Smallpox virus – another chapter

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The Life of Smallpox Virus -- a recent chronology
1973-80

- 1975 -- WHO survey - labs with smallpox virus –74
- Laboratory accidents
  - London School of Trop. Med. – 1973
  - Munich Institute -- 1975
- 1976
  - WHA resolution recommends destruction or transfer of virus stocks to WHO Collaborating Labs (Atlanta, Moscow)
  - First WHO recommendations for lab safety
- 1978 Laboratory accident
  - University of Birmingham
- 1980 Declaration of eradication
  - Only 4 labs with virus but 2 others soon transfer stocks

Pressures to destroy the virus
1980-85

- WHO Advisory Committee established –1980
  - Chairman: Dr. Frank Fenner, Australia, leading international authority on poxviruses.
  - To determine the need for and nature of any research that needs to be conducted
- Developing countries argue for virus destruction privately and at World Health Assembly meetings
  - Concern about possible escape of virus from the laboratory
  - Suspicions about US/USSR motivations in wanting to keep the virus
  - Major disease burden had been borne by developing countries
  - Since decision for eradication had been taken by vote of the WHA, the WHA itself should decide about destroying the virus
  - No country had contributed more than 10-15% of program costs

Factors pertinent to possible virus destruction
1985-1990

- WHO Committee sample survey -- 1985
  60 virologists in 21 countries -- 55 favor destruction
- Preservation of genetic information begun
  - Non-infectious cloned fragments from multiple strains
  - Sequencing of principal strains
- Request for definitive action – 1990 WHA
  Secretary of HHS Louis Sullivan announced the intention of US to destroy its strains as soon as sequencing work was completed (provisionally, December 1993). USSR had been invited to endorse this effort and it had agreed.

Global views on destruction
1990-1995

- Discussion (pro and con) at 1993 International Congress of Virology (Glasgow); summary papers published and widely distributed
- Written support from 5 scientific groups received
  Executive Board of International Union of Microbiological Societies
  Council of the American Microbiological Societies
  Russian Academy of Medical Sciences
  Council of the American Type Culture Collection
  Scientific Counselors of CDC National Center for Infectious Diseases
- Bernard Moss (NIH) announced that the sequencing of the genome had been completed (January 1994)

WHO Advisory Committee
1994 Report to WHO DG

- Report recommended a witnessed destruction of the virus on June 30, 1995
- WHO Executive Board (Jan. 1995) and WHA (May 1995) to decide but consideration blocked by U.S. and Russia
- 1996 WHA –decision on destruction postponed until 1999

Post 9/11 assessment of risk

- Risk of a smallpox virus release was real but much less likely than a release of anthrax or other bioagents that could be more easily acquired, produced, and distributed
- However, the outcomes of a smallpox release were viewed as potentially more catastrophic because of subsequent disease spread without adequate vaccine
- Availability of ample quantities of vaccine would markedly reduce the likelihood of such a disaster
  - Smallpox did not spread rapidly or easily
  - Focused containment measures, used during the eradication program, had been highly effective
- Emergency production of 300 million doses of vaccine begun

Meanwhile at the World Health Assembly

- WHAs 1999, 2002, 2005, 2006
  - U.S. and Russia continue to argue for more time before destruction to complete research studies
  - Meanwhile, two unique provisions
    1) All research protocols to be approved in advance by an international committee
    2) Bi-annual inspection of both labs re: safety
  - U.S. has objected to both provisions
  - U.S. commissioned IOM reports in 1999 and 2010 on the potential importance of continued research if virus retained
  - Developing countries indicate a strong interest in bringing to a vote a decision to destroy the virus
  - An independent WHO committee of experts appointed to review and report to the 2011 WHA.

IOM Committees of 1999 and 2010

- Charge:

  To review "the potential scientific and medical information that would be lost were live variola virus no longer available"

- Restrictions on Committee deliberations:
  1) Not to assess the risks of variola virus being retained
  2) Not to address the question of whether virus stocks should be retained or destroyed
  3) Not to comment on the possible costs or priorities that should be given to research that would require intact, viable smallpox virus

Rationale for retaining variola virus

2010 IOM Report

- Therapeutics
  - Final development and licensure of two therapeutics
  - Development of other therapeutics with different targets
  - Evaluation of therapeutics against a panel of strains to test resistance
- Vaccines
  - Development of a vaccine that produces no skin lesions
- New methods for detection and diagnosis – not needed
- Genomic sequence analysis – not needed
- Discovery research – interesting but not essential

  General understanding of host responses to variola

Are new therapeutics or vaccines required and, if so, in what quantities?

- What is the probability of a smallpox attack and of what nature and magnitude – a changing scenario but what is now the working consensus?
- What is or should be the proportion of the budget apportioned for smallpox vs. other agents
  - Costs are large e.g. 300 million vaccine doses x $10/dose = $3 billion
- Questions are unanswerable without a strategic plan – a basic starting point

  Plan must take into account existing capabilities as well as potential and costs for implementation at all levels of government as well as costs and risks of interventions (including mass vaccination, distribution of anti-virals, clinical care, etc, etc, etc)
- Should the event occur tomorrow implementation would require immediate action by diverse national government agencies, state and city officials. What actions do they take? What messages do they convey?

