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RESEARCH ARTICLES

Exercise Mataika: White Paper on response to a smallpox bioterrorism release in the Pacific

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Abstract

Smallpox was declared eradicated in 1980, with known seed stock retained in two high security Biosafety Level 4 laboratories in the United States and Russia. Experts agree the likelihood of theft from these laboratories is low, and that synthetic creation of smallpox is a theoretical possibility. Until 2017 it was believed that synthetic smallpox was technically too complex a task to be a serious threat. However, in 2017, Canadian scientists synthesised a closely related orthopoxvirus, horsepox, using mail order DNA and $100,000. Simultaneously, terrorist groups have declared intent to conduct biological attacks. In this context an exercise was held on August 16th 2018, with international and cross-sectoral stakeholders to review preparedness for a bioterrorism attack in the Asia-Pacific region and globally. The exercise was conducted by The National Health and Medical Research Council (NHMRC) Centre for Research Excellence, Integrated Systems for Epidemic Response, with contextual input from the Ministry of Health and Medical Services Fiji. The scenario involved a deliberate release in Fiji, followed by a larger release in a more populous Asian country. Mathematical modelling was used to underpin epidemic projections under different conditions. The exercise alternated between clinical, public health, emergency and societal responses, with participants making real-time decisions on cross-sectoral response across the region and the world. Key weak points which are influential in determining the final size and impact of the epidemic were identified (based on mathematical modelling of transmission in Fiji and globally). We identified potential gaps in preparedness for smallpox and factors which influence the severity of a smallpox epidemic. This included identifying which determinants of epidemic size are potentially within our control, and which are not. Influential factors within our control include: preventing an attack through intelligence, law enforcement and legislation; speed of diagnosis; speed and completeness of case finding and case isolation; speed and security of vaccination response, including stockpiling; speed and completeness of contact tracing; protecting critical infrastructure and business continuity; non-pharmaceutical interventions (social distancing, PPE, border control); protecting first responders; operational support and logistics; social mobilisation and risk communication. Based on discussion at the workshop between diverse stakeholders, recommendations were made to guide improved prevention, mitigation and rapid response, thus providing a holistic, cross-sectoral framework for prevention of a worst-case scenario smallpox pandemic.

Introduction

Smallpox was declared eradicated in 1980, with known seed stock retained in two high security Biosafety Level 4 laboratories in the United States and Russia (1). In the decades since eradication, the risk of smallpox has been thought to be from clandestine stockpiles of virus outside of the official repositories. Experts agree the likelihood of theft from these laboratories is low, and that synthetic creation of smallpox is a theoretical possibility (2). Until 2017 it was believed that synthetic smallpox was technically too complex a task to be a serious threat. However, in 2017, Canadian scientists synthesised a closely related orthopoxvirus, horsepox, using mail order DNA and $100,000 (3). The experiment was not detected by any defence, intelligence or security surveillance systems, and was not known until the scientists themselves informed the WHO (3). In 2018, terrorist groups declared an intent for biological attacks against Western societies (4). There is capability for such an attack, with the recent open access publication of methods to manufacture an orthopoxvirus (5). The genome of the smallpox virus, variola, is publicly available, and the world's population is largely susceptible to smallpox due to the cessation of smallpox vaccination programs nearly 40 years ago and waning vaccine immunity in vaccinated older adults (6).

The Pacific is a unique and highly diverse geographic region and includes large islands such Papua New Guinea and Fiji, and small island nations such as Kiribati, with many islands and informal maritime transport networks. The region is affected by many disasters such as cyclones, tsunamis, volcano eruptions, earthquakes, rising sea levels and political conflict, which create systems vulnerability to infectious diseases epidemics (7). The Pacific Island states bear a disproportionate burden of the global crisis of human resources in health because of weak health systems, insufficient production of trained health personnel and significant outward migration. Limited diagnostic and therapeutic capacity and the lack of funding for simple diagnostics and for therapeutic monitoring also impact on epidemic response.

System problems such as coordination across countries, jurisdictions, agencies and disciplines, including those outside of the health system, may hinder emergency response to epidemics. A key aspect of strengthening health security during a bioterrorism incident is improving collaboration of responses between health, emergency management, defence, law enforcement and other sectors. The Pacific region is a critical part of the world in view of its geo-political strategic significance and unique vulnerabilities, which make control of infectious diseases a greater challenge in this region than elsewhere (8). A smallpox epidemic in the Pacific could spread globally and could be challenging to contain due to dispersed island geography, informal maritime travel and shortage of human resources. In this context, a smallpox simulation exercise was held in August 2018, with a focus on bringing together international stakeholders from a wide range of sectors including health, defence, law enforcement, emergency management and relevant non-government organisations.

Exercise Aim

To review preparedness for a bioterrorism attack in the Asia-Pacific region and globally.

Box 1. Dr Jona Mataika

Dr Jona Mataika was a renowned medical professional, both locally and internationally, for his pioneering role in the filariaisis programme in Fiji. He was also the pioneer in the establishment of the virology and filarology services in the country and the region. Dr Mataika also served on the World Health Organization (WHO) steering panel on parasitic diseases. His research has been published widely and used extensively. He was awarded the Order of the British Empire in 1986 for his contributions to medical services. He served the medical sector from 1947 until his death in 1999.

Exercise Objectives

1. To review potential gaps in preparedness for smallpox release.
2. To identify modifiable factors which could prevent a severe smallpox epidemic.

The Exercise

Design and Facilitation

An exercise was conducted by The National Health and Medical Research Council (NHMRC) Centre for Research Excellence, Integrated Systems for Epidemic Response, with contextual input from the Ministry of Health and Medical Services Fiji. The simulation was designed by Professor Raina MacIntyre from the Kirby Institute, who is the head of the Centre for Research Excellence in Integrated Systems for Epidemic Response (ISER), Associate Professor David Heslop, Chief Investigator of ISER from UNSW Medicine's School of Public Health and Community Medicine, and Dr Devina Nand of the Fiji Ministry of Health and Medical Services. Mathematical modelling of smallpox transmission (9) was used to simulate the epidemic under different conditions and to test the effect of interventions. An interactive format was used to explore decision making during the scenario. This paper has been prepared based on discussions during the exercise, and expert input from participants.

Participants

Stakeholders from government and non-government organisations from Australia, New Zealand, several Pacific Island countries (PNG, Tonga, Vanuatu, Fiji, FSM, Samoa, Guam), the United States of America (USA) as well as industry and non-government organisations based in the United Kingdom, Singapore, Denmark and Switzerland were present.

Exercise date and location

Exercise Mataika was held on August 16, 2018 in Sydney, Australia.

