of activity which indicates that long-term storage should indeed be at -20°C or lower. However, the results for Candidate #2 at 342 days exposure i.e. loss of 0.54 $\log_{10}$ pfu/ml, are somewhat disturbing and indicate that over longer periods this sample may be less stable than Candidate #1. Clearly further data are required to elucidate these observations on Candidate #2 and to extend the exposure times on both Candidates #1 and #2. These studies are currently on-going.

Arrhenius Analysis of Data

As already stated, we do not feel that the degradation of vaccinia virus is likely to be a first-order reaction and therefore the Arrhenius model would not be relevant in the analysis of the stability data generated at elevated temperatures. However, the data were analyzed using the DEGTEST (Kirkwood and Tydeman, 1984) program to test the above assumption. This analysis revealed significant deviation from the expected model for both candidates (χ^2 = 20.8, 3 d.f. for Candidate 1 and χ^2 = 27.0, 4 d.f. for Candidate 2). The values generated for the degradation at -20°C of 0.012% per year (of absolute titre) and 0.069% per year for Candidates 1 and 2 respectively should be treated with caution.

DISCUSSION

The baseline -20°C data for the current IRP and the two candidate replacements show that all preparations have good intrinsic stability at the recommended storage temperature. Arrhenius analysis – although probably inappropriate for such samples – do not provide any data that contradicts the above observations and indicate preliminary degradation rates of below 0.1% per year. It is worth noting that the current IS, established in 1962, lost a total of $\log_{10}$ 0.24 infectious units over the course of 42 years - as assessed by CAM assays in collaborative study. This amounts to a total of 43% loss over the original activity over the time period.

The accelerated thermostability studies undertaken at 37°C and 60°C indicate that there is no substantial difference between the stability profiles of the two candidates. Nevertheless, it is interesting to note that, where data are available, the current IRP appears to be more stable than the candidates. These studies however, produced no unexpected results and were clearly in line with what has previously observed for the IRP and other vaccine preparations.

However, the data generated from the 4°C treatments were rather unexpected. In the first instance, there was a small but consistent loss of around 0.2 $\log_{10}$ pfu/ml for the current IRP - irrespective of time of treatment (Table 4). This was also true of the two candidates after short-term exposure (i.e. up to 280 days). However, perhaps most surprising is the result for Candidate #2 after 342 days treatment which showed a substantial loss of activity. How much this result is firstly, reproducible and secondly, indicative of real-time stability at -20°C is currently unknown. However, in making a choice between the candidates for the establishment of the 2nd IRP we feel that it is important to make as informed a choice as possible. On this basis we are proposing to continue with the current stability study for at least another 12 months and to then review the results.

CURRENT STOCKS USAGE OF THE IS

Current stocks of the IRP stand at 375 ampoules. Usage over the last 18 months has been very slow with no samples requested since April 2004. Usage in 2003/04 was 13 ampoules which - was considerably lower than the previous two years (2001/02 and 2002/03) in which around 40 ampoules a year were issued. The above figures do not include usage for the Collaborative Study and the reported Stability Study.

Therefore, even with a final archive to be retained of 100 ampoules, there is still sufficient of the current IRP (270 ampoules) to last for 5-6 years at the maximal usage rate observed over the past 3-4 years.

RECOMMENDATIONS

The stability data generated in the current study have given indications that there may be differences between the candidate replacements for the current IRP in terms of their thermostability. On this basis we are proposing:

1) That the current IRP be retained for at least another 12 months and that the potency be revised to the figure generated in the collaborative study by CAM assay. This would be 8.16 $\log_{10}$ infectious units per ml after reconstitution in 0.25ml of water.
2) That the stability study on the candidates be extended and the data be reviewed for the next ECBS meeting in 2005. Specifically that:

    a) The real-time stability (at -20^{o}C) of the Candidates continue to be monitored on a regular basis.
    b) Additional accelerated thermostability data on the two candidates be generated alongside the current IS at +4^{o}C, +20^{o}C and other elevated temperatures.

The above strategy should allow the best selection of the available preparations to be made for the establishment of the 2nd IS for Smallpox Vaccine.

