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Smallpox containment updated: considerations for the 21st century

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Summary The emergence and re-emergence of infectious diseases since the eradication of smallpox has had a direct impact on preparedness for a deliberately-caused smallpox outbreak, should one occur. The emergence of HIV has placed restrictions on the safe and effective use of smallpox vaccines and made the need for vaccinia immune globulin important for outbreak control. At the same time, the threat of international spread of emerging and re-emerging infections has prompted global investments in surveillance and response mechanisms such as the Global Outbreak Alert and Response Network (GOARN), a mechanism that would enhance the world's collaboration in smallpox containment as it did during the recent outbreak of SARS. Though global preparedness for a deliberately-caused smallpox outbreak has increased with the creation of GOARN, it does not replace the need for increased national public health investment to expand surge capacity for the management of patients and their contacts and to strengthen emergency communication networks to ensure effective response.

Smallpox vaccine: its use and safety over time

The history of smallpox vaccination dates back to 1796, when Edward Jenner demonstrated that subjects inoculated with cowpox were resistant to smallpox. At that time, the disease was present among all classes of European society, and Jenner soon had many followers. By the turn of the 19th century, vaccination to prevent smallpox had become widespread throughout the industrialized countries and some of their colonies, and the incidence of smallpox in these countries was decreasing. The production of smallpox vaccine was undertaken by various government and private laboratories, the precursors of the biopharma industry. Some time prior to this, it appears that the virus used for vaccination against smallpox was either intentionally or accidentally changed from cowpox to another member of the orthopoxvirus family, now know as vaccinia.[1]

Primary vaccination with vaccinia virus is associated with complications that range from vaccinial eruption at sites of the body that are or have previously been eczematous to generalized vaccinia infection and post-vaccinal encephalitis leading to permanent neurological disability or death.[2—4] With a case fatality ratio for post-vaccinal encephalitis of approximately 30%, the risk of fatal complication

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from smallpox vaccine is approximately 1 per million doses of vaccine administered. Strains of vaccinia virus used in vaccine preparation differed from country to country during the 20th century until eradication was completed and vaccine production was stopped; different strains appeared to be associated with different levels of complication, complications being most severe in children under the age of 2 years.[1]

Despite the known risk of complications from smallpox vaccination, the risk-benefit analysis at the beginning of 1967, when the intensified smallpox eradication program was launched, reached an obvious conclusion: smallpox remained endemic in 31 countries, an estimated 2 to 3 million persons in these countries would die from smallpox that year, and countless others would be left with severe facial scarring, corneal scarring and blindness.[1] Vaccination was the cornerstone for achieving eradication. If this goal could be reached, millions of lives would be saved and untold suffering spared. Eradication would also allow a halt to vaccination, resulting in enormous financial savings.[5] The prevention of vaccination-associated complications and deaths was yet another benefit, but was seen as secondary to the much greater goal of ridding the world of one of its oldest and most dreaded infectious diseases.

From 1967 to 1978, the intensified smallpox eradication strategy evolved from mass campaigns to vaccinate entire populations, to vaccination of populations at risk — persons in contact with a smallpox patient or living in households encircling the patient's home, a strategy now commonly referred to as ''ring vaccination''. The strategy also helped overcome one of the greatest obstacles to smallpox eradication: the constant shortage of vaccine supplies. Containment was further facilitated by use of a heat-stable smallpox vaccine and the development of the bifurcated needle that used four times less vaccine than conventional vaccination procedures. The long incubation period of smallpox (12—14 days on average) was yet another advantage, as vaccination within four days of exposure prevented or attenuated disease.[6,7]

