

Rethinking Smallpox

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The potential consequences of a competently executed smallpox attack have not been adequately considered by policy makers. The possibility of release of an aerosolized and/or bioengineered virus must be anticipated and planned for. The transmission and infectivity of variola virus are examined. Arguments for and against pre-event vaccination are offered. The likely morbidity and mortality that would ensue from implementation of a mass pre-event vaccination program, within reasonable boundaries, are known. The extent of contagion that could result from an aerosolized release of virus is unknown and may have been underestimated. Pre-event vaccination of first responders is urged, and voluntary vaccination programs should be offered to the public. Two defenses against a vaccine-resistant, engineered variola virus are proposed for consideration. Methisazone, an overlooked drug, is reported to be effective for prophylaxis only. The extent of reduction in the incidence of smallpox with use of this agent is uncertain. It is useless for treatment of clinical smallpox. N-100 respirators (face masks) worn by uninfected members of the public may prevent transmission of the virus.

Conventional wisdom holds that smallpox presents an unlikely threat to the public health [1–4]. That wisdom asserts that the virus is sequestered in 2 secure sites [5] and that, even if it somehow released, vaccine will abort any potential epidemic [3]. Moreover, conventional wisdom holds that promising drugs are in development to treat smallpox [6–9] and that the virus is not highly contagious [3].

Such considerations could prove to be overly optimistic and do not take into account the many uncertainties regarding transmission and infectivity of the smallpox virus. In addition to the possible existence of more-virulent “weaponized” strains, further advances in genetic engineering may permit construction of strains able to evade the current vaccine. Australian workers markedly increased mousepox virulence by splicing a mouse IL-4 gene into a laboratory strain [10]; similar constructions might be assembled using human smallpox virus (*Variola major*) or another pox virus (e.g., monkeypox virus) and human genes [11]. This article critically examines some of the current tenets of public health policy and highlights the uncertainty of much of the data. We also examine potential defenses against a release of smallpox virus and make recom-

mendations regarding immunization and the development of prophylactic medications.

HOW IS SMALLPOX TRANSMITTED?

Smallpox may be transmitted via respiratory droplets or via fine-particle aerosol. The distinction between the two has critical public health implications.

Respiratory droplets (i.e., sputum and saliva) have a range likely no more than 2 m (~6 ft) and are therefore a threat only to persons in the immediate vicinity of the affected patient. Epidemiological studies support the finding that respiratory droplet spread is the prime route of transmission; the geographic locus of transmission is described as being almost always at the bedside, rather than public areas [12, 13]. Free-floating aerosolized virions, on the other hand, would have a considerably more extensive range. In 1962, Dixon [14] reviewed the evidence for the alternative mode—aerosolized spread—and concluded that true airborne infection was extremely rare. Nonetheless, epidemiological evidence suggests that transmission by means of aerosolized particles may be a real occurrence.

In 1970, persons on 3 floors of a German hospital developed smallpox, despite isolation of the coughing, smallpox-infected patient in a single room [15]. Seventeen cases of smallpox developed; none of the patients had direct contact with the initial patient. Subsequent “smoke” testing demonstrated air flows consistent with an aerosol spread [15].

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The last recorded death due to smallpox, according to World Health Organization investigators, was likely associated with virus that had been transmitted by aerosol [16]. In 1978, Janet Parker, a medical photographer at the University of Birmingham Medical School in England, became ill with smallpox and subsequently died. Her darkroom was 1 story above and several rooms down the hall from the laboratory of Dr. Henry Bedson, a prominent smallpox researcher.

Smallpox virus can also be transmitted by fomites, such as clothing and bedding [14]. Laundry workers have developed smallpox. One study found a much higher recovery of smallpox virus from pillows and bedclothes than from air samples of the patient's coughs [17]. The length of time that these objects remain infectious is unclear, but on the basis of the historical pattern of epidemics, it is likely no more than a few days.

HOW CONTAGIOUS IS SMALLPOX?

Current wisdom holds that smallpox, contrary to its popular reputation, is not a highly infectious disease [3, 12]. Examinations of outbreaks in India and Pakistan in the 1960s showed that each case of smallpox gave rise to only 3 new cases during the infectious (dry) season and to 1 new case during the humid season [3]. Such observations—along with the long incubation period of smallpox (mean, 12–14 days; range, 7–21 days)—suggest that there would be adequate time to vaccinate the public and prevent a more widespread outbreak. Not revealed in these reports is the extent to which the affected public had already been vaccinated. If the percentage of the population that had been vaccinated was high, the aforementioned findings may merely reflect the population's immune status, rather than a low attack rate. Another report placed the vaccination level in India at that time at 80% [18]. If accurate, this would support the reason for the low attack rate as being a consequence of a public protected by immunization, rather than due to a virus with low inherent infectivity. Indeed, there are data that smallpox is highly contagious. During the period of endemic smallpox, in field studies in Africa, 30% of susceptible contacts became infected [19]. Other sources report attack rates of anywhere from 37% to 88% among unvaccinated contacts [20].