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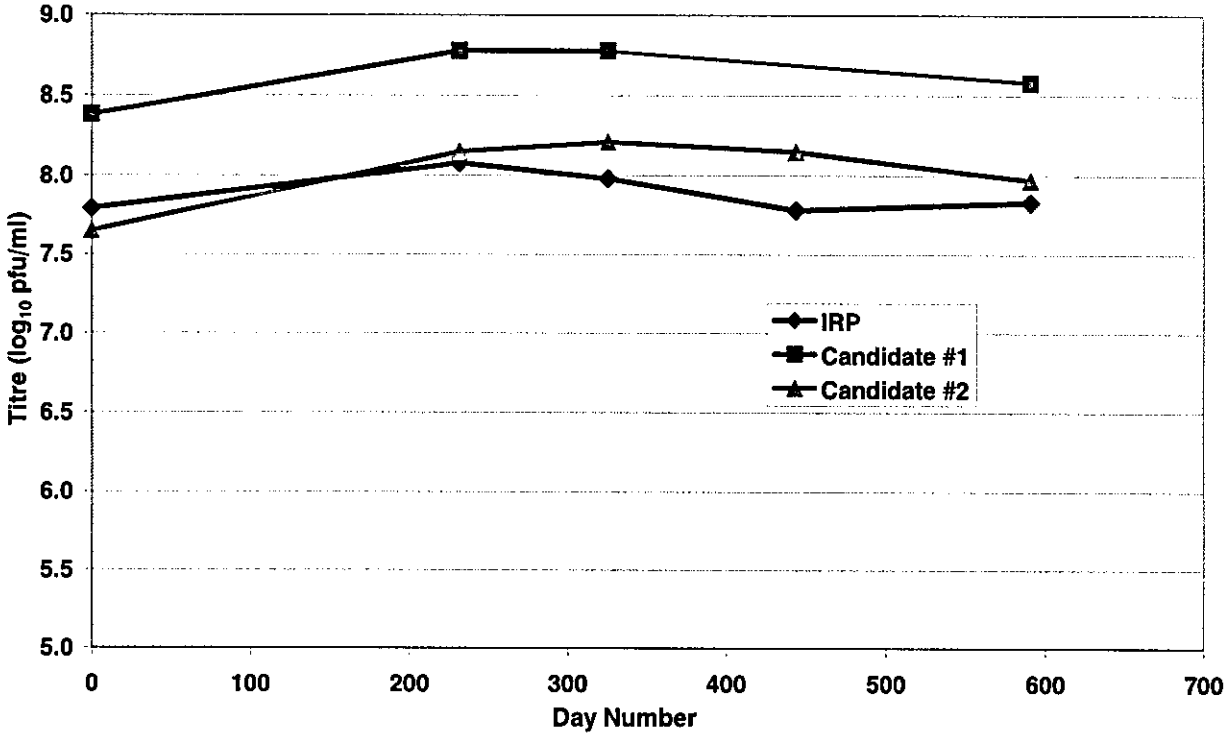
Figure 1

Mean estimates of the titre (A.) and relative potency (B.) of baseline samples of the three vaccines stored at -20°C.

A.



B.