Exercise format

An outbreak simulation tabletop exercise was developed by the ISER team at UNSW. The exercise alternated between clinical, public health, emergency and societal responses, with participants discussing cross-sectoral capability in responding collaboratively across the region and the world. Key weak points that are influential in determining the final size and impact of the epidemic were identified (based on mathematical modelling of transmission in Fiji and globally).Participants analysed the scenario from start to finish and identified and discussed key interventions that could prevent the worst possible outcome. This included identifying which determinants of epidemic size are potentially within our control, and which are not, thus providing a framework for interventions to prevent and mitigate an epidemic of smallpox. Based on the scenario and discussions about response, recommendations were made to guide improved and more rapid and effective responses.

Scenario description

A first case of haemorrhagic smallpox occurs in a private hospital in Fiji, but the diagnosis is missed, as clinicians are not familiar with the disease. It is not until multiple cases are reported to the Ministry of Health and Medical Services that smallpox is considered as a diagnosis. The index case in the scenario was based on the index case in the Yugoslavian outbreak of 1972 (10). The patient had haemorrhagic smallpox, making the rash less obvious than the classic form. The index case in Fiji is misdiagnosed as having an adverse reaction to an antibiotic, which is what occurred in Yugoslavia, a country that had not seen a case of smallpox for over 30 years at the time (10). While autopsy results are awaited, more cases start appearing. A team of four epidemiologists from WHO responds to assist with the outbreak investigation while the diagnosis is still unknown. They, together with local public health officials, consider chickenpox, dengue, monkeypox and smallpox as a differential diagnosis. Samples are sent to Australia for testing. Days after the first case presented, case numbers have risen to at least 200. Initial case fatality estimates are about 40%. The health system is overwhelmed, with multiple hospitals treating cases and media reports causing public panic. Test results confirm variola virus on a Friday afternoon, 13 days after the index case presented, and the WHO promptly declares a Public Health Emergency of International Concern. Hundreds of cases have occurred by this time and case interviews determine that all were at Nadi International Airport, either as travellers or visitors, on August 1st, making this the likely day of infection. Smallpox has an average incubation period of 12 days, with a range of 7-17 days. The index patient presented 12 days after landing at Nadi airport, supporting the airport as the likely site of infection. Law enforcement agencies and military are called in to investigate.

The WHO vaccine stockpile is comprised of 2.7 million doses of first-generation vaccine held in Geneva and 31 million doses (about 2/3rd second generation vaccine) pledged by various member states (11). Vaccine is deployed by WHO on day 27 post-release, the Monday after the diagnosis, reaching Fiji on day 28. However, the public health teams tasked with the initial response are unvaccinated, so they must first be vaccinated and protected before deploying to vaccinate others. Vaccine take occurs after 7 days, so a decision is made to deploy 7 days after vaccination, although there is evidence for protection earlier than this (12). After travel and logistics are arranged, vaccination begins on day 40 in Fiji.

In this scenario, ring vaccination is used. Ring vaccination requires tracing and vaccinating all contacts of smallpox cases, with contacts prioritised by the closeness and degree of contact. Ring vaccination was used to eradicate smallpox and is the most efficient vaccination strategy to control the epidemic if vaccine supply is limited (13).

Forensic investigation by local agencies and Interpol identifies a bioterrorism attack to have taken place at Nadi International Airport in Fiji on August 1st, with many people infected simultaneously and some travelling onward to other countries on day zero. The airport is closed on day 25 post-release, for decontamination and forensic investigation. Many people in Fiji are desperate to leave, but tourists and locals alike are trapped, although boat travel increases and locals move to outer islands and other Pacific Island nations through informal, undocumented travel.

The phylogenetic analysis shows a likely engineered strain. Clinically, it is responsive to available antiviral drugs and vaccine appears to be highly protective. The clinical response comprises case finding, isolation and supportive therapy. There are no supplies of the antivirals cidofivir, brincidofivir or TPOXX in Fiji at this time, and there is limited human clinical evidence of the use of these drugs.

Other pressing issues include protection of health workers and other first responders, crisis communication and management of the worried well. Fiji has 24 public hospitals, 3 private hospitals and 1 military hospital, with a combined total of 1753 hospital beds. By day 25 there are already >2000 smallpox cases, exceeding the total available beds. Other urgent medical care, such as myocardial infarction and trauma, is compromised. Of the 2800 nurses in Fiji, 500 are infected and 320 are dead by day 30. There are 873 doctors in Fiji, of whom 185 are infected and 79 are dead. The health system is in crisis, and there are few other clinicians to draw upon. The Fiji Nursing Association calls a strike, demanding vaccination and personal protective equipment (PPE), which are in short supply. Conflict between private and public hospitals occurs, with rumours that vaccine and PPE will be prioritised for workers in public hospitals.

Based on modelled smallpox transmission using a published model (6), adapted for Fiji and the world, we follow the epidemic as it spreads across the globe in a matter of weeks. The attack at the airport results in cases arising in several other countries from people travelling out of Fiji on day zero. Smallpox has a R0 that may be as high as 4-5 (6) and is therefore potentially more infectious than influenza (R0 ~2) (14) or Ebola (R0 ~2) (14-17). It is spread by the respiratory route and rapidly propagates in a largely non-immune population (6). In the period prior to eradication, smallpox epidemics occurred often due to importations of smallpox by a single infected person, but in a deliberate attack there are likely to be hundreds or more infections on day zero, which makes it much more difficult to control the epidemic, especially as infected people disperse around a highly interconnected world.

Cases that were infected in the initial attack at Nadi International airport have occurred in multiple different countries, and second-generation cases are appearing overseas. Law enforcement investigations identify the method of attack and uncover possible planning for a second or multiple other attacks on the Dark Web. Identification of perpetrators is difficult, but there appears to be a large network of global colluders, which are using cryptocurrency for financial transactions to support their activities.

As the epidemic spreads globally, Australia, New Zealand and other international carriers cease all flights to and from Fiji. Meanwhile, locals and stranded tourists desperately try to escape Fiji. Illegal boat travel escalates between islands in Fiji and within the Pacific, including boats of infected people approaching New Zealand and Australia. The boats are not allowed to land, creating ethical dilemmas and a media frenzy. Cruise ships companies immediately divert and avoid Fiji, and other ports refuse entry to cruise ships which have passed through Fiji. Food and supplies are running short on stranded cruise ships. Regional governments begin to pressure Fiji to assist with evacuation of their nationals.

Multiple conflicting requests and demands are made of Fiji and its government. On the ground responses from key allies of Fiji are not forthcoming immediately, although advice is provided on conference calls and essential supplies are provided by air drop. Countries are also focused on managing their own domestic cases of smallpox by now. There is resistance to military or health deployment into Fiji from other countries, due to a minimal risk appetite and a protectionist mentality exacerbated by upcoming elections in some countries. WHO GOARN puts out an alert calling for volunteers to respond. Compared to past outbreaks, there far fewer offers from trained epidemiologists and 10/39 offers are from people with contraindications to second generation vaccines, leaving 29 potential immediate responders. Another group of 50 offers from semi-skilled or inexperienced people are assessed for suitability for deployment. US CDC offers 10 people, but the remainder of their public health teams are working on their own domestic response.

