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Commentary on the 1971 Smallpox Epidemic in Aralsk, Kazakhstan, and the Soviet Biological Warfare Program (No. 2)

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BACKGROUND

The epidemiology of smallpox varies with the vaccine status of the population.[1] In areas where smallpox has never occurred, the attack rate is high among all ages and the death rate is highest among older children and young adults, as is the case with the introduction into naïve populations of other viral infections such as varicella and measles. In endemic areas, children experience higher attack rates because adults are immune by virtue of past infection. In populations with active childhood vaccination programs, young children have low attack rates because most have been recently vaccinated, while adults have higher attack rates reflecting their waning immunity. In populations with recent lapses in childhood vaccination programs, the attack rate in children is relatively high because many are not vaccinated, and relatively low among adults, reflecting immunity from past immunization.

In the Aralsk outbreak, the population was not well vaccinated, and vaccine status appears to have been worse among younger children than among older children (see Table 1).

These data suggest that the immunity of the Aralsk population was lowest in younger children, probably reflecting a decline in vaccination rates among infants. The data also suggest that previous vaccination had not been highly effective. Furthermore, the Aralsk report cites 10 students in Patient 2's class who had vaccine scars but still developed a primary take on revaccination, indicating low immunity. Since the number of children examined in this classroom was not given, the take rate cannot be calculated. More information on the efficacy of the vaccines and vaccination strategies used in Kazakhstan before 1971 would be critical to understanding the meaning of the Aralsk outbreak.

It seems clear, however, that in 1971 the vaccine coverage of the city's population was suboptimal—certainly low enough to sustain an outbreak until it was halted by widespread vaccination and quarantine—and that the efficacy of the past vaccine was questionable. This concern is further highlighted by Patient 4, who developed classic smallpox in spite of having been vaccinated

Table 1

Population	Percent without scars	Percent with primary take
Grade 2-3	24%	31.6%
Grade 3-10	15%	NA
Adults	10%	?
Total	11.6%	20.6%

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two years earlier. In this case, either the vaccine was of low potency or differed enough antigenically from the infecting strain to provide only partial immunity. Other information on poor immunity after vaccination supports the first hypothesis.

FACTORS THAT AFFECT SMALLPOX VIRULENCE

The virulence of variola virus depends on both host and viral factors, which act in concert to determine the outcome of the host-virus interaction. Host factors include:

1. Acquired immunity, resulting from
   a. *Transplacental antibody*, which appears to be short-lived, providing strong immunity for the first month after birth and partial immunity for the first four to six months after birth.[2]
   b. *Passive immunity*, from infusions of hyperimmune serum from recipients of smallpox vaccine. Passive immunity was not an issue in this outbreak because it was only used to treat (unsuccessfully) infected individuals with serious disease.
   c. *Vaccine-induced immunity*, which varies depending on the ability of the host to mount a robust and specific immune response to the vaccine, on the potency of the vaccine (as a live-virus vaccine, it requires fairly rigorous storage to preserve potency), on the length of time since vaccination or re-vaccination, and on the antigenicity spectrum of the vaccine virus as compared to the outbreak strain.
   d. *Past infection*, which may not have been an issue in this outbreak since endemic smallpox may not have occurred in this region for some time.
2. Innate immunity, or the host's ability to mount an effective response to the vaccine and to mount a protective response to contain variola infection.
3. Unknown host factors that alter the host's response to vaccine or infection, reflecting, for example, polymorphisms in T-cell receptors or genetic variations in immune signaling.

Viral factors that affect smallpox virulence include:

1. Exposure load. Household contacts in close proximity to smallpox-infected individuals are exposed to a higher concentration of virus, increasing their likelihood of becoming infected. Similarly, patients are most contagious at the time they are excreting the highest levels of virus. One aspect not addressed in the official report is why none of the other crew members on the research ship developed smallpox. The answer may be as simple (or as complicated) as that for the two women in the 2001 anthrax outbreak in the United States for whom no specific means of exposure could be identified. The best way to explain these situations is that the level of viral exposure necessary to infect a host is not constant but depends on the immunological characteristics of the host. Thus, a relatively low dose may be sufficient to infect in a small number of individuals.
2. Strain-to-strain differences in pathogenicity. Within any outbreak, variation in the severity of the disease is striking and depends on many factors. The most compelling evidence for strain-to-strain differences in pathogenicity is the existence of geographically defined outbreaks caused by variola major strains (with mortality rates of 5-40%) and variola minor strains (with mortality

rates of 0.1 - 2 %).[3] Biological differences in the effects of variola major and variola minor strains have been described, including differences of haemabsorbtion by infected human cells [3], pathogenicity in chick embryos, and temperature sensitivity. Although the relevance of the animal tissue toxicity tests by Sarkar and Mitra [4] remains unknown, the concordance of such toxicity with the severity of human disease is intriguing. Rough genetic analyses of viral strains have identified truncated peptides and strain-to-strain differences in restriction patterns [5], but these studies have not identified viral factors clearly associated with more severe disease. More sophisticated genetic studies were not possible when epidemic smallpox still circulated. Because studies to explore viral genetic traits associated with increased virulence must be done in the context of careful epidemiological studies stratifying patients by clinical outcome, viral virulence factors are not likely to be defined anytime soon.