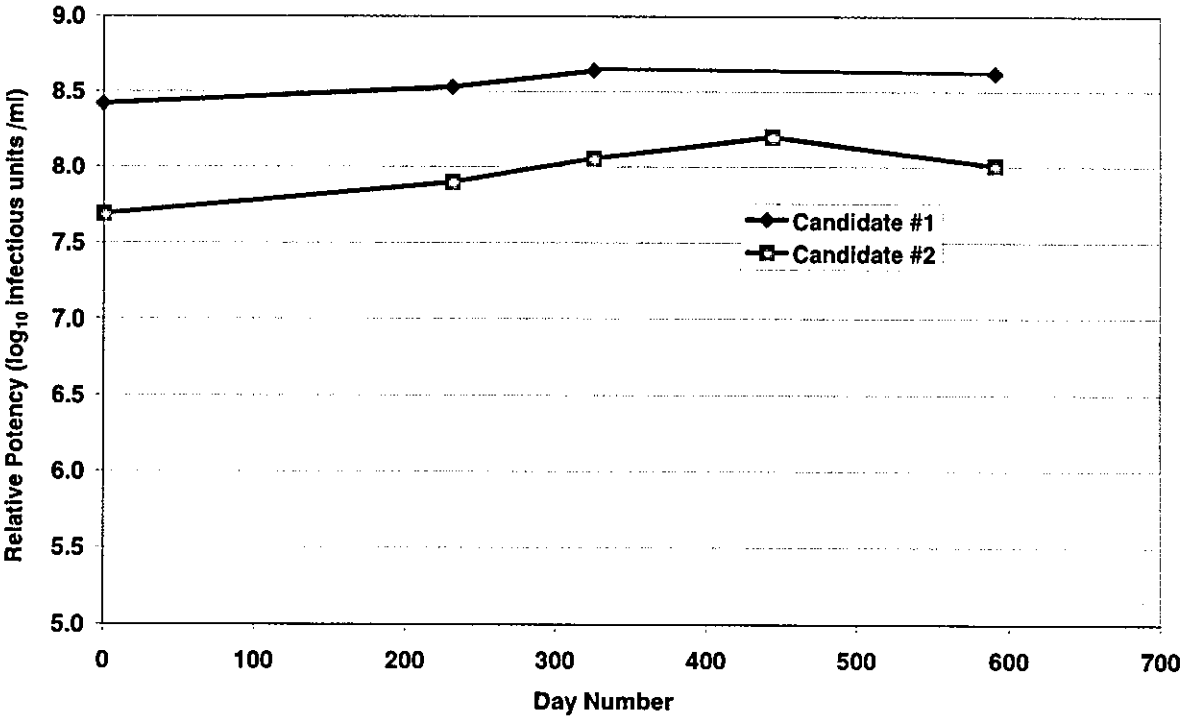
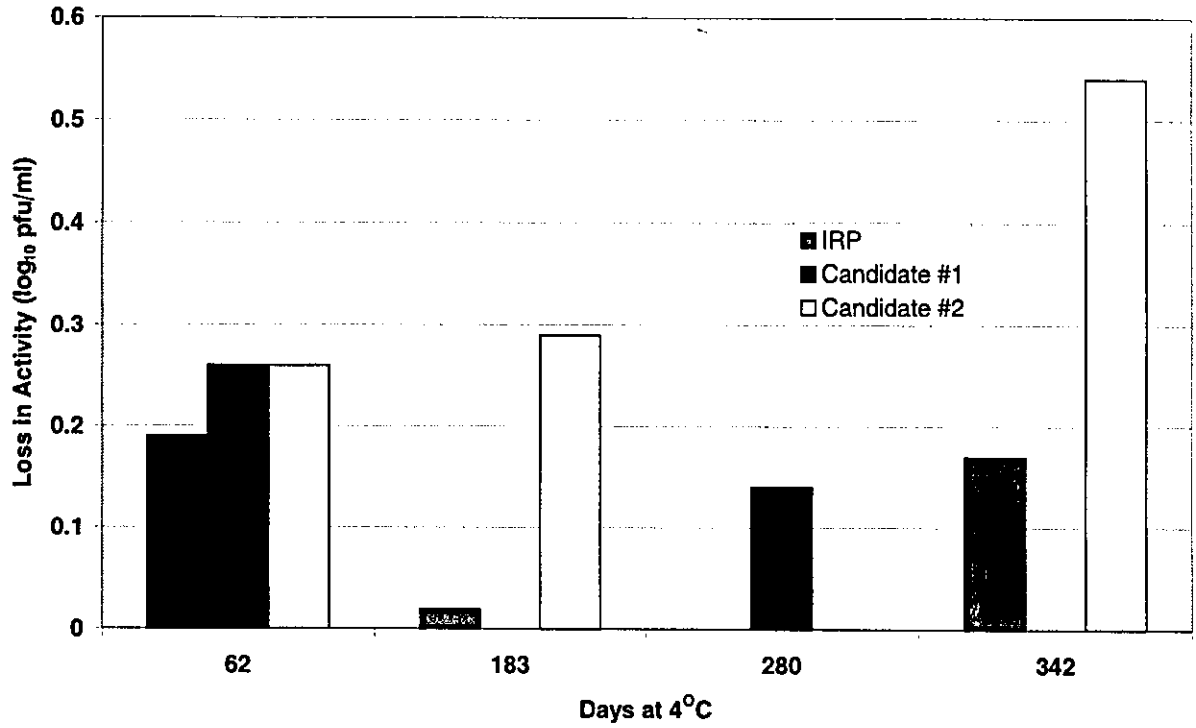


Figure 2

Estimates of activity lost by the IRP and Candidates #1 and #2 after various exposure times at $4^{O}C$.