SHOULD PREEMPTIVE VACCINATION BE OFFERED TO THE PUBLIC?

Potentially fatal reactions to smallpox vaccination include encephalitis, progressive vaccinia, eczema vaccinatum, and myopericarditis. Postvaccinial encephalitis or encephalomyelitis has been reported to occur at an incidence of 1 case per 300,000 vaccinations [21]. In recent data from an ongoing Department of Defense (DOD) study, there was 1 case of encephalitis reported among 623,244 vaccinations [22]; the patient recovered. There was no evidence by either viral culture or PCR for vaccinia being the etiology. Progressive vaccinia (a postvaccination

viral dissemination with subsequent shock and localized gangrene) occurs in persons with immunodeficiencies, and eczema vaccinatum (a generalized spread of vaccinia to skin beyond the vaccination site) occurs in persons with atopic dermatitis; neither was reported in the DOD study [22]. Fifty cases of contact transfer of vaccinia occurred, primarily in spouses and adult intimate contacts [23]. The lower-than-expected incidence of adverse events may reflect more-careful screening of vaccination candidates for immunosuppression and eczema (for whom vaccination is contraindicated), the generally healthy status of the population being vaccinated, the previous vaccination in up to two-thirds of vaccine recipients, and covering of the vaccination site, which reduces inadvertent inoculation of contacts. (In previous vaccination campaigns, the vaccination site was left exposed.)

An unexpected finding in the DOD study above was the occurrence of 83 cases of myopericarditis [23–25]. There was 1 death among these cases [25]. Other than for that fatality, in all 64 cases for which there was follow-up cardiac testing, there was normalization of electrocardiograms, echocardiograms, exercise testing, and functional status [25]. There was no increased incidence of coronary events in the DOD program [22, 25], but in the much smaller civilian vaccination program (involving 36,217 vaccinees), the number of myocardial infarctions observed (5 cases) was higher than would have been expected (2 cases) [26].

Plaque-purified tissue culture vaccines are in clinical trials and may have a lower incidence of adverse reactions than does the standard calf lymph vaccine [27]. In addition, attenuated and DNA subunit smallpox vaccines are under development [28] and may prove to be safer for immunocompromised persons.

There have been attempts to answer the question of how many deaths would arise from preemptive mass vaccination of the public. Depending on the percentage of the population vaccinated, the number of deaths is estimated to be in the range of 125–500 [3, 29, 30].

The likely deaths and morbidity that would ensue from a vaccination program must be weighed against the likelihood—and consequences—of a smallpox attack.

The conventional wisdom, as noted above, is that smallpox “does not spread rapidly under natural conditions” and, in fact, spreads at a “leisurely” pace [3, p. 492]. Transmission usually requires “close prolonged contact” for spread [3, p. 492]. Each case of smallpox “gives rise to (only) about three new cases” [3, p. 492]. The long incubation period of 1–3 weeks “provides the time to intervene and limit secondary spread” [12, p. 460]. We can “readily stop outbreaks within two infective generations (about 4 weeks) after recognition of the initial cases” [3, p. 492].

There is a problem in basing public policy on these principles.

Even if the above is an accurate representation of the contagiousness of smallpox, this paradigm reflects the spread of natural smallpox. Unfortunately, any future smallpox epidemic would likely be an unnatural, man-made event. The natural history of an unnatural event may not be natural.

A second misconception regards vaccination. Contrary to the widely held belief that vaccination is equally successful after implantation of the variola virus, "postexposure vaccination is at best of limited effectiveness" [31, p. 1923]. The most optimistic report on postexposure vaccination, plotting efficacy against time, utilized a presumed average incubation period. It concluded that postexposure vaccination reduced the clinical case rate by 50% when administered up to 5 days postexposure [32]. Concerns over the effectiveness of postexposure vaccination have been raised by others [33, 34].

Bozzette et al. [35] calculate that there would be >50,000 deaths in a "high-impact airport attack," despite the presence of an aggressive postevent immunization program. It could be argued that his calculation may be an underestimation.

