Transcript

Smallpox Eradication: Is the Time Right for Destruction of the Virus Stocks?

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Introduction: Dr David Heymann:

Good evening, everybody. Good evening. My name is David Heymann and I am the Head and Senior Fellow at the Centre on Global Health Security here at Chatham House. I’d like to thank you all for coming this evening to this discussion on the smallpox virus. We are very lucky to have Geoffrey Smith with us. Professor Smith is actually the Chairman of the Variola Virus Research Committee at the WHO and is probably the best person in the world to talk to you about where destruction stands today and the various reasons that have been given. But before I turn over to Geoffrey, I’d like to just say a few words about smallpox and first ask if any of you in the room here have ever seen smallpox? Besides Paul?

Paul, do you want to describe a little bit what you saw?

Paul Fine:

I was in the smallpox eradication program with David in India in 1975 and saw a few cases. Incubation period is roughly a couple of weeks and the rash – the classic rash – which you’ve all seen many pictures of starts with a macular going to a papular going to a pustular stage. So it can be associated with a good deal of malaise or fever. The more severe – the variola major – case fatality rate maybe 30, 40 percent. With variola minor, appreciably less than that. One is talking about five percent. I don’t know that I need, I think everybody here knows a good deal…

Dr David Heymann:

Good. I think what you’ve done though is said how serious this disease really is. 30 to 40 percent of people who were infected died. As recently as 1967 – some of us were alive at that period of time – there were an estimated three million people each year dying from smallpox so it was a very, very serious disease. And those who survived, many were blind because it affected the cornea in the eyes, and those who survived had always severe facial scaring and this was especially a social problem for women in countries where women already were disadvantaged for other reasons. So it was a very, very difficult issue.

And so in 1967, at the urging of the two major Cold War powers at that time – Russia and the US – it was decided that the World Health Organization would create the partnerships necessary to eradicate the smallpox that was remaining in 37 countries. That eradication decision was made because the
smallpox virus existed nowhere but in humans. There was nowhere in nature where it was. And if humans that carried the virus could be isolated and transmissions from them interrupted, the disease would disappear. It had already disappeared from the majority of countries and there was a very strong and effective vaccine that could also prevent infection.

So the decision was made to eradicate smallpox and countries around the world joined together. And in 1977, the last case of smallpox in nature occurred. Does anyone know where that occurred? It was in Somalia. But the last human case of smallpox occurred in a country that we all know well and that was right here in the United Kingdom. Because the last case of smallpox occurred in Birmingham in 1978 in a laboratory accident where a medical photographer working in the same building as the smallpox laboratory became infected, and infected her mother. She died. Her mother became very sick and recovered, but her father died of a myocardial infarct at the same time and the laboratory technician committed suicide. So it was a very serious and very terrible outbreak, the last cases of smallpox were right here in the United Kingdom.

But in 1980, smallpox was certified as eradicated from the world. It was gone from the world and it was very interesting because this disease disappeared in 1980. It was certified gone. And in 1981, a new disease appeared for the first time and was first identified. That was HIV. And, in 1984, a military recruit in the United States was vaccinated with the smallpox vaccine because the military was still using it. This smallpox vaccine is made from a virus very similar to, but not the same as, the smallpox virus. The military recruiter was vaccinated, developed what’s called generalized vaccinia, a very serious illness where the virus spread throughout his body. This, in turn, was an AIDS-defining event because, unknown to the recruit or to the vaccinator, he was HIV-positive. Six months later he was dead from smallpox – from variola – or from AIDS rather. So what this showed at that point was two things: that the smallpox vaccine that was used to eradicate smallpox could no longer safely be used in populations around the world, especially where HIV prevalence would be high. Second was that the world took advantage of a window of opportunity to eradicate smallpox and didn’t even know that that window existed. So it was fortunate that smallpox was certified in 1980.