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Essay on smallpox vaccine and its stockpile in 2005

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Synopsis
Smallpox vaccine was most important tool for the successful eradication of smallpox. In 1980, this achievement made it possible for all nations to cease smallpox vaccination. However, the current threat of possible smallpox bioterrorism has made it necessary to reconsider the need for vaccination. Over the last three years, many nations have set up action plans in the event of a case of smallpox. However, it was not simple. Factors involved include the judgement of risk, vaccine complications, conventional vaccines versus new vaccines, optimal stockpile of smallpox vaccine and its use for different target populations in different emergency situation. This paper reviews measures so far taken by the United States, Japan and other nations, and discusses likely national and global efforts in 2005 and subsequently in view of the fact that 50% of the world's population is currently unvaccinated and this proportion will increase with time.

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Essay on smallpox vaccine and its stockpile in 2005

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Introduction

In 1980 World Health Assembly (WHA) declared that "smallpox eradication has been achieved throughout the world and that there is no evidence that smallpox will return as an endemic disease." Consequently all nations stopped their routine smallpox vaccination programmes. Now, after a quiet period of two decades, followed by the 9.11 attack in 2001, we have begun to debate how we should use smallpox vaccine to defend against or respond to possible epidemics caused by the deliberate release of smallpox virus. This is a threat not only to industrialized nations, but also on a continental or global scale.

I worked as a WHO medical officer for the WHO smallpox eradication programme from 1962 to 1985, a period, which ranged across the three stages of planning, implementation and certification. Thinking about the programme then and now, one may say that the history of smallpox eradication is in fact that of smallpox vaccination. Vaccination played a critical role in the fate of the programme and, at this time, it does so again as we face extraordinary challenges posed by a bioterrorist attack. In this paper, I review briefly, the history of smallpox vaccine in the course of control or eradication programmes and discuss the possible use of smallpox vaccine and research in dealing with bioterrorism. (Photo 1)

Smallpox vaccine –its history of efficacy and safety

Smallpox vaccination, since Jenner's time, was seen to be highly efficacious, for example, the introduction of vaccination in France in the early 19th Century made their life span 15 years longer.[1] However, it gradually became known that the vaccine could produce serious complications such as generalized eczema, progressive vaccinia and post-vaccinal encephalitis. Their frequencies varied substantially depending upon the vaccinia strains in use by different vaccine manufacturers. Reports from the Netherlands, Germany and Austria documented ratios of post-vaccinal encephalitis that ranged from 350 to 1,200 cases per one million vaccinees. Research to find less pathogenic vaccinia strains was most intensive during the first half of the 20th century. Among the more than 30 different strains in use in the world in the 1960s, the Lister and New York City Board of Health (NYCBH) strains were generally found to be the least pathogenic of the effective vaccines. Many manufacturers began to use these strains. However, nation wide surveys in the 1960's in the US revealed the occurrence of serious complications among primary vaccinees and revaccinees to be, respectively, 266 and 10 per million vaccines.[2] Not surprisingly, WHO global smallpox eradication was strongly supported by the industrialized states, in part because of their realization that the only way to eliminate such complications and deaths would be to eradicate smallpox globally. The 1980's World Health Assembly recommendation to stop vaccination was therefore welcomed by the world community.

Attenuated vaccines

Since early last century, vigorous attempts had been made to derive less pathogenic strains of vaccinia virus by serial passage of candidate strains in tissue culture, such as chick embryo fibroblast, rabbit kidney cell etc. Straina tested included CV1-78 and CV-11 in USA, DIs and LC16m8 in Japan and MVA (Modified Vaccinia Ankara) in Germany. None have proved sufficiently immunogenic to warrant further investigation except MVA and LC16m8. Both showed reduced reactogenicity. LC16m8 is replicating strain but MVA is not, which, at the time, was developed to be the first stage in a two stage vaccination procedure with Lister strain vaccination to follow a month after administration of MVA. As for LC16m8, in a study of neurological toxicity in monkey model, it was least pathogenic among various vaccinia strains such as NYCBH, Lister and CV1-78.[3] A relatively large number of clinical studies were performed with regard to LC16m8 strain during 1970s.[4] Studies of the response of various vaccines (LC16m8, EM63, Lister and CV1) revealed that, among the replicating strains, LC16m8 produced the least marked reactions in terms of erythema and induration and the smallest proportion of children with febrile reactions. Of some 50,000 children vaccinated with LC16m8 in 1973-74, detailed clinical observations of 10,578 children revealed one case of eczema vaccination, three cases of convulsions and 8 cases of generalized vaccinia; all were mild. It was not clear whether the convulsions were related to the vaccine. In a study of vaccinees with different strains by encephalography, those with LC16m8 were the least affected. In a follow up experimental immunization of 100,000 children in Chiba prefecture between 1974 and 1976, there were no reports of severe complications despite promulgation of a law providing compensation for persons with vaccine complications (personal communication, S. Hashizume).

