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Smallpox: should we destroy the last stockpile?

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“...the destruction of the current virus stocks means virtually the complete stoppage of variola research...”

The 64th World Health Assembly (WHA) 2011, discussed the long-standing subject: how to destroy the current variola virus stocks in two WHO collaborating laboratories in the USA and Russia? The US delegate drafted a proposal to continue research with the current virus stocks for another 5 years, until the 69th WHA (2016) when its outcomes will be reported. It had supporters of more than a few dozen, while there were groups, as well as individual delegates, who were against or seriously critical of the proposal.

The 64th WHA finally decided to reaffirm the decisions of previous WHA sessions that the stocks of variola virus should be destroyed and also reaffirm the need to reach a consensus on a new proposed date for the destruction of variola virus stocks when research outcomes critical to improved public health response to an outbreak so permit. It was also decided that discussion will take place at the 67th WHA, under the tentative title “Smallpox eradication: destruction of variola virus stocks” [101].

I worked for smallpox eradication programs for 23 years at the WHO in Africa (1962–1964) and at the WHO headquarters, Geneva (1964–1985). I learnt a great deal about smallpox, one of the most miserable diseases in the world. At the WHO headquarters I also campaigned to reduce the number of laboratories retaining variola virus throughout the world to the minimum. At present, I serve as a member of the WHO Variola Research Committee.

Thus, I am interested in what would be the best possible way to handle the problem of destruction or retention of variola virus as discussed in this article.

Should we destroy the last virus stocks?

In recollection, the 52nd WHA in 1999 recommended the destruction of the stocks in 2002. When the 55th WHA took place in 2002, it was decided to postpone it in recognition of the need to continue important research. Since then the subject has been an important subject in the international community. In 2007, the WHA requested the Director General to undertake a major review in 2010 so that the 64th WHA 2011 could reach a global consensus on the timing of the destruction.

The results were as mentioned in the beginning of this article. Notably, the 64th WHA reviewed the Director General’s designated, independent appraisal of needs for continuing research by the special independent experts group, which indicated research having met with public health requirements [101]. Many individuals have been concerned about the existence of the stocks, which would enhance the risk of smallpox returning. Delegates from nations with limited health resources naturally favored the destruction. Owing to the global freedom from smallpox since 1980, when all the nations in the world discontinued smallpox eradication programs, it is estimated that 40% of the global population currently

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have no vaccination at all. This year is the 10th anniversary of the 9/11 terrorist disaster in New York (USA). In a poll survey in the USA, 78% feel there is a likelihood of a terrorist attack in the next decade [1]. Thus, the advantage of destruction appears to be clear. Then, how may we justify the retention?

Is there any advantage to retaining the last stocks?

There has been a cautious approach to retaining the virus stocks. As a *Nature* editorial recently commented: “smallpox is a disease of history, but cannot be consigned to the past”, referring to the report of Jonathan Tucker, who proposed partial destruction of virus stocks and continuation of research with remaining stocks [2]. As already mentioned, destruction, instead of retention, would reduce the risk of smallpox returning from a security point of view, but it should not be forgotten: no assurance that there may be no hidden stock elsewhere or no synthesis work of smallpox virus at some unknown laboratory. The destruction could provide a false assurance; furthermore, the destruction of the current virus stocks means virtually the complete stoppage of variola research, namely disappearing research capability in the future. Once we have lost this research capability, it is hard to regain it, because any good research activities are based on a long history of trial and error work by many interested researchers.

What are the problems of smallpox research?

I am concerned about the status of the current research: recently there have been few public health elements of research, except in some industrialized nations. Namely, how the research results obtained until now be used for prevention or control of possible disaster, if real smallpox outbreaks occurred? For example, in the smallpox eradication program, at that time, one dose of smallpox vaccine cost just one cent, whereas today, new attenuated tissue culture vaccines, such as LC16m8 vaccine derived from Lister strain which was licensed in Japan and MVA vaccine in Austria, are more expensive. LC16m8 vaccine costs approximately US\$3 per dose and I suspect, MVA, perhaps more. Assuming 200 million doses of vaccine should be in international stockpile to cope with the return of smallpox epidemics, we have only 30.5 million doses in stocks and 27 million doses pledged [3]. In today's rapid international traffic, if smallpox were imported and transmission started in Africa or South Asia, how we should solve the problem of vaccine supply there. What is their heat stability? Parenthetically the molecular biology of the attenuated vaccine still needs further study to assure its effectiveness relative to the calf lymph vaccine used for smallpox eradication [4].