Now, the Birmingham incident cause great concern and it was the beginning of an effort to consolidate all viruses that might be in laboratories for research around the world or destroy those viruses. Now the consolidation, again at that time, took place in Cold War powers – Russia and the US. Countries
either provided their viruses to the US or to Russia for safe storage. There was then a movement through the Advisory Committee on Orthopoxviruses, which was where the smallpox virus fit, to destroy the virus because that committee felt that after representative DNA from the virus had been sequenced, there was no longer a need to keep the virus. So finally in 1996, there was a resolution in the World Health Assembly – and a resolution, remember, is political will of ministers of health from around the world – to destroy the virus, but the destruction was delayed until 1999. Since then, there have been a series of times in which there’s been an attempt to destroy the virus and then another decision not to destroy the virus for various reasons. At this point, I’ll turn over to Geoffrey who will be able to tell you more about those decisions at WHO.

**Professor Geoffrey L Smith:**

Well, thanks very much David, and thanks for the organizers for asking me to come here. I should say that I’m a virologist and I’m not a clinician. And I’ve never seen a case of smallpox like most of you in this room. But I’ve worked with pox viruses and particularly the vaccinia virus, the live vaccine that’s been used to eradicate smallpox for 30 years. It’s been a privilege to chair the committee at the WHO for most of the last ten years.

So I wanted to say a few words at the beginning to place us in context as well as David has done already and to reiterate that smallpox was a greatly feared disease. You know, it’s killed hundreds of millions of people. Thirty percent mortality in unvaccinated populations. Together with some other members in the room like Adrian Hill here we were at a meeting with the Royal Society today looking at human populations and human evolution. Of course, it was only when humans stopped being hunter gatherers and adopted intensive agriculture that population densities could build up such that highly infectious, contagious diseases like smallpox or measles could persist in the human population because, before that time, there just weren’t enough susceptible people in which the virus could be transferred. And so, it’s our own fault, and that’s true of many diseases. We create niches into which viruses and other pathogens jump when that opportunity is given to them.

So smallpox was eradicated by vaccination and the vaccine is called vaccinia virus after the Latin vaca for ‘cow’, but actually that’s probably a misnomer. The origin of vaccinia virus is unknown. It is an enigma of virology. It’s the only vaccine that’s ever been used to eradicate a human disease and yet it’s origin and natural host are unknown. Quite remarkable. It’s thought that
Jenner first used cow pox virus in 1796 when he vaccinated his gardener’s son, James Phipps with material taken from the hand of a milk maid, Sarah Nelmes, who caught it from her cow called Blossom. Jenner then went on to challenge this child with smallpox, a horrendous experiment which, by today’s standards, would be banned outright by the health and safety executive. In fact, he would probably have been in jail. But he, of course, was correct and having shown this child was protected against smallpox and then repeating his experiment with ten or so other children – now including his own son – he wrote up his seminal paper which he published privately in 1798. He predicted only three years later that it now became too manifest to admit of controversy that the annihilation of the smallpox – the most dreadful scourge of the human species – must be the final result of this practice. And as we heard, he was correct, although I suspect it took rather longer than he would have liked to be fulfilled. In fact, another 177 years.

But it was certified by the WHO as being eradicated in 1980 and it remains the greatest triumph for the WHO. It really is a magnificent achievement and all those people who were involved in the eradication campaign should be rightly proud of their role. It’s also a wonderful example of how when nations work together rather than squabbling they can achieve something which is for everybody’s benefit. Now the eradication was welcomed, not only because smallpox was eradicated, but also because the need for vaccination was discontinued. This was not a safe vaccine. By today’s standards, it would be very poor and would not be licensed as a new vaccine today. There were complications that ensued in people who had some medical contraindications such as immune-suppression or eczema or pregnancy. So it was welcomed as getting rid of the need for vaccination as well as the disease itself.

So following the eradication, the WHO led a program to identify, then centralise all the stocks of virus. These are now kept in only two places in the world: one, the Centers for Disease Control and Prevention in Atlanta in the United States, and secondly, in the Russian State Centre on Virology and Biotechnology in Koltsovo, Novosibirsk in the Russian Federation. These are maximum security laboratories – that’s BL4. They are inspected annually, I think, by the World Health Organization to ensure that the practices are being strictly obeyed and the labs are up to standard.