In Fiji there were >1000 first generation cases infected at the airport and >5,000 second generation cases, with case numbers rising rapidly. The Fiji MOH is conducting contact tracing but has over 100,000 contacts to trace and only 50 trained public health staff and 20 NGO volunteers, none of whom are yet vaccinated. Non-government aid agencies are unable to come to Fiji because of travel bans. With a shortage of hospital beds for patients, the issue of who will trace contacts and where they will be quarantined is discussed in Fiji and other affected countries. Community mobilization is recognized as critical.

As 32,000 doses of vaccine arrive in Fiji, a larger scale attack occurs in a much larger, more populous country in Asia. With resources focussed on Fiji, this catches the world off guard and stretches the limited global stockpile of vaccine. Globally, critical delays occur in coordination of the response, including the need to vaccinate first responders before they can deploy. Staff need to be trained in vaccination procedures, care of the vaccination site and assessing vaccine take. Vaccinating the vaccinators and procuring supplies of bifurcated needles cause some delays. As the epidemic escalates, hospital beds reach capacity and other industries are affected by severe absenteeism. Lack of resources, including human resources, is a major problem. Modelling shows that the epidemic is most sensitive to case isolation, contact tracing and vaccination, and speed of response (9). Speed of response for isolation, contact tracing and vaccination is most critical in the early stages of the epidemic.

Shortages of human resources and physical space to isolate cases are a problem, and health workers are dying of smallpox. Community engagement and mobilisation are recognised as essential but are not well coordinated, and crisis communication is poor. In a worst-case scenario, at the peak of the epidemic, worldwide, only 50% of smallpox cases are isolated (mostly through use of community volunteers and use of makeshift buildings as isolation facilities) and only 50% of contacts are tracked and vaccinated, causing a catastrophic blow-out in the epidemic. Under these conditions, modelling shows it will take more than a billion doses and 10 years to stop the epidemic (9). The WHO stockpile comprises less than 10% of doses held by WHO, with the remainder of doses being pledged from donor countries (11). Stockpiles of certain countries remain unknown, but WHO estimates there may be up to 900 million doses in the world. The world's population is 7 billion. There is up to a 12-18 month lag time in vaccine production, and it is estimated that 300 million doses could be produced in this time by the very few producers of smallpox vaccines globally. In the scenario, countries are reluctant to provide pledged doses, as they are facing domestic epidemics of smallpox. Fiji must manage with 32,000 doses and must decide the best use of these doses. Discussions about diluting the available vaccine are held. The U.S. sends 1000 doses of the antiviral drug TPOXX from their stockpile to Fiji early in the epidemic but retains the rest for domestic smallpox cases.

Critical infrastructure, travel and trade are affected, and countries scramble to get access to limited antiviral drugs, vaccine and personal protective equipment supplies. Foreign aid is reduced as countries divert resources to managing their own crises. Managing communications becomes challenging. Rioting besets major cities and both military and police responses are required. Mass gathering bans are implemented in Fiji and other countries. A black market has emerged in illegal boat travel, with irregular movements between outlying islands increasing and limited capacity to patrol all parts of the maritime border. Border disputes occur between countries. By day 40 post-release, the epidemic has spread to 26 countries. Around 50% of staff at key services in affected countries are absent during the peak of the epidemic. Reasons for absence include fear, family obligations and illness. Basic services supporting the economy and critical infrastructure including power are now impacted and economic activity is severely impacted. Supply chains are disrupted globally, causing shortages of essential medicines, supplies and food.

PPE is in short supply and vaccine is prioritised for health workers. Health workers, police and military are dying of smallpox, leaving systems weakened and unable to cope with the response. There is not enough vaccine, antiviral or personal protective equipment for health workers, police and military, who require protection as critical first responders. Police use riot gear as improvised PPE, but supplies are minimal. Health workers use home-made PPE. Other at-risk groups such as mortuary workers, waste services, cleaners and service personnel are also affected. Management of dead bodies and disposal of medical waste is a major problem, with transport companies refusing to transport medical waste.

In the final phase of the epidemic, which becomes a pandemic, the workforce is decimated, leaving critical infrastructure, transport, power, communications and food supplies compromised. Government assets are generally dispersed, depleted, and not readily available, resulting in severe conflicts regarding prioritization of limited supplies to health, police and border protection. Dissent is quashed using various means and penalties for insubordination are increased in uniformed services. Key modern systems become unreliable, including wireless and data communications, economy and banking (cash supply), replacement parts and manufactured items, processed food, and medications.

Globally, due to lack of human resources and physical space for patient isolationbo and the larger attack in a highly populated developing country, only 50% of case are isolated and 50% of contacts traced and vaccinated. Recovered people are mobilized to help with contact tracing and case finding, but food supplies are short and resilience is low. Vaccine production by the few manufacturers is occurring but cannot meet demand. Available supplies go to wealthier countries and not to the areas of greatest need where transmission is most intense. A major donor's funding is helping novel vaccine development and scaled up production. Trials of reduced dose schedules have commenced and accelerated vaccine development has been approved, with mixed academic and public reaction. Ethicists are alarmed about the possible harms of rapidly implementing human experimentation and caution that the risks may outweigh the benefits. Misinformation and poor crisis communication exacerbate the situation. Differentiation between accurate and inaccurate information is now impossible. Reported information about case numbers, fatalities and affected regions vary drastically. Many governments attempt to control information and establish authoritative information sources, but frequently contradict themselves. Trust in government and authority structures has disappeared, and legitimate attempts at communication by authorities are viewed with suspicion and fuel conspiracy theories.

Rural areas, including Pacific islands, are more resilient due to retained skills in subsistence living, including basic primary healthcare, but large urban cities are badly affected. Mass displacement and migration of human beings occurs within countries and across national borders. This situation may meet the definition of a Global Catastrophic Biological Risk (GCBR) event (18). The final impact of the pandemic is more severe than a single nuclear strike and societies are left decimated. Societal recovery worldwide starts from a lower baseline than in the pre-epidemic era.

The Response

Key factors that are influential in determining the final size and impact of the epidemic were identified (empirically and based on mathematical modelling of transmission in Fiji and globally). Input was provided from multinational experts in health, defence, law enforcement and emergency management. Based on the scenario and discussed response, recommendations were made to guide improved, more rapid and effective response. The purpose of exercising a severe scenario was to analyse the conditions that gave rise to the situation and how these can be modified and mitigated. Participants analysed the scenario from start to finish and identified and discussed decision making and key interventions that could prevent the worst possible outcome. Polling software was used to record individual decision making, results were provided in real time to the group, and participants reviewed responses and reached consensus. To conclude the exercise, participants identified determinants of epidemic size. These were then divided into those which are potentially modifiable, and those which are not, thus providing a framework for feasible interventions to prevent and mitigate an epidemic of smallpox (Figure 1). The general principles would apply to prevention and mitigation of any contagious serious infectious disease. Key recommendations around each of the modifiable factors shown in Figure 1 are summarised below.