The risk-benefit analysis changed in 1980 when smallpox became the first disease in history to be eradicated. In its final report, the Global Commission for the Certification of Smallpox Eradication weighed the risk of vaccine-associated complications against the risk of smallpox infection and recommended that vaccination be discontinued in every country.[7] Further confidence that smallpox was now a disease of the past was expressed the following year, when the World Health Assembly amended the International Health Regulations to exclude reporting requirements for smallpox.[8] Stocks of variola virus held in laboratories around the world posed the greatest risk that smallpox might return, and this risk was dramatically illustrated by a laboratory accident, resulting in a fatal case of smallpox in the United Kingdom in 1978. That highly-publicized event persuaded national authorities to either destroy virus stocks or transfer them for safe-keeping to designated high-security WHO collaborating centers. The Global Commission cited scientific reasons for preserving virus stocks, and by 1984, all known stocks of variola virus had been consolidated at two centers, in the USA and the former Soviet Union, now the Russian Federation, where they remain today.[9]

The Global Commission also recommended that WHO maintain a reserve of smallpox vaccine sufficient to vaccinate 200 million people as prudent preparation for ''unforeseen circumstances''. A committee on orthopoxvirus infections, established following the certification of eradication, was entrusted with the responsibility of overseeing vaccine distribution during an emergency.[7,10] In 1986, the committee considered that ''unforeseen circumstances'' had become so unlikely that WHO no longer needed to maintain such a large reserve, which was costly to store.[11] As a result, the reserve was reduced to the present stockpile of 2.5 million doses of potent vaccine and a small supply of bifurcated needles. Vaccine in this reserve has not been replaced by second-generation vaccines that have recently been produced. Although the vaccine is outdated, routine titration for viral activity indicates that potency has been maintained.

In order to treat adverse reactions to smallpox vaccination during the period of smallpox eradication, countries maintained stocks of vaccinia immune globulin (VIG) for use in treating persons with adverse reactions to smallpox vaccine. VIG was prepared by pooling of plasma from recently vaccinated humans and was widely available as an injectable immunoglobulin. After certification of eradication no international stockpile of VIG was constituted nor maintained, and national stocks were not renewed as they decreased in potency.

In 1981, within a year following the certification of smallpox eradication, AIDS was identified for the first time in the United States; the international spread that would rapidly lead to endemicity had already begun. In 1984, the US practice of vaccinating military personnel as protection against the possible use of variola virus as a biological weapon led to recognition of a fatal link between smallpox and AIDS. In that year, a young military recruit with latent HIV infection developed generalized vaccinia and died following smallpox vaccination.[12] This demonstration of the fatal potential of smallpox vaccination in HIV-infected persons suggests that, had AIDS emerged

earlier, it would have undermined chances for the eradication of a disease that depended on the existing vaccine as the cornerstone for control. At a minimum, evaluation of HIV status would have been required prior to vaccination, and those who were at risk of HIV or had tested positive could not have been vaccinated. An alternative protective measure such as isolation, vaccinia immune globulin (VIG) or some other type of prophylaxis would have been required, thus adding greatly to the costs and logistic complexities of the eradication campaign. In some developing countries with high prevalence of HIV and limited resources for HIV testing, case isolation and contact tracing without vaccination may have been the only option.

The threat of emerging and re-emerging infectious diseases: national and global investments for public health security

The AIDS virus is only one of more than 40 infectious disease agents newly identified over the past three decades.[13] These agents have caused diseases ranging from the Ebola and Marburg hemorrhagic fevers to hepatitis C, Nipah virus encephalitis, *E. coli* O157, and variant Creutzfeldt-Jakob disease. The SARS coronavirus is the most recent — and perhaps one of the most highly publicized — addition to this list.

Outbreaks of three emerging and re-emerging infectious diseases during the last decade of the 20th century — cholera in Latin America, pneumonic plague in India, and Ebola hemorrhagic fever in the Democratic Republic of the Congo — caused great international concern for public health security. They demonstrated the consequences that delayed national recognition and response to outbreaks could have: suffering and death of national populations including health workers, potential spread to other countries, and significant disruptions to travel, trade and economies.[14]

Outbreaks of emerging and re-emerging infectious diseases have also pointed to the need for global surveillance and response mechanisms to detect and contain the international spread of these naturally occurring emerging and re-emerging infectious diseases. As a result, investments in surveillance and response have been made at both national and global levels. One such global investment is the WHO-coordinated Global Outbreak Alert and Response Network (GOARN). Set up in 1997 and formalized in 2000, GOARN is a network of over 120 surveillance and response partners world-wide that helps identify, confirm and respond to more than 50 naturally occurring outbreaks in developing countries each year.[15–17] These outbreaks range from predictable recurrences of epidemic meningitis and cholera to unpredictable outbreaks such as SARS and cases of human infection with H5N1 avian influenza. GOARN provides the world with a safety net when national surveillance and response mechanisms fail to detect, report or contain infectious diseases with the potential for international spread.