And indeed any work that the scientists working in those establishments wish to do that requires use of the live virus have to first be submitted to WHO and then considered and approved or rejected. There is a committee which Dave has mentioned – it’s called the Advisory Committee for Variola Virus
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Research – which considers the proposals and meets annually to review the work that has been going on and to keep an inventory of the virus stocks.

So following eradication of smallpox, many considered that the destruction of the causative agents – variola virus – was the next logical step that would have drawn to an end the concerns about smallpox, prevent absolutely the escape of the virus, again, from even these very high security laboratories which, I would have to say, the chances of escaping from there are remote. But it would also be the natural conclusion of the eradication campaign. As we heard, the WHO passed a resolution in 1996 stating that the last known stocks of the virus would be destroyed. So that decision has been taken. And the current debate is not so much about whether that decision is correct or not. It’s about when that decision will be implemented.

So why not destroy the virus immediately? Indeed, why not destroy it 15 or more years ago? What were their reasons for keeping it? Well, there are several reasons. One was that some scientists have argued that if we understood why variola virus was such a dangerous pathogen and how it was able to overwhelm our bodies’ natural defences, then that greater understanding of how viruses can cause disease may lead to therapies to control or eliminate other virus infections as well as pox viruses. Others wanted to better understand the genes and the genetics of the virus and to understand the genetic relationships between variola virus and other members of this family and to study the functions of the individual proteins encoded by the virus. There was also a desire to produce a safer vaccine that could be used in all people and to make drugs that prevented smallpox should someone ever become infected in the future. Of course, proving that new vaccines were effective would require the live virus. A minority of people even argued that destruction of the virus would be a destruction of biological diversity and argued against destruction for that reason. You can imagine members of the Green Party perhaps taking this point of view.

But anyway, after hearing all these arguments, the World Health Assembly decided in 1999 to postpone the destruction until the research which had been authorized was complete. But the decision to destroy the virus remained. And then came the terrorist attacks in the USA in 2001. Following those events, it was hypothesized by some that if terrorists would be prepared to fly airplanes into densely crowded buildings, why would they hesitate to release a deadly virus such as variola virus [inaudible] terrorism. And in considering this possibility governments were faced in 2001 with the following scenario: one, vaccination against smallpox had been discontinued in most
countries since the mid-1970s and therefore an increasingly large proportion of the world’s population was non-immune, susceptible to smallpox. The remaining stocks of vaccine were old and in limited supply and, indeed, the WHO had authorized destruction of millions of doses of vaccine during the 1990s because it was expensive to keep and it was deemed surplus to requirements. There were then and are now no licensed drugs for smallpox. So if someone was able to get hold of the virus, were to release it, say, in a crowded airport terminal, people might become infected and they would transmit the virus to other parts of the world and it would be several weeks – two to three weeks minimum – to realize that this was smallpox. By then, there would be an epidemic that would represent a global emergency.

So the outcome of this scenario was two-fold. Firstly, that several nation states including UK, USA, France and others, and also the WHO, started to replenish their stocks of the smallpox vaccine. Indeed they also started to vaccinate a limited number of their citizens. In the UK, for instance, we vaccinated about 300 health care workers who were divided up into regional teams such that if there ever were a case of smallpox again in the future, there would be a team of healthcare workers who would be able to care for the patient without themselves contracting the disease and possibly spreading it to others. The second outcome was that the research on variola virus was intensified. This work, that had been authorized already, had really three objectives and this remains the case. So the first one was to develop diagnostic kits that would accurately and rapidly diagnose smallpox and detect variola virus and distinguish that infection from infections caused by other related viruses. The second objective was to develop a new smallpox vaccine that was effective, but also safer than the existing vaccine so it could be used in all people. And the third objective was to develop anti-viral drugs that could treat patients that had become infected with variola virus and prevent them from dying from smallpox. It was [inaudible] that it was desirable to find drugs that targeted virus replication at two distinct stages of the replication cycle such that, if the virus mutated and became resistant to one of those drugs, then the other one would still be effective.