Recommendations on modifiable determinants of a smallpox attack

The recommendations arising from discussion at the workshop are summarised in Boxes 2-11.

Figure 1. Factors affecting epidemic severity which can and cannot be modified.

Factors we cannot control:

- The pathogen
- Incubation period
- Size of initial release
- Infectiousness and mode of transmission
- Genetic engineering of the virus

Factors we can potentially control:

- Preventing an attack through intelligence, law enforcement and legislation
- Speed of diagnosis
- Speed and completeness of case finding and case isolation
- Speed and security of vaccination response, including stockpiling
- Speed and completeness of contact tracing
- Protecting critical infrastructure and business continuity
- Non-pharmaceutical interventions (social distancing, PPE, border control)
- Protecting first responders
- Operational support and logistics
- Social mobilisation and risk communication

Box 2. Preventing an attack through intelligence, law enforcement and legislation

Identifying and stopping bioterrorist attacks before they occur through a combination of intelligence, law enforcement and new legislative approaches is the most effective primary prevention approach and should be given high priority.

Legislation

Technology has advanced at a more rapid pace than legal or regulatory frameworks and the risk posed by technologies such as synthetic biology and dual-use research of concern is not fully understood. The synthesis of an extinct horsepox virus closely related to variola in 2017 not only showed that smallpox can be created in a laboratory, (2) but the methods to do so were published in an open access journal in 2018 (5). Many capabilities for such an attack (such as synthetic biology and genetic engineering) are self-regulated. Attempts at risk analysis of dual-use research of concern by the U.S. and the European Union have been inconclusive (19, 20). Discussions around regulation have been held mainly within the health and scientific communities, but global discussions are required with broader stakeholder groups including defence and intelligence agencies, law enforcement and legal experts. Global legislation and regulation could be improved for prevention of such an attack. Available tools include the International Health Regulations (applicable only after an attack), The Cartagena Protocol (for transport of genetically modified organisms), the Biological Weapons Convention (BWC), and domestic criminal and anti-terrorism legislation. The latter may have greater powers to stop a planned attack but vary by jurisdiction and country and have not been widely used or tested against planned biological attacks. The BWC focuses on nation states and is not enforceable. The Global Health Security Agenda (GHSA) Action Package Respond-2 touches on some relevant aspects, but is more relevant to response than prevention and is a voluntary framework that remains health-centric in scope (21). Given the risk of insider threat (22), legislation to create greater accountability of scientists should be explored, but is likely to be met with resistance from the scientific research community. The Thomas Butler case saw radically different perspectives of the law enforcement and scientific communities, with the latter opposed to the prosecution of a renowned scientist (23). Anti-terrorism laws, which allow enhanced police powers, are framed around the risk posed to society outweighing individual rights and are controversial (24). In considering the need for legislation specifically to stop potential bioterrorism, the risk posed to the community by a suspected rogue scientist working with an infectious pathogen in a legitimate, DIY or clandestine laboratory must be weighed against the individual rights of that scientist. The potential harm of a biological attack with an infectious agent may be greater than a physical act of terrorism because a contagious pathogen may spread and cause harm beyond the initial attack. Existing anti-terrorism laws could potentially be used to prevent planned bioterrorism but may need to be modified. We recommend a global dialogue, as well as dialogue between scientists and law enforcement to seek new legislative and regulatory approaches to prevention and mitigation of biowarfare and bioterrorism. Given past disagreements and tensions between the scientific and law enforcement communities in high profile insider cases, this will require careful navigation to ensure a positive outcome. It should also be noted that in the event of an attack, the perpetrator may be unknown, so the differentiation between warfare and terrorism may not be possible, with implications for whether defence or law enforcement agencies have primary responsibility.

The important role of the Aviation Sector in managing suspected communicable disease or other public health emergencies on board aircraft and in airports under the Chicago Convention of the International Civil Aviation Organization ((ICAO) - Article 14) must also be considered. Article 14 of the Convention is titled Prevention of Spread of Disease and encourages contracting States to take “effective measures to prevent the spread of communicable diseases” and to collaborate with other relevant agencies to this end (25).

IATA (International Air Transport Association) and ATS (Air Transport Services) also have a major role in identifying travelers who appear unfit to fly, either at the counter, in the passenger lounge prior to boarding or at the time of boarding. The passenger agent should seek medical advice before allowing the ill passenger to check in or to board the aircraft. The traveler may be requested to delay travel until they are well enough or have received medical approval to travel. If a traveler refuses to delay his/ her travel, the airline may exercise their right to refuse boarding.

In the event of illness on board an aircraft, the pilot and cabin crew must report this to the ICAO. All cases of illnesses or deaths on board must be reported to public health authorities (via ATS). The pilot should notify air traffic control, as per ICAO provisions (2- Annex 11), of any suspected cases of communicable disease or evidence of a public health risk on board. IHR Annex 9 “Health Part of the Aircraft General Declaration” is available to be used after landing to report an ill person on board.

Preparing countries through simulation exercises and health systems strengthening measures, including IHR joint-external evaluations, and the development of costed national action plans are also seen as important mitigation measures. Strengthening global response mechanisms through better funding, including strengthening of GOARN, and funding the partner institutions in the region area are also important. Better epidemic preparedness in communities will be of vital importance, as will empowering community volunteers to adequately detect and respond to epidemics in their earliest stages.

For global risk management, public health events of international concern require robust global systems for detection, risk assessment and mitigation, as a platform for effective coordination. WHO’s mandated role in this situation is clearly defined through the International Health Regulations and its instruments, such as the IHR Emergency Committee (EC). Timely information sharing between countries affected by multi-country deliberate release events would be essential for proportionate and defensible public health recommendations from the EC, including border closures.

Intelligence and law enforcement

Intelligence and surveillance for planned attacks, including monitoring of orders for materials, equipment and tools required for synthetic biology and genetic engineering of pathogens, is needed. The required intelligence may be different to methods used in detection of planned physical terrorism attacks or may require modification of currently used methods. Intelligence requires recognition of the unique nature of the threat, the role of insider threat and potential involvement of scientists, the possible sites of nefarious biological experiments (legitimate versus clandestine or DIY labs), prioritisation of intelligence gathering, and global discussion and coordination between intelligence and law enforcement agencies, with input from public health experts. We recommend global consensus and cooperation in developing better intelligence and surveillance systems for planned attacks that include rumour surveillance using expert input for key words and terms; tracking of trade in synthetic DNA, laboratory equipment, genetic code and supplies; external regulation of synthetic biology companies; and recognition of insider threats and monitoring of legitimate laboratories for movement of equipment and supplies, especially at the BSL 2 and 3 levels, which is the greater area of risk given strict monitoring of the far less numerous BSL 4 facilities. Whilst many agencies conduct surveillance for potentially harmful experiments, none appeared to identify the synthetic horsepox research (26). Although the researchers presented their research to WHO after it was completed (3), there did not appear to be awareness of the research through surveillance systems of intelligence agencies, highlighting the gap in intelligence and need for better surveillance.