Added to the heightened concerns around naturally occurring emerging and re-emerging infectious disease, have been concerns that infectious disease agents might be used deliberately to cause harm and terror. This concern was confirmed in the United States of America in 2001 when anthrax spores were sent through the US postal system.[18] Now, just over two years later, preparedness and surveillance for deliberately caused infectious disease outbreaks have become high on the list of national defence and security concerns, and bio-terrorism has moved from a theoretical risk to a distinct possibility.

Increasing global preparedness and response capacity for smallpox

Debates about the possible deliberate use of the smallpox virus to cause harm and terror have taken place in several countries.[19] At the request of these countries, and with consensus of all 192 WHO member countries, WHO has prolonged the period until destruction of existing smallpox virus stocks and established a scientific advisory committee to oversee a research and development agenda that requires use of live smallpox virus.[20] This agenda includes research and development of new and safer smallpox vaccines, effective anti-virals and more specific diagnostic tests.[21]

WHO has also reconvened the ad hoc advisory committee on orthopox infections, placed the committee's updated guidance for smallpox containment on the web, and is taking measures to begin to replace at least part of its stockpile of smallpox vaccine with second generation vaccine and bifurcated needles. At the same time, several countries are investing in national stockpiles of smallpox vaccine and bifurcated needles as a preparedness measure and possible deterrent, and in vaccinia immune globulin (VIG) for use as treatment in persons with severe adverse reactions to smallpox vaccination, or for prophylaxis in HIV-infected persons who may have been exposed to smallpox.

The performance of GOARN during the SARS outbreak demonstrated the strength of international outbreak response mechanisms that would also be critical in containing a deliberately-caused outbreak.[22] During the response to SARS, GOARN linked some of the world's best laboratory scientists,

clinicians, and epidemiologists in virtual electronic and telephone/video networks that rapidly provided real time knowledge about the causative agent, management of those infected, mode of transmission, and other epidemiological features. By the time the outbreak had been fully contained, 152 experts from institutions in 17 different countries had become part of these networks as they responded at sites where the outbreak was under way, or worked with the causative agent in laboratories distant from these sites. The networks provided the real-time information that made it possible for WHO to provide specific guidance to health workers about clinical management, to public health authorities about effective containment measures and to airport authorities and international travellers about the risks of infection associated with travellers.[22,23]

The similarities between SARS and smallpox are striking. Like smallpox, SARS is transmitted by droplets through close person-to-person contact. In the SARS outbreak, health care workers were initially at greatest risk of infection, just as first responders would be in the event of smallpox or other deliberately-caused outbreaks. A relatively long incubation period allowed SARS to spread internationally in unsuspecting air travellers, as would also be the case with smallpox. National containment activities of case finding, isolation and infection control, contact tracing and surveillance of contacts were effective in containing the SARS outbreak, just as they would be in the control of a smallpox outbreak. The effectiveness of such activities for smallpox, however, would be augmented by the availability of an effective vaccine, bifurcated needles and VIG. The GOARN mechanism will continue to play a role in the control of infectious disease outbreaks of international importance, be they naturally occurring or deliberately caused, and would be called into play should there be an outbreak of smallpox.

Strengthening global surveillance capacity for smallpox

WHO intermittently receives rumours of smallpox outbreaks from various sources. Since 1997 these rumours have been confirmed and responded to through the GOARN mechanism. Between 1 January 2000 and 15 July 2002 GOARN received 8 reports of suspected smallpox from 5 different WHO Regions. One of those reports was confirmed as accidental exposure to vaccinia virus in which 8 children were hospitalised with generalized vaccinia. Two reports were confirmed as varicella, and one as measles. For four suspected cases, the causative agent could not be identified, but clinical features were not consistent with a diagnosis of smallpox.