As for immunogenicity, the response of MVA (originally 572 serial passages of Ankara strain in chick embryo fibroblast) was never adequately tested at the time but recent studies indicate that the strain has produced a reasonably good immune response in various animals, including immunodeficient mice and monkeys.[5,6] Its use for vaccination of immune compromised individuals would be worth considering as it is non-replicating. In challenge virus studies of monkeys, using monkeypox, it appeared to protect monkeys reasonably well but further studies are needed.

As for LC16m8 (45 serial passages of the Lister strain in primary rabbit cells at 30°C), studies with rabbitpox and mousepox models showed that animals vaccinated with this vaccine were protected from challenges of rabbitpox and mousepox infections (LC16m8 Animal Study Results 27 May 2004, VaxGen – C. Empig, National Foundation for Infectious Diseases 7th Annual Conference on Vaccine Research, May 26, 2004). Further recent study on monkeys challenged by monkeypox virus showed protection ability of vaccine with LC16m8. (Annual Meeting of the Japanese Society for Virology, 21-23 November 2004, Japan, M. Saijo, National Institute of Infectious Diseases, Japan) (Photo 2) According to a study, in early 1990 LC16m8 lacks the ps/hr gene (later considered as B5R) which affects plaque size and growth in Vero cells and in the present Lister strain.[7,8] As mentioned above, however, the immunogenicity has been tested in the three animal models in all of which provides proection and a good serological response. Extensive clinical studies also showed good take and high immunogenicity. [4]

The basic problem in evaluating any of the attenuated vaccinia strains is that, having been developed after the eradication of smallpox, they have never been tested under circumstances of a natural challenge. Is a protection level by LC16m8 similar to Dryvax or conventional calf-lymph vaccine in human? Nobody can answer, but it could be safely assumed that it is so in view of the above mentioned studies in animal models as well as clinical studies.

In summary, clinical studies of the large number of vaccinees in 1970s, as mentioned above, support the finding that LC16m8 vaccine is the least pathogenic of all vaccines using replicating viruses. Depending on national policy, its use may include immunization of a population before smallpox has been detected, or populations at risk of smallpox infection. The only contraindication would be immune compromised individuals, where there may be a role for MVA.

National stockpiling of vaccine

Today, because of the threat of bioterrorism, many national health services have developed biodefense measures. Smallpox is regarded as one of the most serious threats because it is a lethal disease that can be transmitted from person to person. A former official of then USSR biodefense research laboratories[9] reported that:
"the ways of attack under study at that time included use of aerosol mechanically produced, of public transports and possible genetic engineered variola virus. Also the shift of target from defence force to public was noted, which may result in damage of not only health but also social-economic".

In case of an emergency or for preparedness, the potential population for smallpox vaccination can be divided into three groups, first group – the healthy general public without a known contact history with a smallpox patient, second group – individuals with contraindications to vaccination (in the US: atopic dermatitis, pregnancy, immune-suppressive disease or treatment, infants, the elderly, those with certain cardiac risk factors and the families of those with contraindications– at least 25% of the general population) and a third group –medical and public health personnel who have a high probability of being in contact with a smallpox patient should an outbreak occur.

In USA

In the US, since the September 11th attack, more than a half million military personnel and some 40,000 medical and public health staff considered to be at highest risk (group 3) have been vaccinated. However, the goal of immunizing a half million high risk medical and public health staff has failed because of the concerns of local medical and public health leaders about the occurrence of vaccine complications and a perception that the risk of a smallpox bioterrorist attack was diminishingly low.[10]

