

## Smallpox: A Possible Comeback

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Smallpox (Variola) has been known to mankind for 10,000 years [3], with epidemics inflicting heavy loss of life, severe morbidity and lifelong disfigurement. Smallpox is caused by orthopox, which is the largest DNA virus known. There are several "ortho-poxviruses" – smallpox, monkeypox, vaccinia, cowpox, parapox viruses, molluscum contagiosum, tana pox, and whitepox. Transmission is by air from lesions in the respiratory tract and fomites that are formed by dried crusts of skin lesions. It is highly contagious and lethal. The mortality rate from variola major is 20–50%, reaching up to 98% in children [1], while variola minor has a mortality of about 1%.

The history of mankind is replete with examples of the decimation of populations from smallpox. Following the Spanish invasion of America, 2.5 million Native Americans perished within 9 years. In the early eighteenth century 90% of the Native Americans in Massachusetts died as the result of a variola epidemic.

Monkeypox, which was first isolated in 1958, was not associated with humans until 1970. It was considered to be restricted to monkeys, with rare human involvement. In the 1980s there were several outbreaks of monkeypox, with mortality rates close to that of variola minor. From 1981 to 1986 in the Democratic Republic of Congo there were 338 cases (67% confirmed by virus culture) with a case-fatality rate of 9.3% among people who were not previously vaccinated by vaccinia. Of these, 28% reported contact with other patients [2]. In 1996–1997 another outbreak occurred in Zaire, with a total of 511 human cases (World Health Organization press release no. 86, 2 December 1997). The rate of human-to-human transmission was 73% and most infections occurred in youngsters (under age 15 years) who were not previously vaccinated, with a relatively much higher mortality (3.7% in those under the age of 3). Genetic studies of the isolated virus showed a close relation to the isolates of the 1970s and 1980s [2]. Antibodies to orthopox viruses were found in 14 animal species [2]. The implication is that the variola virus may be eradicated but the monkeypox virus is progressively replacing it as a threat to mankind. While this view is not shared by all researchers who study poxvirus diseases [3], the notion that it could happen was raised publicly by Peter Jahrling of USAMRIID and Ali Khan of the U.S. Centers for Disease Control, as well as by others.

The eradication of smallpox by the WHO was a historic achievement. However, it turned out to be a Pyrrhic victory – new generations of children were not vaccinated and today between 30% and 50% of the world population are susceptible to infection! This poses a risk that the disease could be re-introduced by a natural or malicious course. It is therefore important to examine the potential

risks in view of historic events [4,5]. In 1970, a tourist who returned from Pakistan to be hospitalized in Germany for "hepatitis" caused 20 cases of smallpox and 4 deaths despite being in "isolation." Thus, even in the 1970s, 2.7–4 cycles of transmission occurred before a correct diagnosis of smallpox was made because doctors in Europe and Britain were not familiar with the disease [5]. In 1972, a Moslem pilgrim who returned to Yugoslavia from Mecca infected 140 people. Twenty of them 20 died, one of whom was diagnosed when the patient was already in Germany. There were simultaneous reports of dozens of cases in Iraq and Syria. These outbreaks occurred despite the fact that most of the population had been previously vaccinated. In "virgin populations" without herd immunity the toll would have been much worse.

Given the cross-country and international travel of today, even one to two cases in one country could cause a major public health catastrophe. It is therefore extremely urgent to reappraise the situation and be ready to reinstate vaccination, especially in view of possible terror activities. In an "Attack Scenario" recently published by O'Toole [6], it was estimated that a single terrorist act that begins with just a few cases in April would end in the disease becoming endemic in 14 countries by the end of the year. The WHO Assembly will have to consider a new eradication program. The threat of smallpox as a biologic weapon has been studied extensively in recent years [7], and the WHO released a Note for the Press, No. 15, on 19 October 2001, announcing that it will "review smallpox vaccination guidance." The *New York Times* announced on 18 October 2001 that the "U.S. seeks to stock smallpox vaccine for the whole nation."

Vaccination has been practiced for many decades. Teresa Thiel of the University of Missouri, St. Louis, recounts that "as early as 300 BC the Chinese applied such powders [crusts from old cases] to their nostrils." The first recorded observation, however, comes from a letter written by Lady Montagu, wife of the British ambassador to Turkey in 1717, in which she describes how old women were invited to use "matter of the best sort of small-pox" with a needle to vaccinate young unexposed people. But the most deserving of credit is Edward Jenner, who developed and introduced the vaccination using lesions of cowpox infections and later the vaccinia virus, which is still the accepted method.

Vaccination is not always innocent. Several reports [5] have estimated that following one million "primary vaccinations" there will be one death, 2.8 cases of post-vaccinal encephalitis, 0.9 cases of vaccinia necrosum, 38 cases of eczema vaccinatum, 249 of generalized vaccinia, 529 of accidental infections, and thousands of

erythematous urticarial reactions. However, following a second vaccination, the case fatality rate was 1:4,000,000 and other reactions were similarly rare. In another report [8], post-vaccination encephalitis rates were 0.16–1.47 cases per 10 million vaccinations. Another intriguing question is how long will the protection by vaccination last. Tudor and Strati [9] estimate that the risk of smallpox after primary vaccination is 1:1,000 after 1 year, 1:200 after 3 years, 1:8 after 10 years and 1:2 after 20 years. These figures are based on a survey conducted in India, which was a highly endemic area at the time. They also stated that “although the risk of contracting the disease is fairly good the mortality rate is very small even after many years... Emergency re-vaccination on the outbreak of an epidemic, in a community vaccinated many years before, is far more efficient...” Christie claimed that “for at least 10 years there is complete protection against death, and substantial protection against attack.”

In 1972 the U.S. put a halt to smallpox vaccination. The WHO followed in 1979, and since the early 1980s most countries in the world do not vaccinate. There are still some stocks of vaccines but their quantities and protective values are insufficient.

In view of the recent decisions by the U.S. and the WHO, we may expect renewal of mass production of vaccines. Now is the time to decide how to proceed with vaccination. Revaccination of people who were vaccinated once or more in the past will enable us to acquire vaccinia immune globulin in substantial amounts. This should be used for people who are prone to immune deficiencies. Other measures may also be applied to reduce the risks from vaccination, although these risks may be acceptable in view of the

risks of smallpox re-introduction. The time has come for governments and health ministries to sit down, prepare plans, and implement them without delay, especially in countries that are already exposed to terrorism and/or heavy international traffic.

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### Addendum

On 17 June the *Promed Digest* (ref: Promed Digest V2002#144) reported “A Smallpox Outbreak” concerning a “Soviet field test of weaponized smallpox” that killed three persons (two of them children) and involved the disinfection of homes, quarantine of hundreds of people, and administration of 50,000 vaccine units. The onset of the outbreak was due to a single person who was accidentally infected during the test and carried the virus to a nearby city in Kazakhstan. It should be noted that in 1971 most people were still being vaccinated; if that were not the case the dimensions of the outbreak would have been very much greater.