  Vaccinate everybody? Barricade borders? Quarantine cities?
- There is today no agreed-upon strategic plan

  Note, the anthrax attacks occurred 8 years ago.

Smallpox: should we destroy the last viral stocks?

For the **WHO smallpox factsheet** see http://www.who.int/mediacentre/factsheets/smallpox/en/

For the **Institute of Medicine 2009 report *Live Variola Virus: Considerations for Continuing Research*** see http://iom.edu/Reports/2009/LiveVariolaVirusContinuingResearch.aspx

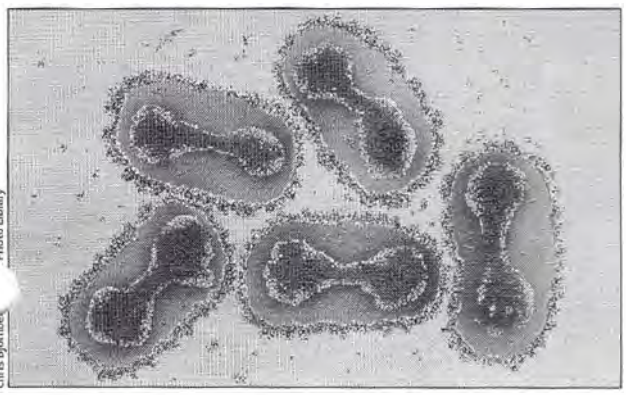
An International Symposium held in Rio de Janeiro, Brazil, on August 24–27, has focused on the lessons learned from the smallpox experience and featured debates on one very thorny issue still surrounding smallpox—whether we should destroy all stocks of the viral strains held in the world. WHO declared smallpox officially eradicated 30 years ago and it is still the only infectious disease that vaccination has succeeded in completely removing from the human population worldwide. Smallpox was highly virulent and killed 20–60% of those it infected, and caused long-term disability, such as deafness and blindness, in many of the rest. "Originally, stocks of the smallpox virus were held at dozens of locations but this was reduced to only two WHO Collaborating Center repositories—the State Research Centre of Virology and Biotechnology (VECTOR) in Russia and one at the Centers for Disease Control (CDC) in the USA", notes Gilberto Hochman (Oswaldo Cruz Foundation, Rio de Janeiro, Brazil), one of the conference organisers. "The others were destroyed after the accidental infection and death of a lab worker in Birmingham in the UK in 1978."

The decision to destroy all smallpox virus stocks has been made, but since 1999 several World Health Assembly (WHA) resolutions, such as WHA Res 60.1, have put off this final action. "All authorise further temporary retention of the two official WHA-sanctioned stocks of live variola to facilitate outcome-oriented, essential public health research; they also require review and approval of the research by a technical committee", explains Inger Damon, Chief of the Poxvirus and Rabies Branch at CDC (Atlanta, GA, USA). Research towards the development of diagnostics, antivirals, less reactogenic vaccines, and animals in which to best study these countermeasures, continues only under WHO auspices. "The continued retention of the official stocks will again be addressed in 2011, when WHO will provide a major review of research completed, products developed, and considerations for further essential research for global public health, through the WHO Executive Board, to the WHA", Damon told *TLID*.

The benefit of destroying all remaining stocks would be to further reduce the already unlikely possibility that a lethal epidemic might result from the theft or accidental release of the virus from one of the remaining laboratory stocks. "However, the governments of both the USA and Russia have thus far resisted any recommendations for destruction of their stockpiles because of the very serious drawbacks that such action would have", comments Raymond Weinstein (George Mason University, VA, USA).

One major disadvantage is that we would lose the smallpox virus as a research tool. Smallpox is one of the oldest diseases known and the human immune system evolved under the influence of smallpox. "To see the importance of smallpox in human immune evolution one need only look at the success of the mutation in the CCR5 chemokine receptor, which first appeared in a single northern European individual about 1000 years ago and is now present in around 10% of all northern Europeans", notes Weinstein. People who have it lack the cellular transmembrane immunological receptor CCR5 and show substantial resistance to smallpox—and nearly complete immunity to HIV. "We are only just beginning to unravel the complex pathophysiology and virulence mechanisms of smallpox but we do know that the variola virus produces important short-term and long-term alterations in the human immune system. Gaining a better understanding of these changes could lead to new therapeutic options for a host of diseases, but if all smallpox samples are forever destroyed the medical and scientific communities would lose a potentially valuable research tool", adds Weinstein. "It is certainly true that smallpox research has had important spin-offs for other viral infections; the research is not only applicable to a disease that no-one can catch anymore", stresses David Evans (University of Alberta, Edmonton, AB, Canada).