An additional concern was the occurrence of myopericarditis after vaccination in about one in 10,000 primary vaccinees.[11,12] This was only reported twice during the whole of the global eradication programme. The first report indicating cardiac complications among vaccinees in Australia between 1960 and1976[13] and second report in 1968, minor cardiac complications among United States military personnel.[14] Hence, some details are given here.[15] The vaccine used in the vaccination effort was one that had been produced in 1978 and had been kept in a deep freezer. It

was the same as had been used in the US for many decades. Three factors may account for this. Prior to 1980, virtually all children were given primary vaccination before school entry; thus, virtually all adults who received vaccination were revaccinees. Moreover, the myopericarditis was mild and transient, consisting of fever, malaise and often some substernal chest pain. Electrocardiograms and enzyme studies have been needed to confirm the diagnosis. Physicians who were in practice during the 1960s now generally believe that most vaccinees presenting with such symptoms would not have been subjected to special diagnostic measures but would have been reassured and told to return if the problem persisted. Finally, the public, as well as health personnel, have become less tolerant of possible risks associated with taking of any vaccine. The US smallpox vaccination programme, except in the military, has now been suspended with emphasis now placed on improving national readiness to respond rapidly and effectively should an outbreak occur. This change in policy has influenced that of other industrialized nations.

The current stockpile of vaccine of consists of about 95 million doses of calf-lymph vaccine provided by Wyeth Laboratories and Aventis Pasteur. Only about 8 million doses are licensed. There is an additional 200 million doses of Vero tissue cell culture vaccine produced by Acambis and Baxter Laboratories, using the NYCBH strain.[16] It is currently under Phase III studies, preparatory for licensing. In addition, the US Government has a contract with Acambis to maintain production capability over the next 20 years to meet critical demands at anytime. The clinical trials of the Acambis vaccine are proceeding slowly because of the cases of myopericarditis that have occurred. Licensure before early 2006 seems unlikely. In meantime, the vaccine has been packaged and is available for emergency use.

An attenuated vaccine (MVA) is also under study and is expected to begin to be produced in the spring of 2005, assuming the required clinical studies are satisfactory. Thus in the US in 2005, there may be stockpiles of three types of smallpox vaccines: first generation (conventional vaccine), second generation (tissue culture vaccine) and third generation (attenuated strain). How these might be developed is still to be decided. Additionally VIG will be stockpiled to cope with cases of complications.

In Japan

In Japan, LC16m8 is the only vaccine strain in stockpile, perhaps the only stockpile today comprised solely of an attenuated tissue culture vaccine among nations throughout the world. This vaccine was licensed in Japan more than 20 years ago, but it should not prevent further research, because of recent progress in technology. The quantity available currently is sufficient to deal with an emergency. Whether the vaccine would be safe enough to use for some or all of those with contraindications (group 2) is not known. Further studies would be most desirable and urgent. A determination of vaccine efficacy in monkeys with monkeypox would be most useful if the studies were further done in parallel with studies of MVA, Acambis tissue culture vaccine and Lister calf-lymph vaccine for purposes of comparison under international collaboration. The results would be useful not only to Japan but also to international preparedness.

Stockpiles in other nations

The situation in other industrialized status is not clear, but in EEC the Netherlands initiated to

stockpile the calf-lymph vaccine, of which efficacy proved the same as that during the smallpox eradication campaign. The quantity is enough to vaccinate the entire population in 4 days. (Personal communication, A. Plantinga)

Further, based on the information provided by the Center of Biosecurity, Pittsburgh University at least 40 nations have stockpiles of vaccine, much of which is the conventional vaccine kept in suitable storage (personal information, DA Henderson); In addition to the US and the Netherlands, those nations have sufficient stockpile to cover total of their own population or more; Denmark, France, Germany, Israel, Singapore and UK. This indicates that throughout the world, that at present there would be a total of some 800 million doses of vaccine or more. As for production capacity, manufacturers situated in Denmark, Germany, Japan, the Netherlands and Russia may produce some 300 to 350 millions a year. In the year of 2005, the world population is estimated to be 6 billions. Perhaps, it could be broadly estimated that the size of the current vaccine stockpile may be roughly 10 % of the world population.

It is difficult to assess at present as to what is the optimal stockpile worldwide in dealing with smallpox bioterrorism. However, one thing is apparent that if it occurs, nations of limited preparedness in Africa, Asia and South America would be mostly affected because of rapid transmission rate due to developed world traffic and ever increasing unvaccinated population. It is assumed that a preemptive mass vaccination is not in practice throughout the world.
Some incidental vaccination of defence personnel in limited scale and of personnel of poxvirus research or surveillance laboratories may be taking place in 2005, but details are unknown.