Box 3. Speed of diagnosis of smallpox

Failure of diagnosis and triage has been seen recurrently with emerging infectious diseases in a globalised world. For example, during the height of the Ebola epidemic in West Africa in 2014, the diagnosis of Ebola in travellers from the affected area were missed in Nigeria and the U.S, resulting in a preventable epidemic in Nigeria. (27, 28). The index case of MERS Coronavirus was missed in South Korea in a returning traveller from the Middle East, giving rise to the largest nosocomial outbreak outside the Arabian Peninsula (29). The last European epidemic of smallpox epidemic in Yugoslavia also featured a missed diagnosis of the index case, with smallpox only recognised after occurrence of second-generation cases and the consequent epidemic (10). There is therefore a high likelihood of delayed diagnosis in the event of a smallpox attack, particularly because it is an eradicated disease, of which the majority of practising clinicians have no clinical experience. The principles of recognition and triage of potentially serious infections should be broadly applied:

- Rapid diagnosis of early cases through improved awareness and emergency department triage protocols. Protocols themselves are of no use if clinicians at the front line are not aware of them or fail to use them. Effort must be put into training and awareness of frontline clinical staff in emergency departments and in primary care for key syndromes.
- Triage for rapid identification of patients which could reflect a biological attack, which should be based on key syndromes. Syndromes may include severe acute respiratory illness (SARI), rash and fever (RAF), neurological syndromes (such as encephalitis or meningitis), or vomiting and diarrhoea.
- Clinical, epidemiological, and contact and travel history aspects should be evaluated as soon as possible, and travel history should be a part of triage.
- Isolation protocols should be triggered by the syndrome rather than a laboratory diagnosis. Clinical syndromic triage should be used for early identification of all patients with SARI or RAF in the emergency rooms and the clinics.
- Appropriate infection control precautions and respiratory etiquette for source control should be promptly applied.
- Recognise that in some settings, laboratory confirmation will be delayed and isolation must therefore occur based on the clinical syndrome alone.
- Patients fitting a syndromic definition should be placed in an isolation room as soon as possible.
- If SARI or RAF patients cannot be evaluated immediately, they should wait in a waiting area dedicated for the RAF/SARI patients with spatial separation of at least two meters between each RAF/SARI patient and others. Source control (use of a surgical mask by the sick patient) may also be beneficial (30).
- Rapid diagnostic tests, including point of care tests (POCT), should be developed for smallpox. Such testing will need to include near patient or point of care testing (POCT) and definitive confirmatory testing needs to be available in laboratories with biopreparedness capacity.
- POCT and laboratory testing for confirmation are only useful if there is first a suspicion of smallpox, which triggers the use of such technology.
- POCT for smallpox must include ongoing experience with such testing platforms and availability of proficiency testing programs (PTP) in order to validate accuracy of test results. Such testing will be maximally useful where there is clinical suspicion of smallpox, although increasingly there are screening platforms for multiple biothreats. It is noted that protocols around ordering a test for smallpox may result in delay of laboratory confirmation and POCT would need to fit into such protocols.
- Surge capacity needs to be built into laboratory and clinical services as rapid spread of variola is one scenario. This needs to include training and availability of trainers for rapid POCT testing.

Box 4. Speed and completeness of case finding and case isolation

Case finding and isolation is critical, as it may reduce transmission of infection to nearly zero (31). It was a pillar of the eradication program and, in the event of vaccine shortages, case isolation is even more important. Undetected transmission in the community, including through global travel, is a risk to epidemic control. In a large epidemic, case finding and isolation will require:

- Mobilising adequate human resources to effect rapid isolation through public health workforce and other workers who are trained in case finding. This requirement is in addition to the clinical workforce, as health workers will be occupied with the clinical response and may also be affected by smallpox.
- Identification and designation of large-scale physical spaces for isolation and treatment to ensure that at least 60-70% of cases are isolated rapidly. This could include use of facilities such as hotels or sports stadiums as surge capacity, as hospital beds will quickly run out.
- If possible, general hospitals should be avoided for treatment of cases, especially since available antivirals (which would reduce infectivity) may soon run short.
- Designated smallpox treatment facilities should be identified, with as few of these sites as possible to avoid nosocomial outbreaks in general hospitals. The response to the Nigerian Ebola epidemic in 2014, which involved use of an abandoned building as the initial treatment centre, is a possible model (32). During the last Yugoslavian outbreak of smallpox, motels on the outskirts of the city were commandeered for case isolation, with separate such facilities for quarantine of contacts. (Personal communication, JM Lane)
- In planning for designated smallpox treatment facilities, identify where these will be located and who will staff them (including pre-vaccinated first responders) and reduce the number of facilities to a minimum. Avoid treatment in primary care and ensure active messaging to avoid patients seeking primary care.
- Designated treatment facilities should be spatially designed for triage areas and separate areas for suspected and confirmed cases.
- Active messaging and communication to the community, including symptoms to look for, risk factors, and where to seek help (designated treatment and screening facilities), and how to handle the suspected cases.
- A hotline (telephone or web-based) for assistance for people with symptoms.
- Engaging with communities rapidly, using transparent communication and all means of communication, including social media, will be of critical importance given high levels of uncertainty about the geographic scope of further deliberate release.
- Mobilising community volunteers, including recovered patients, to assist with case finding and ensuring at least 60-70% of cases are tracked and isolated.
- Community volunteers that are susceptible to infection should be vaccinated.
- Military may have a role in the fitting-out of temporary facilities, especially those potentially in green-field sites or stadiums. Military tentage, bedding, catering, hygiene, water purification, fencing, and other items can be mobilised relatively rapidly with endogenous logistic support. This approach was very successful during the 2014 West African Ebola epidemic to improve case isolation and treatment rates (33).

