The End of Smallpox?

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Introduction: What is (or was) smallpox?

Before we can consider the end of smallpox we need briefly to look at it as it was. We need a platform from which we can look forwards. Is there any real hope that it has gone for ever?

Firstly, how was it eliminated as an existing entity? Could it ever return out of the blue? Lastly, could it come back through bio-terrorism?

The 1400 page, World Health Organisation (WHO) book entitled ‘Smallpox and its Eradication’ weighs eight pounds, but contains the overall history regarding how we got rid of the disease.\(^1\) The following is a brief, and personal summary.

Smallpox is acquired by inhalation, and the primary site of infection is in the oropharynx (the back of the throat). Here the virus quietly multiplies for about ten days. It then floods into the bloodstream. The patient becomes febrile and ill, and the rash starts to show. The red spots begin to blister and become full of pus (pustules). Clinically the diagnosis is fairly obvious at this point, since the rash in smallpox mainly affects the face and trunk, whereas chickenpox more commonly affects the arms and legs.

Confirmation of the diagnosis needs scrapings from the floor of a pustule and laboratory examination. We used to fix and stain them with a standard bacteriological pigment, crystal violet, when the virus particles can just be seen with an ordinary microscope at 1000 fold magnification. With an electron microscope, giving much higher magnification (up to 100,000 fold) the particles with their beautiful complex structure are evident. They can be distinguished from most other pox viruses (but not with any confidence from monkey pox).

The virus can be grown on the chorio-allantoic membrane (CAM) of 12 day old chick embryos, producing large numbers of white circular lesions one millimetre in diameter, each derived from a single virus particle. This, however, takes three days and modern techniques give a quicker confirmatory answer. The specimen yields the genetic footprint, DNA, which is further analysed in a machine, using the polymerase chain reaction

(PCR). In this way the DNA sequence of the virus (that is, the sequential arrangement of the different nucleotide molecules along the DNA chain, specific to each virus) can be quickly discovered. This newer method saves time which is essential to trace contacts. The unfortunate patient has a 30% chance of dying after about 10 more days, but speedy vaccination may save the lives of the contacts. There is also hope that a new drug, a derivative of cidofovir (akin to aciclovir and ganciclovir) may be developed; hopefully it will never be needed!

With such a high mortality, the desire to be rid of smallpox was (and is) self evident. Edward Jenner, a Gloucestershire doctor, introduced cow pox vaccination at the end of the eighteenth century, but even two hundred years later eradication was little more than a vain hope. The structure of society militated against it. However, as communications and roads and medical knowledge improved it became possible to make efficient use of vaccination of contacts and isolation of the patient (and diseased contacts). The long incubation period of smallpox allowed 10 or 12 days between exposure to the prime case and the onset of disease and infectivity in contacts. Hence contacts could be identified, traced and vaccinated in time to abort, or at least reduce the severity of, disease. Secondary contacts of the original contacts could also be identified in good time to limit the size of an episode.

This policy of isolation of the primary case, and secondary cases, together with selective vaccination of primary (and secondary) contacts in a given outbreak was called ‘ring vaccination’. This is a reference to the original case, in the centre, and the concentric expansion of contacts, secondary cases and contacts, etc. It has nothing to do with the nursery rhyme ‘Ring-a-ring of roses’.

Some countries introduced universal vaccination but many societies were unable to accept this as an essential medical procedure, particularly one with possible side effects. As a universal public health policy, it never worked. Thus there were, in the middle of the 20th century, only about 30 countries (out of more than 170 listed in the United Nations Charter) that were free from endemic smallpox.

At this time the WHO was doing nothing about the problem. However, in 1959, Victor Zhdanov, a Russian Professor of Epidemiology, and Deputy Minister of Health in Moscow, tried hard to persuade them to embark on a vast programme of worldwide universal vaccination. It was hoped that this programme, started in 1966, would result in the complete eradication of smallpox. Given the differences in cultures, economies and
religions across the globe, and perhaps the origin of the proposal, it could never have worked; and it didn’t!