Along with these reports were 25 reports of suspected human monkeypox, all but one from the Democratic Republic of the Congo where frequent transmission continues to occur as the mean age of those not vaccinated for smallpox continues to increase. The GOARN response to these monkeypox outbreaks, and several that occurred before 2000, has provided support for their investigation and containment.

National surge capacity and the need for enhanced communication

GOARN is a global mechanism that serves as a safety net when national surveillance and response fail or require support. From its repeated response to diseases such as epidemic meningitis and yellow fever, GOARN has also acquired logistic experience using mechanisms such as vaccine stockpiles and systems for rapid distribution during emergencies. GOARN cannot, however, provide the increased surge capacity that would be required within countries following a terrorist attack using an agent such as variola virus, the emergence of a severe new disease such as SARS, or a major disease event such as the emergence of a pandemic strain of the influenza virus. For example, SARS overwhelmed health systems in many countries not only because health workers became infected and died, but also because infrastructure was insufficient to treat and isolate all those infected, and to trace and monitor close contacts of patients.[24]

Global pandemics of influenza during the 20th century have similarly overburdened patient management facilities and the public health support system.[25] A deliberately caused infectious disease outbreak of a transmissible agent could be of much higher magnitude, and might easily overwhelm existing national infrastructure. Countries must increase their surge capacity for infectious disease outbreaks, possibly linking it to surge capacities being enhanced for other emergency events such as natural or human-caused disasters, in order to be prepared.

Likewise, though GOARN mobilizes and maintains real-time networks of experts globally and provides information to WHO for global dissemination through the world wide web and other information outlets during infectious disease outbreaks, there is a need for enhanced national communication capacity. This need is especially critical in countries with federal systems of government where health

responsibility has been decentralized to the state or provincial level. Difficulties in communication between states or provinces and the central level during the SARS outbreak at times resulted in delays in reporting, confusion, and in some instances open disagreements among health professionals and politicians working at various levels of state, provincial and national.[24] To be prepared for deliberately caused outbreaks of smallpox or other infectious agents, tried and proven communication systems must be developed and maintained, perhaps linked with national disaster or other emergency communication systems.

Conclusion: The need for investment in public health infrastructure

At the beginning of the 21st century, the world has experienced three infectious disease events that threatened public health security: the deliberate release of anthrax in 2001, the emergence and subsequent spread of SARS in 2003, and the threat of an influenza pandemic in early 2004. The anthrax outbreak in the United States incited terror that rapidly spread around the world, and stimulated efforts to prepare for the much more deadly situation that would arise should variola virus be the agent used in a bioterrorist attack. It also resulted in modelling exercises with predictions about the impact that could be caused by a severe and transmissible disease with no effective cure, in a highly mobile, interdependent and widely interconnected world.

SARS showed the validity of those predictions. However, unlike when AIDS was first identified and rapidly established endemicity, the public health community was prepared to recognize the significance of SARS, and ready to collaborate in a global effort to prevent it from becoming established as yet another endemic threat to health.

Bioterrorism, emerging infectious diseases, and influenza pandemics share two characteristics: their unpredictability and their capacity to endanger public health security when they do occur. International mechanisms such as GOARN strengthened the global response to SARS. These international mechanisms are again being strengthened by the development of influenza pandemic preparedness plans in response to human cases of H5N1 avian influenza in Asia. The measures now being explored are the same as those needed to protect public health security should smallpox be used deliberately in an act of bioterrorism. They include increasing national surge capacity, rapid and increased production of vaccine, stockpiling of antivirals, improvement of global surveillance capacity and evaluation of the effectiveness of international travel recommendations.

With each threat caused by an infections disease, the arguments for investing in public health infrastructures have been strengthened. Experiences at the start of this century are providing compelling evidence that such investments are a wise way to protect the world against events that are unpredictable and have potentially enormous consequences for health, societies, and economies.

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