Box 5. Speed and security of vaccination response

In the scenario, a delay of 7 days occurs because the vaccinators must first be vaccinated themselves to enable deployment. The scenario design was intended to illustrate the critical nature of a delay of even a matter of days in commencing the response. We used an optimistic assumption of almost-immediate deployment of vaccine from the WHO stockpile, but the process of releasing the stockpile in reality may add further to delays to the time to commencing ring vaccination (11). Following our exercise, WHO is currently planning to conduct a smallpox simulation exercise that would help understand the validity of these assumptions. We recommend:

- Having a small cohort of pre-vaccinated and trained workforce of first responders including public health staff and vaccinators, police and defence forces, who can form teams to respond immediately to an attack (assuming the attack strain of smallpox is vaccine sensitive). Non-replicating vaccine would minimise the risk of this approach.
- Vaccine could be sent with a group of vaccinators who are immunised when the stockpile is mobilised to commence immediate ring vaccination.
- Use of N95 respirators and other PPE for airborne disease precautions can accelerate deployment after vaccination.
- Consider mobilising people who have been vaccinated in the past, as they would respond to revaccination faster, and potentially be able to deploy earlier. More research is needed on this (34).
- Ensuring training materials are up to date and available and that a critical mass of responders have recency in smallpox vaccination techniques prior to any epidemic occurring, to avoid delays during an epidemic.
- Ensure adequate vaccine and bifurcated needle supplies and rapid scale-up plans. Given a 12-18 months lag time in vaccine production, in the event of a critical shortage, vaccine dilution can be considered while formal vaccine surge production is commencing (35).
- Physical security of vaccine and antiviral manufacturing sites should be a priority, as these sites may come under attack in the event of shortages.

Box 6. Speed and completeness of contact tracing

Rapid contact tracing is part of the ring vaccination strategy and requires planning. This will require human resources for contact tracing, physical space for quarantine, a protocol for transferring contacts who develop symptoms, and trained, protected public health staff to monitor contacts. On average, each infected case will have 10-11 contacts (36).

- Given that physical space requirements for case isolation may exceed available health system capacity (and will be a higher priority), alternative plans for quarantine of contacts should be made.
- Mobilising adequate human resources to effect rapid contact tracing and quarantine is crucial, as health workers alone will not be able to do this and may also be affected by smallpox. The requirement for contact tracing will be an order of magnitude greater than for case finding. No health workforce in the world will have capacity for contact tracing by trained public health staff in a large-scale epidemic, therefore community volunteers will likely be required.
- Capacity will be needed for daily monitoring and surveillance of contacts. This could include POCT devices and training in their use, in order to rapidly diagnose cases arising in contacts, but could be done with clinical protocols for triaging contacts who develop symptoms. Self-reporting systems for contacts who develop symptoms can also be used.
- Use of home quarantine, coupled with follow up and surveillance of contacts may be the only feasible option in some settings. Contacts could be provided free mobile phones for communication.
- Ensuring adequate food and other supplies for quarantined contacts.
- Plans should be in place for rapid transportation to health facilities of contacts who develop symptoms.
- Group quarantine can be considered for low risk contacts, and was used during the Ebola epidemic (37)
- Engaging with communities rapidly, using transparent communication and all means of communication, including social media, is recommended.
- Mobilise community volunteers to assist with tracking of contacts of cases, ensuring at least 60-70% of contacts are tracked and vaccinated.
- Consider financial incentives for community volunteers – this approach was used during eradication.
- Vaccinate community volunteers and provide PPE.
- Establish systems to ensure quarantined contacts are followed up for development of symptoms, transferred to isolation if they become ill, or released from quarantine after the upper limit of the incubation period.
- Generate the evidence with investigational tools to determine if vaccination is required for contacts of contacts.

Box 7. Social distancing, PPE, travel and border control

- Given there is little pre-symptomatic transmission of smallpox, and people tend to be too ill to leave home if they have symptoms, the relative benefits of social distancing will be much less than for pandemic influenza or other infections with pre-symptomatic transmission. In a crisis with limited resources, it would not be an efficient use of those resources to invest in excessive social distancing. The only instance where this may be useful is to contain an epidemic originating on an island, where containment within the island would be desirable.
- Social distancing may be introduced as a formal public health measure during the early phases of a pandemic, including the closure of public spaces or schools and public events, avoidance of crowded spaces, delay of travel.
- Personal protective equipment (PPE) was discussed. PPE was not routinely used during eradication, with vaccination being the mainstay of protection for health workers. However, it was felt in current times that health workers would expect to be provided PPE and airborne precautions. Community volunteers engaged in the response could also be provided with PPE.
- Preventing or at least slowing the movement of infected people across borders is a strategy that is included in most pandemic plans for influenza, though the emphasis varies greatly depending on the circumstances of specific countries. This approach should also be applied to smallpox. Such measures are more relevant for island states than for countries with multiple porous borders.
- In the case of the Pacific or an island being the site of attack, sequestration of an affected island could be considered to stop outward transmission.
- Border closure, or protective sequestration, was effective at slowing and even preventing entry of pandemic influenza into some Pacific Islands in 1918 (38). Faced with an epidemic of the severity described here, complete border closure for unaffected island countries such as NZ could be highly cost effective, even if such closure had to be extended for many months (39, 40).
- Entry and exit screening may also have a role in protecting island countries from severe epidemics. Entry screening generally has limited effectiveness because of the asymptomatic incubation period of smallpox (and most other infectious diseases), but combined with rigorous quarantine might be effective for islands with low visitor numbers (41). Exit screening could also be considered to reduce transmission of smallpox between islands and island states. For example, NZ Ministry of Health guidelines include the option of exit measures, such as screening, for passengers departing on ships and aircraft from NZ to small Pacific nations, especially those where most of the air traffic is via New Zealand (42).
- Thermal image scanning and other forms of entry and exit screening at airports may be more useful than for influenza, as the prodrome (prior to the rash erupting on the skin) involves fever (43, 44). Whilst people who have symptoms generally would be too unwell to travel, someone on a long-haul flight may board with mild or absent symptoms but may be severely ill upon disembarkation. However, people may also disembark during the incubation period and become sick afterwards. Protocols for managing for these possibly exposed asymptomatic people need to be in place.
- Airport protocols are required for triaging and isolating sick individuals and for protecting customs and immigration staff.
- Plans are required for border control and management of unofficial/illegal maritime transport, which may increase in the Pacific region in the event of travel bans.
- Travel advisories and impact of travel bans should be considered.
- Plans for evacuation of nationals from foreign countries should be negotiated.
- During air travel, the challenges of reaching travelers is inherently difficult due to factors including the volume of travelers and dispersal to distant points across the globe, language barriers and challenges related to public trust. Information provided on screens, monitors or static displays at airports in boarding or arrival lounges may be one of the best methods of raising awareness of public health issues.
- In the Mataika exercise, Fiji may issue a travel alert, providing health information at airports and other neighboring countries that have direct flight to and from Fiji. The aviation sector in Fiji can also provide sample scripts to be read on board aircraft. The use of consistent public health messages by countries and the air industry increases the potential for traveler awareness of potential risks and actions to take.
- Travelers should also be advised to visit a travel health clinic or international vaccination centre to collect health information about the country they are going to visit and be vaccinated if needed. A key feature of successful communication is the "one voice" where any one agency provides consistent and timely information.