In their model, Bozzette et al. [35] used a pattern of spread based on outbreaks that occurred after World War II in a largely smallpox-immune population. *Vis-à-vis* smallpox, the immune status of the older portion of our population is uncertain. It was generally accepted that the immunity provided by vaccination deteriorates with time. Two-thirds of persons with smallpox in the 1960s had preexisting vaccination scars [19]. However, Hammarlund et al. [36] found substantial humoral and or cellular immunity against vaccinia persisting in persons who had been vaccinated 25–75 years earlier and cite epidemiological studies that argue for long-term protection. Regardless, the immune status of our younger population (i.e., those aged <37 years), with regard to smallpox, probably resembles the status of the Aztec, Inca, and 17th Century American Indian populations, rather than that of a vaccinated people. It is possible, therefore, that each index case would give rise to considerably more than just the 3 secondary cases in the outbreaks that occurred after World War II. As is reported in a consensus statement by smallpox authorities, "A clandestine release of smallpox, even if it infected only 50–100 persons to produce the first generation of cases, would spread rapidly in a now highly susceptible population, expanding by a factor of 10–20 times or more with each generation of cases" [22, p. 2132]. This pattern of spread likely occurred in the population of central Mexico, which, according to Aztec tribute rolls taken before their exposure to smallpox in the early 1500s, was 25 million. The Spanish, in 1620, estimated that the population was 1.6 million, but other factors, including measles, also probably played a role in the decline [37]. Bozzette et al. [35] ascribe a mortality rate of 22.5% to the unimmunized population. However, there are data showing a mortality rate of 52% in an unvaccinated population [38].

The same long incubation period that some authorities hold to be an advantage in control of the disease [12] could actually prove to be our Achilles' heel. Even within the limits of the shortest possible incubation period (7 days), high-impact attacks could be repeated—at the same site or at different sites, with no one aware that attacks were taking place.

SMALLPOX AS A BIOLOGICAL WEAPON

To make a cogent assessment of the consequences of a smallpox attack, several questions must be answered. Otherwise, we are engaged in no more than guesswork. The questions are these: (1) Can smallpox virus be aerosolized? (2) If it can be aerosolized, for how long does it remain viable, and how far can it be carried? (3) Even if it can remain aerosolized and viable for a prolonged period of time, just how infectious is it by this route?

Smallpox virus can be aerosolized [21]. However, the current opinion on how long the virus can remain viable in this state is that the viability rapidly decreases after 60 min ("no more than 20%–30% survived" [31, p. 1923]), implying that there is nil viability left soon thereafter and, thus, that aerosolization does not represent much of a threat [31]. Unfortunately, closer scrutiny of the science underlying that assertion shows less reason to be sanguine. The great majority of the loss in variola virus viability was already present when first measured 5 min into the study. Thereafter, there was but modest further decline over the remaining 60-min length of the study [39]. The virus may therefore persist at a relatively stable level of viability for hours. How long the virus can actually remain aerosolized is unknown, as is its infectivity in this mode. If one extrapolates from the results of studies of vaccinia, aerosolized variola virus that is protected from UV light survives for 24 h [21].

A critical caveat that was not addressed above is that the discussion has been limited to natural smallpox in a natural setting. The Soviet Union is known to have engaged in an active program to aerosolize bioweapons, including smallpox, for use in bioweapons [40]. If modified or attached to the appropriate carrier, variola virus could possibly remain suspended and infectious for a considerable period. On the other hand, dissemination of variola virus into the air (e.g., via crop dusters or bomblets) subjects the virus to variables such as UV light, thermal factors, humidity, and wind. The virus might not survive, or it might be dispersed in the atmosphere into such low concentrations that it is no longer infective. Because the minimal infective dose has not been determined, the efficacy of such dissemination is unknown.

The current Bush administration sought widespread prevent vaccination of the public over concern as to whether an effective vaccination program could be implemented after an attack on an unvaccinated public [41]. The public health com-

munity, however, citing safety issues, has opposed immunizing the public [41].

PROPHYLAXIS

Animal studies demonstrate that cidofovir (Vistide; Gilead) has activity against poxvirus infections [42–45], but only when it was administered either concurrently or, in one study, within 3 days after the initial challenge with the virus. If its effectiveness extends to humans, this drug would have a prophylactic effect only. It would not be of benefit for treatment of established clinical smallpox.

Cidofovir has been modified to render the drug bioavailable by the oral route. This modification (adding a lipid tail to produce hexadecyloxypropyl-cidofovir [HDP-cidofovir]) resulted in a new drug, which, in vitro, is 100 times more effective against variola than is unmodified cidofovir [46].