WHO policy soon changed over to ‘ring vaccination’ for individual outbreaks, as described above. It was enormously more costly, because it was more labour intensive, but they persevered. Thus, in October 1979, the last case of smallpox on Earth was recorded. A local microbiologist, Professor Allan Downie, of Liverpool University had much to do with this success.

The WHO committee responsible allowed two years to go by before announcing that smallpox had gone for ever. They were worried about another pox virus which caused a similar disease in chimpanzees and other monkeys. It occasionally spread to humans and was occasionally lethal for man, although it seemed not to be very infectious from man to man, and soon died out. However when grown on the chick embryo chorio-allantoic membrane it produced tiny white lesions, just like smallpox. The only difference was that the outline of the white lesions changed slightly by the fourth day. The other oddity was that it only seemed to occur in Zaire in small, densely wooded, humid, isolated areas.

**The last case of smallpox in England**

The WHO held its hand while efforts were made to sort out these virus strains. They were given the name ‘whitepox’. The WHO wanted a better way of distinguishing whitepox virus from smallpox before they could announce the eradication of smallpox. Two cooperating laboratories were asked to study the relationship of whitepox to smallpox. One was headed by Dr Marrenikova in Moscow, and the other by Prof Henry Bedson in the Birmingham Medical School, England. The Moscow laboratory arranged to send a virus, believed to be a whitepox isolated from a piece of chimpanzee tissue which they had, to Birmingham. Curiously the chimpanzee had lived in India, where no whitepox had been found.

The specimen was inoculated onto the CAM chick embryos on 28 July 1978. Bedson went away for a few days, leaving one of his senior staff to harvest and passage them (keeping the virus alive by inoculating and infecting a series of fresh chicken embryos) when the next batch of 12 day old eggs were ready. This was on the 31 July.

On 10 August 1978, Mrs Parker, a photographic technician from the floor above the virus laboratory and three rooms along, felt unwell. On 14 August she called her general practitioner because she had a very bad headache. (The virus group on the floor below of course knew nothing of
this). On 17 August she developed a rash. Feeling ill, she moved into her mother’s house. On 24 August she was admitted to the Catharine de Barnes fever hospital and skin scrapings were taken to the Birmingham laboratory. Harvested after three days inoculation on the CAM, the membrane showed numerous tiny white lesions.

The Public Health Authorities came in and fumigated the laboratory, including the chick embryo membranes bearing the spots which were in the safety cabinet. This was certain to kill any virus.

*The Liverpool link (again)*

At this point I was called to come from Liverpool to see the now very sick Mrs Parker and to take new skin scrapings. Back in Liverpool I was able to grow a virus. It looked like smallpox but I could not exclude whitepox. Professor Bedson, myself in Liverpool and Professor Keith Dumbell at St Mary’s Hospital in London, had all trained in Liverpool under the world expert on smallpox Professor A.W. Downie (mentioned above). I was able to transfer the virus which I had isolated to Professor Dumbell who did the PCR and sequenced the virus DNA. The finding was astonishing and very worrying! The virus was indeed smallpox. Dumbell had the DNA sorted out and found that it was a particular strain called Harvey. It was a strain which Professor Downie had isolated many years before, from a man whose infection, in England, had originated in India. Samples of the strain had been issued to diagnostic laboratories worldwide at the start of the WHO eradication campaign so that all involved would have the same reference material.

The way in which the Harvey smallpox strain had finished up in Birmingham remains a mystery. It cannot be the strain isolated by Dr Marrenikova in Moscow from the chimpanzee from India, because chimpanzees do not get smallpox. Neither could it be a strain of whitepox carried by the chimpanzee, because the animal had come from India and whitepox is only found in West Africa. The only explanation seems to be that the culture sent out from Russia as whitepox was, in error, the Harvey reference strain of smallpox. One suggestion made (without support) is a possible error by a Russian technician. It is certainly not a mistake that Dr Marrenikova would herself have made.