International stockpile by WHO

A role of WHO has to be mentioned here. During the smallpox eradication programme in 1970s WHO established the international smallpox vaccine stockpile donated by member states and quality control system in collaboration with WHO International Reference Centre, the Netherlands and the Regional Centre, Canada. All the vaccine batches in use for the global programme were tested for its safety and efficacy according to WHO minimum requirements. Surprisingly, when it first started, only 30% of batches tested met WHO standards, but in three years later improved up to 80%. The seed lots with strain of the Lister together with working reference preparations were also supplied to many manufacturers who needed. This international coordination of the use of better quality vaccine played a significant role in the success of the smallpox eradication programme.[17] In view of past experience, together with the fact that there are many poor nations without stockpiles, especially in Africa, WHO has agreed to develop an international stockpile of smallpox vaccine, both calf-lymph and tissue culture, with bifurcated needles. It will consist of small portion stocked at Geneva (5 million doses) and arrangements, in an emergency, for selected donor states to supply vaccine when it is needed (200 million doses). A decision on the system is expected at the World Health Assembly 2005.

During the smallpox eradication programme, the potency of the vaccine was determined to be $10^{8.0}$p.f.u. At that time, vaccine batches of which titres were below this after heat stability test of 4 weeks at 37°C was rejected by WHO to include then WHO stockpile. In recent years experiences have shown that stored vaccine was effective after several fold dilution, it is important for WHO to

review the required potency for vaccine in the stockpile.

Bifurcated needles are unquestionably the best device for vaccine administration. However, the suggested frequencies of punctures by bifurcated needles now varies in different countries. For instance, some recommend 3 punctures for primary vaccination, and 15 punctures for revaccination, others 15 punctures for both. During the smallpox eradication programme, after extensive studies, 15 punctures were used in both in primary and revaccination, with a vaccine titre of $10^{8.0}$ p.f.u. per ml. To-day, for example, 3 punctures with $10^{7.7}$p.f.u. titre, if it is implemented, mean that actual inoculum would be one log lower than that of standard method during the eradication programme. Is the changing significant or not? It would be most desirable for WHO to coordinate and recommend a standard method, as in the eradication programme, because many nations will have difficulty making a decision.

Finally, we should not ignore the cost. During the eradication programme, one dose cost one cent. Now the costs of tissue culture and attenuated vaccines are exceedingly high. Further if the shelf life of the stockpile is short, the cost proportionally increases. It would be important for WHO to find a solution, as the WHO stockpile essentially aims at preventing the establishment of smallpox endemicity in the poor countries in Africa, Asia and South America.

Research topics

Much good research was carried out on smallpox vaccine during Jenner's time, for years afterwards, when control was the goal, and during the eradication campaign. Since eradication, it is not possible to do phase 1, 2 and 3 human trials. One alternative would be to use animal models, another, to develop a surrogate animal model, such as a transgenic mouse for variola virus, as with poliomyelitis.[18] This would not be easy, but may be essential. Recently, a study reported DNA vaccine which protected monkeys against monkeypox virus.[19]

There is interest in the production of a "second generation", tissue culture vaccine because "it has far higher quality in terms of purity and freedom from unwanted agents than the vaccine of animal skin origin".[20] However, the tissue culture vaccine may be associated with similar complications as the vaccine used in the eradication programme as far as it uses the vaccinia strains. Also, in tissue culture vaccine "the vaccinia strains should adopt to that cell substrate and such effects may be related to immunogenicity and safety." On these bases, the relevant studies on Acambis 1000 and 2000 have been conducted in the United States.[16] Now Acambis 2000 is in the US stockpile for emergency use, but the study continues.

Another way would be to rely on the vaccine which has proved to be effective, such as calf-lymph vaccine. The advantages are its proved efficacy and its potency during stockpile will be satisfactory over 20 years at least as already shown in WHO's experience. Tissue culture vaccine may not last that long which needs studies as suggested by a preliminary study done by WHO collaborating study.[21] In this context, the Netherlands produced the calf-lymph vaccine for the stockpile. Notably, choice of vaccine type for the stockpiles would be an important subject for research and national consideration.

Summing up

Smallpox vaccine has made a great contribution to the reduction of human misery and death. However, the frequent occurrence of severe vaccine complications has caused concern. Substantial efforts are now being made to reduce or minimize the risk, including the development of attenuated vaccines. Meanwhile, the success of smallpox eradication in 1980 led to the termination of smallpox vaccination. Now, global threats of terrorism make the return of smallpox vaccine again a necessity.