Methisazone, a thiosemicarbazone, has been reported to be effective for smallpox prophylaxis. A clinical trial in India in the 1960s involving >5000 contacts claimed a 96% reduction in the incidence of the disease ($P < .001$) [47, 48]. However, this study has been criticized elsewhere [49]. Treatment and control groups were incompletely randomized, with a possible bias in favor of methisazone. A subsequent fully randomized—but considerably smaller—trial reported favorable but less-impressive results (the incidence of smallpox in the control group was almost double that in the methisazone group) [50]. This finding did not reach statistical significance. Methisazone was stated to be effective prophylaxis in the eighth edition (from 1977) of *Harrison's Principles of Internal Medicine* [51], but it is doubtful that many made note of it. By then, smallpox had essentially been eradicated, and there was little reason to pay much attention to the entry. Later editions of *Harrison's* virtually eliminated the smallpox chapter, along with discussion of the drug. The agent has since fallen off of our radar screens [52].

A panel of smallpox authorities assessed methisazone and determined that it had only modest benefit, probably reducing the incidence of smallpox by only 30%–40% [53]. This reduction should not be dismissed as inconsequential. In the event of a smallpox attack with an engineered virus, even such modest efficacy could prove critical.

Not addressed, however, is the question of just how effective methisazone would be without coadministration of vaccine. (Vaccine could be useless in an attack with a modified virus.) In all of the aforementioned studies, contacts simultaneously received postexposure vaccination and methisazone. One study, on a related poxvirus, suggests an answer to this question. Methisazone was investigated as prophylaxis for variola minor (alastrim), where contacts were not vaccinated, and was found to be effective for the prevention of alastrim at a significance level of .01 [54].

Methisazone is not without side effects. Nausea and vomiting have been reported in one-tenth to two-thirds of persons who receive the drug [52, 54]. For prophylaxis, the drug must be given within 8 days of the initiation of infection with variola major [55].

Methisazone has a significant weakness: without patent protection, it is essentially an orphan. A pharmaceutical company is unlikely to expend research effort or promotion on such a drug. That weakness, however, is also a strength: in the public domain, it would likely be inexpensive to produce.

MASKS

The smallpox virus is 200–300 nm in size. N-100 respirators, with ULPA (ultra-low penetration air) filters, are 99.999% efficient in filtering particles of ≥ 120 nm in size [56]. The retail cost of these masks is \$7. N-95 respirators, which are less effective respirators, have been reported to be protective in preventing transmission of severe acute respiratory syndrome coronavirus (size, 100 nm) in health care workers [57, 58], but use of these respirators failed to prevent a cluster of cases in one hospital [59]. Concerns have been raised over leakage around the mask, especially in the absence of fit testing [60]. Nonetheless, these masks, if distributed to the public, could prove to be critical for the control of a smallpox epidemic that was overwhelming our health care system, and they might also prove to be effective in limiting contagion of smaller viruses, such as influenza virus (either natural virus, as in 1918, or engineered virus [61]). Additionally, an aerosolized smallpox attack would likely paralyze our cities. Availability of masks might allow some measure of confidence for essential services to continue.

CONCLUSIONS

A focus on the hazards of smallpox vaccination without consideration of the potential consequences of a competently executed smallpox attack may lead to skewed analyses and flawed decisions. In particular, the use of a more virulent, “weaponized” strain of smallpox virus could mean that the epidemic would outrun the currently planned postevent vaccination/isolation measures. Although conventional wisdom suggests that smallpox, in its natural state, is largely limited to spread via respiratory droplets, concern about the potential for aerosol transmission is real and might be a greater problem in a developed society with large urban populations. Despite the potential hazards, we believe that greater efforts should be made to promote pre-event immunization—especially in emergency providers and health care workers. Furthermore, consideration should be given to allowing the public voluntary access to the vaccine. With proper informed consent and careful screening to minimize the risk of adverse side effects, such a program could reduce the risk of a runaway epidemic. Because of the

possibility of an attack involving bioengineered smallpox virus that is resistant to the current vaccine, methisazone should be reexamined, and research should be continued on other antiviral agents. Also, an adequate supply of masks should be assured. Although unlikely at the present time, the possibility of a future bio-engineered attack using smallpox should not be arbitrarily rejected.

Because of scientific advances (the polio virus has recently been synthesized de novo) [62] and ready access to those advances (complete genomes for viruses, including variola, are available on the Internet), we face a potential vulnerability. Although that threat may not be immediate (variola would be a complex genome to synthesize, and its DNA requires the activity of associated proteins to be infectious) [63], it may not be long in coming.

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