Meanwhile Mrs Parker sadly had died. She (to date) was the last person ever to die of smallpox.

To summarise the story so far: we know for certain that human infection with smallpox no longer can happen in the wild, and there are no
animal vectors. How Mrs Parker became infected in the Medical School in Birmingham remains a mystery. The safety cabinet in which the work was done in the virus laboratory was in good working order. However, since the Mrs Parker episode a decision has been made that such work should only be undertaken in a closed cabinet fitted with gloves for the worker.

It had been suggested that a duct carrying telephone cables linking different parts of the building might have played a part. Certainly it provided a connection between the two relevant rooms, but this was conclusively dismissed when a team from the Ministry of Defence Microbiological Establishment at Porton Down in Wiltshire tested the degree of connection between the two rooms. Radioactive tracer gas released in the virus laboratory and tested in the upstairs laboratory gave a dilution factor such that 1000 gallons of virus suspension released as an aerosol would not have got through. Added to this, the duct was capped at all times. It was only removed by the fumigation team.

**The political dimension and bio-terrorism threat**

After the Birmingham episode in 1978 all laboratories in the world which held the smallpox virus were required to destroy or transfer any holdings to either Atlanta in the USA or to Moscow. There was an unexpected, unwanted and unexplained reluctance in the Union of Soviet Socialist Republics (USSR) to cease vaccination of its military manpower and this led to a deadlock. Furthermore, everyone remembered that it was the USSR, in the person of Victor Zhdanov, who had pressed the WHO to start the smallpox eradication programme in 1959.

In 1980 smallpox was declared eradicated by the WHO. However, in 1990 there were still suspicions in the west that secret work on biological weapons was continuing in the USSR.

In those ten years the USA had sequenced the whole of the DNA of smallpox. They proposed that all variola (smallpox virus) stocks worldwide be destroyed and that no country should hold the full DNA sequence.

The Russians procrastinated and did nothing. This was of course because their government had bigger worries! President Gorbachev was trying to hold together a country in which a rebellion was threatening to break out. He wanted to make the country more open both internally and internationally. He and other world leaders, including President Ronald Reagan (USA) and Prime Minister Margaret Thatcher (United Kingdom), found that they could talk to each other in open discourse.
Meanwhile in the USSR, and unknown to the west, dozens of vast and very expensive factories and laboratories devoted to biological warfare were running out of money for maintenance and for staff. Many of these were in far away parts of the Soviet Union. As a result of the growing international understanding, limited though it was, a reluctant agreement had been made to have mutual inspections of biological warfare establishments, supposedly to show that they were no longer in use. (In one of our teams from the UK was the late Dr David Kelly, who was to be involved in the microbiological politics in the aftermath of the invasion of Iraq, in 2003, and may have committed suicide). But in 1991, when multilateral inspections took place, the then government of the USSR collapsed and the USSR ceased to exist. It was replaced by a federation arrangement between all or most of the states that the USSR had captured in the days of Stalin and later. The Russian Federation had come into existence.

In the following year, 1992, a Russian team had gone to the United States to inspect the bio-warfare establishments at Fort Detric and Salt Lake City. They were trivial in comparison with those in Russia. However we believe that the huge group within the former USSR, sharing the name Biopreparat, had fallen into disuse through lack of funding and loss of staff. Many, from other countries had gone home. (We can only hope, empty handed!!)

The final chapter in this confused story was the most dramatic. In October 1992, Dr Kanat Alibekov, the deputy chief of the whole Biopreparat system throughout Russia, defected with his wife and children to the USA. He spent his first year in the USA giving a full account of the dozens of Russian bio-establishments. He later published a book ‘Biohazard’, under his new name, Ken Alibek. ² When you have read the book you may feel that the threat from the Russian Federation has died.

But there must be an after-thought: Ken Alibek gives us a list of the countries to which staff will have returned. Were they really empty handed?

² K. Alibek and S. Handelman, *Biohazard: the chilling true story of the largest covert biological weapons program in the world – told from the inside by the man who ran it* (New York, Random House, 1999).