Vaccine stockpiles are needed (Figure1). Conventional vaccine strains are apparently being used in most countries, but attenuated vaccines should also play an important role in programmes. There are two promising attenuated strains; MVA and LC16m8. Both require more studies, which may best be carried out through international collaboration under the leadership of WHO. WHO vaccine stockpile should be promoted by member states as we cannot ignore global risk. It is also proposed that Japan, because of its advanced research and biotechnical enterprise, should take a lead in promoting research on biodefense, especially with regard to the smallpox threat.

It is important that we now prepare for coping with the steadily increasing level of susceptibility to smallpox in the world population. In 50 years from now, if no vaccinations are done, more than 90% of the world's population will be unvaccinated. The situation would be more dire and dangerous than at any time in history. Even before Jenner's time, a large proportion of the adults were immune, as survivors of earlier epidemic smallpox. Our preparedness for such situation is of complex. One definitely important measure would be research even on long term basis, although it is handicapped with no availability of target illness, smallpox. Perhaps, first priority would be completely new vaccine based on genetics or proteo-mix technology, secondly, rapid diagnostic technique and lastly new therapeutic substance. This order is based on our experience having interrupted smallpox transmission during the eradication programme. We now have a lesson in the difficulty of controlling the HIV pandemic with drugs. If we had a preventative vaccine we should be in a much better position.

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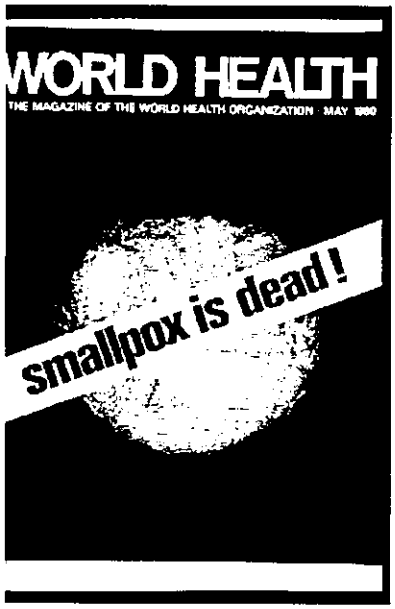
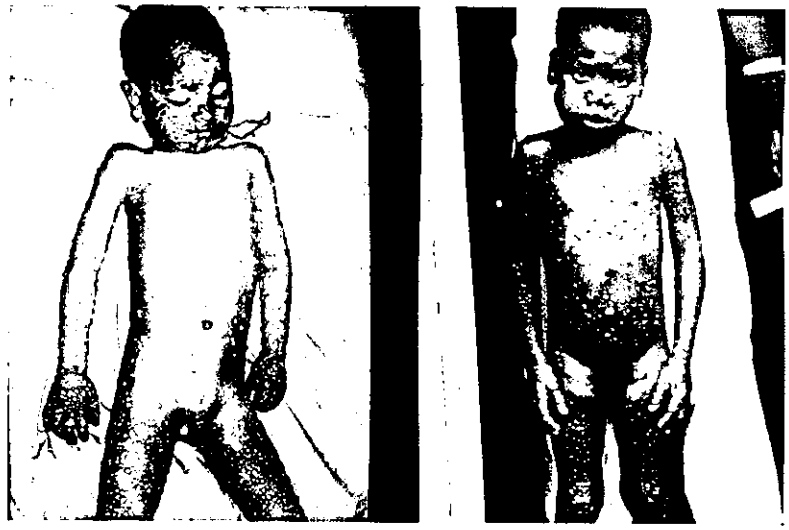
Photo 1



Source: WHO

Photo 2



smallpox
day 7

monkeypox
day 7

Source: WHO

Figure 1

Presumptive Use of different types of smallpox vaccine in U.S. and Japan as of Jan.05

	Conventional vaccine (Calf Lymph)	Tissue Culture Vaccine[1] (second generation)	Attenuated[2] vaccine with replication in cells	Attenuated[3] vaccine without replication in cells	Future new vaccine[4]
Group 1 General Public	U.S.	U.S.	Japan	- - -	- - -
Group 2 Individual with risk of vaccine contraindications	- - -	- - -	- - -	U.S.	
Group 3 Emergency team who will be exposed to smallpox	U.S.	U.S.	Japan	- - -	

Foot Note:
(1) Conventional strain in tissue culture
(2) LC16m8 licensed in Japan
(3) Modified Vaccinia Ankara (MVA) – Bavarian Nordic
(4) Include vaccine made of immunogenic gens or vaccine vector inserted by immunifgenic gens

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