Complete destruction of the smallpox virus would also be difficult because no-one knows exactly what viable stocks still remain. "At least 461 isolates of variola have been deposited with the CDC; the DNA of nearly 50 of these virus isolates have been sequenced and are in the public domain, but less is known about viral sequences of the stocks in VECTOR", says Robert Drillian (IGBMC, Illkirch, France). Undisclosed stocks of smallpox virus may also exist. "It has been virtually impossible to verify whether or not the Russians fully destroyed their weapons-grade variola stocks that were created by Biopreparat in the 1980s", says Grant McFadden (University of Florida, Gainsville, FL, USA). Theft or movement of stocks during the breakup of the former USSR could have resulted in terrorist acquisition of smallpox viral stocks. It is state-sponsored terrorism that we have to worry about here, rather than



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TEM of the smallpox virus (Poxviridae)

splinter groups in hiding, believes Evans. "Unless it is stored carefully at very low temperatures, the smallpox does not survive well and needs to be cultured every few years to remain viable. Stocks that have been stored improperly for the last 10 years are likely to be dead by now. To maintain a terrorist threat, groups would need to have access to the highest level containment facilities and the expertise to passage and re-store the virus", he explains.

The argument for destroying remaining smallpox virus stockpiles may also be rendered moot by two possibilities. "Creating smallpox, of course, would be unethical and probably illegal but certainly could be done from a technical point of view. To create live poxviruses from scratch, all you need is time (maybe 6–12 months), money (maybe US$100 000 at today's prices), and the technical know-how (pretty much available to anyone with basic knowledge in molecular biology and synthetic gene constructions)", explains McFadden. A further sobering thought is that nature might do the job for us. "Studies suggest that both variola and vaccinia probably emerged from either camelpox or taterapox, an enzootic poxvirus of a small African rodent; it is not impossible that nature might once again create variola from a near relative poxvirus or even create a distinct, smallpox-like virus from a more distant yet clinically similar poxvirus such as monkeypox", adds Weinstein.

The need to protect the global population from the smallpox threat, whatever its source, has led to some consensus. "Broad international agreement has enabled the development of up-to-date methods of virus detection, safer vaccines, and effective therapeutics, the latter being in existence before eradication", comments Drillian. Stockpiles of second-generation smallpox vaccine ACAM2000 have been amassed by many countries in the world, and by WHO. Despite that, we still have much to fear; immunity to the smallpox vaccine 40 years after population wide vaccinations ceased in most countries would be low in all age groups. Even if vaccination could be mobilised quickly enough, people with HIV/AIDS, transplant recipients, or anyone with immunosuppression could not be protected. "The only validated vaccine we have is a live vaccine and this would certainly be fatal to the immunocompromised", concludes Evans.

Kathryn Senior

Infectious disease surveillance update

Pan(dem)ic over

On August 10, the WHO Director-General's statement after the ninth meeting of the Emergency Committee declared the 2009–10 influenza A H1N1 pandemic over. WHO estimates that 18 449 people have died as a result of the virus in 214 countries and overseas territories or communities.

Polio in Angola

As of July 19, the Angolan Ministry of Health had reported 15 cases of wild poliovirus type 1 (WPV1) since February 2010. All cases were detected in the capital Luanda or in provinces previously free of polio (Bie, Bengo, Huambo, Lunda Norte, and Lunda Sul). A region of DR Congo bordering Angola (Kasai Occindentale) reported a genetically related case.

Since 2007 there has been a persistent outbreak of WPV1 in Angola. And with the recent expansion of the outbreak, WHO judges it of high risk of further international spread into neighbouring countries. Angola was free of polio between 2001 and 2005, genetic markers suggest importation of the virus from India.

In 2010, Angola targeted high-risk provinces from May 7–9 with a subnational round of immunisation with monovalent oral polio vaccine type 1 (mOPV1). From June 11–13 there was a national round of immunisation with a combination of trivalent oral polio vaccine and mOPV1. Mop-up immunisation campaigns with mOPV1 were done in response to cases of WPV1.

Measles in Greece

As of July 25 there have been 126 cases of measles reported to the Greek Centre for Disease Control and Prevention in 2010 related to a recent outbreak in Bulgaria. Infected individuals were mostly unvaccinated. 77 of the reported cases were laboratory confirmed, with remaining cases classified as probable (31 cases) or possible (18) on the basis of the European Union case definition of 2008. All 19 cases genotyped by the Greek National Measles Reference Laboratory were genotype D4.

78 of the reported cases were in children age 0–14 years, 34 of which were in children in the 1–4 year group, and ten were in children younger than 1 year. 106 people with the infection had known vaccination status: 93 were unvaccinated and 13 had received at least one dose of the combined measles, mumps, and rubella vaccine.

Information on foreign travel was available for 114 of the people with measles: 104 people had no recent history of foreign travel, eight people had recently travelled to Bulgaria, one to France, and one to an unspecified destination.

In response to the outbreak vaccination campaigns have targeted groups with low vaccine coverage, prioritising high-risk communities in affected areas.

Onisillos Sekkides

For the **WHO Director-General's statement** see http://www.who.int/csr/disease/swineflu/9th_meeting_ihr/en/index.html

For more on **polio in Angola** see http://www.who.int/csr/don/2010_07_19/en/index.html

For more on **the measles outbreak in Greece** see http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19629