Box 8. Protecting critical infrastructure and business continuity

- The vulnerability of critical infrastructure during bioterrorism or epidemic events is not often considered in health sector planning and preparedness, which may assume these systems are functional. Given the heavy reliance of certain critical infrastructure on normal social interaction, interaction points are in reality numerous and significant.
- The proper functioning of key critical infrastructure – such as telecommunications, bulk transportation, essential emergency services, electricity, water collection and distribution, waste services, and health care services – depends on a segment of the working population to carry out essential operator, maintenance and sustainment tasks.
- Absenteeism in sectors delivering critical infrastructure of only a few percentage points will cause both direct and indirect impacts on service quality, error capture, and fault correction.
- There is a need to identify interdependencies between critical infrastructure in normal operational states and estimation of likely interdependency and collective system failure states when under stress such as during significant epidemics. Risk controls should be directed at not only individual infrastructure vulnerabilities, but also systemic and interdependency vulnerabilities identified through these processes.
- Maintain emergency governance to coordinate the response.
- Cascading failures, characterised by the alignment of multiple failing components of critical systems supporting society, are likely.
- Rewards for presenting to and undertaking critical infrastructure work duties, as well as punitive measures for failing to report to work, may be necessary.
- Developing resiliency, flexibility and depth in critical infrastructure staffing pools to draw from during a crisis will be helpful.

Box 9. Protection of all first responders (staff health and welfare)

First responders include clinical health workers, public health workers, defence forces, police, paramedics, emergency services, fire fighters, customs and immigration staff, and workers in critical infrastructure such as energy. Each are equally important to the response and their protection must be planned for. The capability of first responder sectors is critical to an effective response. Workers may refuse to work if they do not receive adequate protection.

- Stockpile supplies of PPE for all first responders. In the absence of vaccinated responders at the beginning of an epidemic, PPE is the only protection available. The precautionary principle should be used and airborne precautions should be used (45). The last case of smallpox involved probable transmission through air conditioning ducts to a photographer working on the floor above a smallpox laboratory in the UK (46). Other studies have also documented variola in air samples (47, 48).
- At a minimum, stockpiles should contain enough vaccines (replicating and non-replicating) and antivirals for all first responders (not just clinical health workers).
- Consider pre-vaccinated personnel who can form an immediate response team comprising of clinical health workers, public health workers, defence forces, police, paramedics, emergency services, customs and immigration staff.
- Police, paramedics and customs staff are likely the least prepared but should be given equal protection to ensure response capability. They may consider their own stockpiles. Defence forces in some countries hold their own stockpiles.
- Protocols for decontamination of first response sites and ambulances should be in place.
- Energy supply and critical infrastructure for first responders should be ensured.
- Location-specific medevac protocols will be required to ensure a clear understanding and actions associated with infected responders.

Box 10. Operational support and logistics

- Burial procedures and protocols are needed, as well as supplies such as protective body bags (treated with hypochlorite).
- Recognise that pandemic events may last 1-4 years or longer, requiring long-term stockpiles and supply plans for drugs, vaccines and personal protective equipment.
- Public-private partnerships for accelerated research and development during epidemics may be important.
- In a pre-epidemic period, research on optimising the cross-sectoral response to such an attack should be conducted.
- Exercising the response should go beyond the health sector response – joint exercises with health, defence, law enforcement, emergency management and community representatives would assist in planning and defining roles and key needs (49).
- Coordination of technical support to affected countries should occur via Global Outbreak Alert and Response Network (GOARN), but may be challenged by reluctance of countries to provide support in the context of heightened uncertainty around likelihood of geographic spread.

Box 11. Social mobilisation and risk communication

In addition to social mobilization (described above under case finding and contact tracing) other areas for planning include:

- Informing the public and travelers about disease control measures that may be in effect (eg. introduction of voluntary isolation, location of treatment centers that are open for ill individuals, hand hygiene, and early treatment).
- Public Health and other agencies take responsibility for communicating potential public health risks in a timely and appropriate manner. Sometimes the message fails to reach the intended communities, including those people most at risk of the diseases and frontline workers.
- Consistent messaging should be used by all relevant agencies.
- Volunteers in the response could be provided financial and other incentives.
- Civilian preparedness programs should be considered in non-epidemic periods to provide surge capacity of trained civilians who can take up various roles in the response.

Conclusion

Exercise Mataika enabled cross-sectoral expert input into considering many aspects of a smallpox release and subsequent pandemic. We provide a framework for identifying and focusing on factors potentially within our control along the entire spectrum from pre-attack to recovery, from intelligence, legislation and law enforcement to public health measures and social mobilisation. We recommend that critical weak points be mitigated with prior careful planning, maximising prevention of planned attacks through intelligence gathering, and optimising a timely response and the recovery phase, whilst recognising substantial physical, infrastructure and human resources surge requirements in a pandemic. The exercise also highlighted the importance of international cooperation and the tensions which may arise between this need and domestic responses within each country, especially regarding the WHO pledged vaccine stockpile. Preparedness for a potentially catastrophic epidemic requires an inclusive and collaborative approach with all first response sectors and across nations, rather than a health-centric, localised approach to planning. Traditional planning focuses predominantly on medical counter-measures after an attack has occurred.

The impact of an epidemic and subsequent pandemic of smallpox would be substantial if arising in a low-income country with weak health systems and may have a very long duration. Practical aspects, like communication, the need to use community volunteers, requirements for case isolation, protection of first line responders, vaccination strategies, international cooperation and having surge capacity in both personnel and physical facilities should be central to planning. Planning for such an event is often based on assumed probability of the event alone. However, risk analysis is required which considers impact of such an attack and other factors such as human to human transmission potential (50), intent and capability. We know that there is declared intent for bioterrorism attacks against Western societies (4). There is also capability for such an attack, given the recent publication of synthetic biology methods to manufacture a virus very similar to smallpox. The genome of the smallpox virus, variola, is publicly available. We do not know if those with intent have the capacity to generate variola virus *in vitro*, but the possibility is higher now than any time in the past. As synthetic biology and genetic engineering technology continues to advance and become cheaper and more accessible, the risk will continue to increase. The principles of identifying influential and modifiable factors along the entire timeline of an event (from planning of an attack to recovery) and focusing on these factors for preparedness can be applied to any serious emerging infectious disease threat

