

## Rinderpest, smallpox, and the imperative of destruction

In June, The Pirbright Institute (UK) announced that it had destroyed its final archived stocks of rinderpest, the devastating viral disease of cattle that was declared eradicated in 2011. Rinderpest is only the second infection to be eradicated from the wild. The decision raises the question once again of what to do with the remaining stocks of the first eradicated virus—smallpox.

The Pirbright Institute did not hold the final stocks of rinderpest in existence; samples are also known to be stored in a handful of facilities in China, Ethiopia, France, Japan, and the USA. Still, The Pirbright Institute is the World Reference Laboratory for rinderpest, previously storing more than 3000 viral samples. That it has taken the decision to destroy them represents a bold commitment to permanently ridding the world of the disease and should encourage others to do the same. France plans to destroy its remaining stocks, and discussions continue at other facilities.

There are pros and cons to destroying such samples. On one hand, maintaining stock risks accidental infection and reintroduction, which could devastate susceptible populations with neither natural nor vaccine-induced immunity. The last cases of smallpox occurred in Birmingham, UK, in 1978, following accidental laboratory exposure—Janet Parker, a medical photographer, died. While samples of live virus are kept, the risk of further infections remains.

On the other hand, no more live virus means no more research. Expertise acquired from studying smallpox could prove invaluable for related infections such as monkeypox, which seems to be filling the same ecological niche. The most pressing concern is what would happen should the virus re-emerge. As far as we know, variola virus exists only in two BSL-4 laboratories in Russia and the USA. But unknown samples might exist elsewhere (in 2014, vials labelled “variola” were found in a freezer in a National Institutes of Health site in Bethesda, MD, USA; they were destroyed under observation by WHO). Some countries might secretly maintain stocks for potential use as a bioweapon or the virus could exist in an unknown reservoir. Without maintaining samples of live virus, further research to develop treatments, vaccines, and diagnostics in case of re-emergence would be impossible. The destruction of the final stored samples would be irrecoverable.

But no longer. The Pirbright Institute’s policy has been to “sequence and destroy”; they sequenced the genomes of each sample before destroying them. Should we ever need live virus again, it could be reconstituted with relative ease thanks to advances in synthetic biology. Variola has a larger genome than rinderpest but reconstruction is feasible, although because of tight controls on research, it has not yet been done. A paper in this journal on reconstruction of Ebola virus shows the possibility of reconstructing even highly dangerous viruses from a genome sequence quickly enough to inform an outbreak response.

Ironically, the advances that have made destruction more palatable have raised the risk of reintroduction greatly. Now, anyone with an undergraduate degree, access to a laboratory, and a little time on their hands could conceivably rebuild variola virus. This possibility has the global health community concerned.

Smallpox stocks have been earmarked for destruction since eradication of the disease in 1980. Yet, successive meetings of the World Health Assembly have postponed making a final recommendation while the threat of re-emergence from elsewhere remains. At its last meeting in September, 2018, the Advisory Committee on Variola Virus Research told WHO that live virus is still needed for the development of new antivirals, with split opinion on whether it is needed for diagnostics. Huge strides have been made in these areas in recent years. New more advanced and safer vaccines have been developed; new diagnostic tests are in development; and the first specific antiviral for smallpox—tecovirimat—was approved by the US Food and Drug Administration in June last year, after some innovative regulatory manoeuvres.

The deliberations over smallpox stocks happen regularly, but the decisions are ad-hoc. For rinderpest, destruction seems only a matter of time. Smallpox stocks will also likely be destroyed once diagnostics are finalised and a second antiviral, with a different mode of action in case of resistance, is approved (many are in development). And in the future, what might happen for polio? For mumps? For measles? Destruction of all stocks should be the ultimate goal of eradication. What is needed are clear requirements for exactly what medical countermeasures are required before that final step is taken. ■ *The Lancet Infectious Diseases*



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For more on **reconstructing Ebola virus from its genome** see **Articles** *Lancet Infect Dis* 2019; published online July 9. [http://dx.doi.org/10.1016/S1473-3099\(19\)30291-9](http://dx.doi.org/10.1016/S1473-3099(19)30291-9)

For more on **the approval of tecovirimat** see **Personal View** *Lancet Infect Dis* 2019; 19: e221–24