We have now developed ST246 and CMX001, which are antivariola drugs [4]. However, what is the price and how it can be used for treatment of smallpox patients in tropical regions of health resource-limited areas? The 2007 WHO annual report indicated “the greatest fear is that in the absence of global capacity to contain the outbreak rapidly might reestablish endemicity, undoing one of the public health greatest achievement.” Having worked in Africa and south Asia, it seems to me that special research is needed to work out how the research results so far obtained can be utilized to establish ‘the global capacity’ to prevent smallpox

pandemics. Price, manufacturing capacity, supply route and so on, require urgent study. After all, how we can increase the stockpile to 200 million doses as the WHO has planned? The researchers may say it is not their responsibility. However, how to make efficient production with skilled technology at reduced cost often depends on the experts advice on their production technology.

Another example: molecular biology or genetic research has been well developed, introducing the new laboratory diagnosis technique, but how it can be practical in terms of rapidity and accuracy for surveillance in less developed nations? How long does it take to make it effective?

The genetic maps of smallpox, vaccinia and monkeypox viruses are already available in the two laboratories and have been published. Such findings would lead to important discoveries, for example, without animal models but *in vitro* work for study of variola antigen in relation to cellular and humoral immunity. It would be risky to conduct an *in vivo* study, but a safer *in vitro* study, if to be done, needs variola stocks.

Proposal: UN/WHO premises for smallpox virus repository

I would propose that the research with live variola virus stocks be completed in 2012 to 2014 and the remaining small quantity of live variola stocks be transferred to, and kept at, a special repository on UN/WHO premises with a strong security system, designed by appropriate security experts. The two laboratories, then, will continue research as previously mentioned without the live variola virus. Also, the UN/WHO should declare a special worldwide announcement of such transfer, to include the following:

- If there is anybody who discovered smallpox virus stocks previously unknown, such report is most welcome so that it can be placed in UN/WHO repository;
- Any scientists who recommend new research with smallpox virus, please report to UN/WHO so that appropriate research may be safely considered and arranged by a special UN/WHO committee. Notably the two laboratories that transferred the virus stocks should be entitled to have priority if they apply to conduct special research;
- If any smallpox virus research other than above is found, which might cause smallpox epidemics, including synthesis of the virus, the responsible person will be under special investigation because the act as such should be regarded as a risk of a pandemic. This is important since it intends to prevent synthesis of smallpox virus owing to ‘dual research dilemma’ This would help the prohibition of virus synthesis.

Summary & conclusion

In a sense, smallpox eradication was the fight by human species to make its vicious enemy, variola virus, extinct in the history of biological evolution. It is interesting to think, following Charles Darwin, that the worst human experience of smallpox over the past 6000 years built into the human genome to fight with it as a high priority for survival [5].

Concerning future research, and this is my speculation, but future development of molecular biology could lead us to a study specialty of variola virus with such unique characteristics as:

- Having human species as a sole natural reservoir, to identify what genes are involved in species susceptibility;
- Having seen greatly different pathogenesis of variola virus in humans, such as variola minor and major, there has been no use of modern technology such as genetic analysis on such phenomena: we may encounter the need for such research in the future if we have to cope with an appearance of a variola-like virus, including the development of therapy.

In recollection, I have been contemplating how to handle the smallpox virus stocks. I touched on my tentative view in my book 'Smallpox Eradication Saga' (2010) [4] and in my brief letter to the editor of a relevant medical journal of biosecurity, last May [6]. And now, in this article, at the time of critical decision by 64th WHA, I reviewed, from various angles, my view that the last virus stock be kept at UN/WHO premises for future research as needs arise. Many researchers felt that its destruction would be the completion of the global eradication of smallpox,

but I feel it would be too superficial from the viewpoint of the history of biological evolution. Martin Rees discussed in his book, 'Our Final Century', 2003, on smallpox bioattack as one of the possible causes for extinction of human species. In his book 'Common Wealth' (2008), Jeffrey Sacks pointed out the environmental, economic and political hazards in the future, but offered encouragement that "Ours is the generation that can harness science and a new ethic of global cooperation to bequeath a healthy planet to future generations". I know it is not easy to set up a UN repository for the virus stock, but the creation of the UN having been the remarkable wisdom of human species, can we not try for the next 3 years to accomplish this set up?

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