QUESTION 1: Is Dr. Zelicoff's analysis correct that the source of the Aralsk smallpox outbreak was a field test of a smallpox weapon on Vozrozhdeniye Island?

The timing of the index case and the secondary cases are consistent with this hypothesis. The only uncertainty is the possibility that Patient 1 may have been exposed to smallpox from some other source during the boat trip around the Aral Sea. Since the Soviet governments of the region had many incentives not to report smallpox outbreaks (and did not report this one), relying on the official outbreak report to discount another type of exposure could be misleading.

QUESTION 2: Do the data presented in the official Soviet report indicate that the causative virus strain was weaponized to be especially virulent and/or vaccine-resistant?

Increased virulence is a multifactorial characteristic that may result from increased transmission or pathogenicity of the virus. Increased transmission may involve two different scenarios:

a. Expanded distribution of the virus after an event of mass exposure, such as a terrorist attack or an accidental exposure from a common source. Zelicoff presents compelling evidence to support the hypothesis that the strain initiating this outbreak was able to infect individuals at a distance of some 15 kilometers from the source, or further away than previously thought possible.
b. Increased transmission from person to person. The official Soviet report does not provide adequate data to assess this possibility, as the contacts are poorly described in terms of vaccine status or degree of contact. A virus that had been formulated to increase its length of survival as an airborne aerosol may not necessarily be transmitted from person to person at an increased rate.

Dr. Zelicoff's hypothesis of increased pathogenicity of the virus rests on the observation that in the Aralsk outbreak, three of the 10 cases (one adult and two infants, four and nine months of age, all unvaccinated) died of the hemorrhagic form of smallpox. He cites evidence from the studies of Rao in India that the hemorrhagic form is rare in infants, which is puzzling considering that death rates in the patients studied by Rao were highest in young children. [2] In fact, the diagnosis of hemorrhagic smallpox may be subjective and open to question. Plate 2 in

Dr. Rao's book is labeled as showing flat-type smallpox lesions on Day 8 of illness. Yet many of the lesions appear hemorrhagic, consistent with the late type of hemorrhagic smallpox—as opposed to the early type, which is purpuric, most likely reflecting a generalized bleeding diathesis that occurs just as the rash is emerging. Since so many questions surround the diagnosis of "hemorrhagic" smallpox, death is a better endpoint to use as a measure of serious disease.

Although the role of host susceptibility versus viral pathogenicity in causing the hemorrhagic form of smallpox remains unresolved, two pieces of data support the view that hemorrhagic disease is the result of host factors:

a. The hemorrhagic form occurs in equal proportions among patients with variola major and those with variola minor. This finding suggests that the hemorrhagic form of the disease does not correlate with strain pathogenicity, as reflected by the death rates associated with variola major and variola minor strains.
b. The hemorrhagic form occurs in equal proportions among vaccinated and nonvaccinated patients. Interpreting this observation is difficult, but it may reflect the occurrence of the hemorrhagic form in patients with altered T-cell function who do not generate optimal immunity from the vaccine and do not contain the virus well when infected with either variola major or variola minor (a so-called lacular defect).

The hemorrhagic form of smallpox needs to be better understood in light of the host's innate immune system, possibly using meningococcemia as a model. The various clinical forms of meningococcal disease do not appear to be strain-dependent, yet they range from fever and bacteremia with or without petechial rash, through bacteremia and meningitis, to overwhelming sepsis with disseminated intervascular coagulation and death.

What about Zelicoff's claim that the Aralsk strain was vaccine-resistant? Microbial antigenic variation, in which a vaccine that contains antigens from one strain provides only partial immunity against other strains, is well known for viruses that recombine readily with related viruses, the best known being influenza virus. We know too little about variola virus and its interactions with other poxviruses to suggest a mechanism for antigenic shift, and too little about its natural genetic variation to support significant antigenic drift. Other potential (and probably more likely) explanations for vaccine failure are poor quality of the vaccine, host inability to mount an optimal virus-specific immune response, or waning immunity over time since vaccination. Thus, the Aralsk report includes too few patients and too little information on the vaccine status of the contacts and their degree of contact to the cases to make strong statements about the transmissibility, virulence, or vaccine resistance of the virus.

QUESTION 3: Does the Soviet report have implications for international biological arms control?

While the Soviet report and Dr. Zelicoff's analysis do not prove that the Aralsk outbreak involved exposure to a hypervirulent or particularly robust virus, they do remind us that we know little about the activities of the former Soviet Union in developing biological weapons. Accordingly, it would be wise to consider many possibilities.

QUESTION 4: Does the Aralsk outbreak have implications for the development of a national smallpox vaccine strategy?

No one familiar with the current live-virus vaccine, which was originally prepared using 1950s technology, should be satisfied with the use of this vaccine as the sole method of preventing smallpox should outbreaks be assessed as likely. The U.S. Government appears poised to devote significant resources to improve our understanding of variola virus and its potential pathogenic and immunogenic factors, with the aim of developing safer yet highly effective vaccines. In this context, information concerning the antigenic variation of variola virus, both naturally acquired and biologically engineered, is critical to developing newer vaccine components.

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