So research to meet these objectives has been going on for a decade and very good progress has been made. We do have sensitive diagnostic tests that have been developed and, indeed, those have been field tested. So, for instance, in 2003, there was an outbreak of monkeypox in the United States that clinically looks very much like smallpox, the difference being that the virus does not transmit efficiently from person to person unlike smallpox. When that outbreak arose in the midwest in the USA, there was a concern
that someone had released variola virus and this was smallpox. These diagnostic kits were able to rapidly prove that that was not the case and that it was monkeypox and not smallpox.

However, there are also unique difficulties in completing these research objectives. For instance, regulatory authorities require evidence that a drug or vaccine is effective against the organism in its natural host. Since smallpox was a strictly human disease and there is no animal model, obtaining such data is impossible. So therefore, one has to rely on surrogate models with related viruses and, using those surrogate models, it has been shown that there are new vaccines that can be effective at preventing infections by those viruses in those models. Also, two excellent drugs have been developed which have been able to prevent disease caused by those orthopox viruses and including variola virus in a primate model. But someone could always ask, well, how do you know that those animal data are really reflecting what would happen in man? I guess one can never be absolutely certain of that and that’s the dilemma facing the Federal Drug Administration in the US and the Medicines Control Agency in the UK. How do you prove that these are actually sufficient? But my own feeling about these drugs is that they are absolutely effective. They have worked in every model in which they have been tested. They are safe in man. They have good pharmacokinetics. And I have no doubt whatsoever that if smallpox arose, they would one, be used, and two, be effective.

Now while this research was going on, other scientific developments have made it possible, via synthetic technology, to recreate infectious orthopox viruses. So from scratch, you could synthesize the DNA, stitch it together and recreate the virus. This, of course, has never been done with variola virus, the cause of smallpox, because that is prohibited. But there is no reason to suppose that it would not be possible if one was so minded. This impacts, then, on the debate about destruction. For me, it weakens considerably the argument for retention because destruction is no longer irrevocable. One could remake it if one had to.

So after about a decade or so of this research program, last year, the WHO organized a major review of the research progress against the stated research objectives. Six review articles were written by experts in the field and then experts from outside the field reviewed this work. Those articles and their conclusions and indeed the views of the expert review group were considered by the Advisory Committee of Variola Virus Research last November and are published. At the Committee, last November, I think it
would be fair to say that there were mixed views about whether the research programmes had achieved their stated objectives. Some, perhaps the majority of the committee, felt that the objectives had been attained as well as they ever could be and therefore further research with live virus was not necessary. But others who largely do come from the two collaborating research centres in the USA and Russia, who are authorized to work with the virus, felt that more work was necessary and were certainly against destruction at the moment until the new drugs, for instance, were licensed. So these documents were considered by the 64th World Health Assembly recently and the decision was to postpone the destruction of the virus again and to revisit this in 2014. Presumably, in the meantime, the work authorized by the WHO will continue and this work will be continued to be monitored by the WHO Advisor Committee.

Dr David Heymann:

Thanks very much, Geoff. We’ve had apologies from Dr Robert Drillien this evening who, because of a sickness in the family, has not been able to come over from France. I wonder Geoff if you would like to say any words about… I know you spoke with Robert earlier today. Did he provide any words that he would like you to say this evening?

Professor Geoffrey L Smith:

Well, he sent me a text. Some of it, I guess that we have already covered, but there are certainly some parts that might be worth reading out. He said for instance that it is peculiar that smallpox has been extinct for 30 years and yet we are still talking about it. No doubt because it was such a dreadful terror for mankind, killing the poor and the wealthy alike, and because the two collaborating centres still have samples of the virus. In fact, the CDC have got 451 distinct variola virus isolates and the Russian collection is a mere 120 isolates. In each centre, many of those isolates have been amplified and are kept in numerous vials. In fact, I would suspect that over the decade of this research program, the number of those vials has increased appreciably and that’s probably a British understatement.

I think the reasons for retaining the virus, I’ve gone through, and Robert’s text is certainly overlapping with what I have stated. He does have a slightly more political content to his text though which I think might be interesting to read out. He said, ‘It should also be added that 12 years ago there was certainly the feeling amongst scientists that more knowledge of the virus was
warranted before destruction and that this knowledge could probably contribute to solving some of the health related issues with the vaccine. And last, but far from least, the two countries that had possession of the virus were superpowers that seemed to be inclined to view possession of the smallpox agent as a deterrent in itself. Despite the declaration of eradication, a number of countries have maintained smallpox vaccination for some of their citizens. Even to this day, a clear illustration of the perception of a threat and lack of trust.’

There are strict rules about handling variola virus, apart from the fact that only two laboratories in the world are authorized to have it and must get permission to work for it. There are also rules about genetic engineering. For instance, it’s prohibited to genetically engineer variola virus. It’s also prohibited to take any gene – any single gene – out of the 200 the virus has and to insert that into any other orthopoxvirus because one wouldn’t really know what the outcome of that might be. It is prohibited for any laboratory to have more than 20 percent of the entire genome of the virus, even in cloned DNA forms which themselves are non-infectious.

He also points out the development of these two excellent drug candidates and they are called F.T. 246, for the record, which is an inhibitor of the final stages of virus morphogenesis. So although you can produce infectious particles inside a cell that has been infected and treated with that drug, that virus is not released and therefore spread is prevented. We know from many studies of orthopox viruses that if you diminish the spread of virus, you render the virus avirulent. So this particular drug has been very effective at preventing disease caused by these viruses in many different animal models. The second drug is cidofovir or its related lipid-soluble derivative called CMX001, is effective at blocking virus DNA synthesis. Cidofovir is actually licensed for treating some herpes viruses such as human cytomegalovirus infections. It’s also a potent inhibitor of orthopox virus replication including variola virus. So Robert goes on to point out that the drugs which have been developed, although they are very effective in these animal model and in cell culture at preventing variola virus, replicating or causing disease, they have not been licensed. They have got investigational drug status issued by the FDA so they could be used under emergency circumstances. But they have not been licensed.

And perhaps I’ll just read out the last half page or so of his text as a wrap up:

‘In light of the fact that the World Health Assembly, as you know, has decided once again in May of this year to postpone destruction of variola virus stocks,
how can this issue apparently be solved or will it be delayed indefinitely? I’ve tried to outline briefly the issues and the problems faced are scientific, medical and political. There are great obstacles in gaining more detailed knowledge of smallpox because of the lack of a good animal model and because, fortunately, there is none. It’s my opinion that more knowledge of the unique features of variola virus can be acquired without actually using live virus, but by studying its genes and gene combinations as is carried out currently in several laboratories.

Whether the restrictions on such research can be relaxed somewhat while ensuring complete safety merits further debate and the ability to convince the public that it is performed in a responsible manner. The potential to recreate variola virus through synthetic biology, without access to any live virus stocks, completely changes our outlook. First, the destruction of the current stocks no longer removes the smallpox threat. Second, if variola virus stocks are finally destroyed and future generations think this was a mistake, then the virus can be regenerated. It’s not even inconceivable that variola virus, properly disarmed, may be put to good use, in one form or another, of medical strategy as is practised today for other dangerous pathogens.

‘So in my opinion – this is Robert speaking – the public health goal set by the World Health Assembly 12 years ago has been achieved. Registration and approval of new diagnostics, vaccines and drugs cannot be definitively accomplished in the absence of smallpox. We can’t prove that they work. Of course, public health measures progress with time and the state of variola preparedness may be outdated in the not too distant future. However, in the absence of the disease, do we really care? Finally, a brief glance at some, I think he means, political issues. The goodwill of the two nations that maintain virus stocks would be nicely demonstrated by destruction of virus samples for which no further research is warranted and this is actually the case for most of them (he means most of the stocks). One would also like to hear some public recognition that the stocks belong to the world community and not to any particular country. An interesting question to raise is what would be the policy of the USA and Russia if the variola stocks were held in other countries than their own. My guess is that both of them would be the strongest advocates for destruction.’ And with that, he thanks the organisers for the opportunity to come.
Dr David Heymann:

Thanks Geoffrey. With that, I will open to questions.