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References

1. World Health Organization (WHO). WHO Advisory committee on variola virus research: report of the nineteenth meeting, 1-2 November 2017, Geneva, Switzerland: World Health Organization; 2018 [cited 2018 October 23]. Available from: http://apps.who.int/iris/bitstream/handle/10665/272441/WHO-WHE-IHM-2018.2-eng.pdf?sequence=1&isAllowed=y.
2. Koblentz GD. The de novo synthesis of horsepox virus: implications for biosecurity and recommendations for preventing the reemergence of smallpox. Health security. 2017;15(6):620-8. DOI: https://doi.org/10.1089/hs.2017.0061
3. Kupferschmidt K. How Canadian researchers reconstituted an extinct poxvirus for $100,000 using mail-order DNA. Science, July. 2017;6. DOI: https://doi.org/10.1126/science.aan7069
4. Coats DR. Statement for the Record, Worldwide Threat Assessment of the US Intelligence Community: Office of the Director of National Intelligence; 2018 [cited 2018 October 23]. Available from: https://www.dni.gov/files/documents/Newsroom/Testimonies/2018-ATA---Unclassified-SSCI.pdf.
5. Noyce RS, Lederman S, Evans DH. Construction of an infectious horsepox virus vaccine from chemically synthesized DNA fragments. PloS one. 2018;13(1):e0188453. DOI: https://doi.org/10.1371/journal.pone.0188453
6. MacIntyre CR, Costantino V, Chen X, Segelov E, Chughtai AA, Kelleher A, et al. Influence of Population Immunosuppression and Past Vaccination on Smallpox Reemergence. Emerging infectious diseases. 2018;24(4):646. DOI: https://doi.org/10.3201/eid2404.171233
7. McIver L, Kim R, Woodward A, Hales S, Spickett J, Katscherian D, et al. Health impacts of climate change in Pacific island countries: a regional assessment of vulnerabilities and adaptation priorities. Environmental health perspectives. 2015;124(11):1707-14. DOI: https://doi.org/10.1289/ehp.1509756
8. Coker RJ, Hunter BM, Rudge JW, Liverani M, Hanvoravongchai P. Emerging infectious diseases in southeast Asia: regional challenges to control. The Lancet. 2011;377(9765):599-609. DOI: https://doi.org/10.1016/S0140-6736(10)62004-1
9. MacIntyre CR, Costantino V, Mohanty B, Nand D, Kunasekaran M, Heslop DJ. Epidemic size, duration and vaccine stockpiling following a large-scale attack with smallpox. Global Biosecurity. 2019; 1(1). DOI: http://doi.org/10.31646/gbio.13
10. Ilic M, Ilic I. The last major outbreak of smallpox (Yugoslavia, 1972): The importance of historical reminders. Travel medicine and infectious disease. 2017;17:69-70. DOI: https://doi.org/10.1016/j.tmaid.2017.05.010
11. Yen C, Hyde TB, Costa AJ, Fernandez K, Tam JS, Hugonnet S, et al. The development of global vaccine stockpiles. The Lancet Infectious Diseases. 2015;15(3):340-7. DOI: https://doi.org/10.1016/S1473-3099(14)70999-5
12. Kennedy R, Lane, JM, Henderson, DA, Poland, GA. Smallpox and vaccinia. In: Plotkin SA, Orentein WA, Offit PA editors. Vaccines, 6th ed. Amsterdam: Elsevier Inc. 2012; 718-745.
13. Porco TC, Holbrook KA, Fernyak SE, Portnoy DL, Reiter R, Aragón TJ. Logistics of

community smallpox control through contact tracing and ring vaccination: a stochastic network model. BMC public health. 2004;4(1):34. DOI: https://doi.org/10.1186/1471-2458-4-34
14. Biggerstaff M, Cauchemez S, Reed C, Gambhir M, Finelli L. Estimates of the reproduction number for seasonal, pandemic, and zoonotic influenza: a systematic review of the literature. BMC infectious diseases. 2014;14(1):480. DOI: https://doi.org/10.1186/1471-2334-14-480
15. Gomes MF, y Piontti AP, Rossi L, Chao D, Longini I, Halloran ME, et al. Assessing the international spreading risk associated with the 2014 West African Ebola outbreak. PLoS currents. 2014;6. DOI: https://doi.org/10.1371/currents.outbreaks.cd818f63d40e24aef769dda7df9e0da5
16. Fisman D, Khoo E, Tuite A. Early epidemic dynamics of the West African 2014 Ebola outbreak: estimates derived with a simple two-parameter model. PLoS currents. 2014;6. DOI: https://doi.org/10.1371/currents.outbreaks.89c0d3783f36958d96ebbae97348d571
17. Althaus CL. Estimating the reproduction number of Ebola virus (EBOV) during the 2014 outbreak in West Africa. PLoS currents. 2014;6. DOI: https://doi.org/10.1371/currents.outbreaks.91afb5e0f279e7f29e7056095255b288
18. Schoch-Spana M, Cicero A, Adalja A, Gronvall G, Kirk Sell T, Meyer D, et al. Global catastrophic biological risks: toward a working definition. Health security. 2017;15(4):323-8. DOI: https://doi.org/10.1089/hs.2017.0038
19. Gryphon. S. Risk and benefit analysis of Gain of function research Final Report-April 2016. 2016 [updated 2016 April; cited 2018 August 27]. Available from: http://www.gryphonscientific.com/wp-content/uploads/2016/04/Risk-and-Benefit-Analysis-of-Gain-of-Function-Research-Final-Report.pdf.
20. House T, Hall I, Danon L, Keeling MJ. Contingency planning for a deliberate release of smallpox in Great Britain-the role of geographical scale and contact structure. BMC infectious diseases. 2010;10(1):25. DOI: https://doi.org/10.1186/1471-2334-10-25
21. The United Nations Office at Geneva (UNOG). Investigations of Alleged Biological Weapons Use: Overlap with Public Health Assistance under Article VII of the Biological and Toxin Weapons Convention: United States of America. 2018 [cited 2018 November 1]. Available from: https://www.unog.ch/80256EDD006B8954/(httpAssets)/30A686E930E89D75C12582E8003DD111/$file/MX4+WP+2+-+UNSGM-Art+VII+working+paper+FINAL.pdf].
22. Butler D. Anthrax case not closed, says Nature: Declan Butler. Report. 2008 [updated 2008 August 20; cited 2018 August 27]. Available from: http://declanbutler.info/blog/?p=136.
23. Murray BE, Anderson KE, Arnold K, Bartlett JG, Carpenter CC, Falkow S, et al. Destroying the life and career of a valued physician-scientist who tried to protect us from plague: was it really necessary? Clinical infectious diseases. 2005;40(11):1644-8. DOI: https://doi.org/10.1086/431348
24. Gonzalez T. Individual Rights Versus Collective Security: Assessing The Constitutionality Of The USA Patriot Act. 2003 [updated 2003 January 10; cited 2018 October 10]. Available from: https://repository.law.miami.edu/cgi/viewcontent.cgi?article=1102&context=umiclr.
25. Amanna IJ, Slifka MK, Crotty S. Immunity and immunological memory following smallpox vaccination. Immunological reviews. 2006;211(1):320-37. DOI: https://doi.org/10.1111/j.0105-2896.2006.00392.x
26. MacIntyre CR, Engells TE, Scotch M, Heslop DJ, Gumel AB, Poste G, et al. Converging and emerging threats to health security. Environment Systems and Decisions. 2017:1-10.
27. Smith CL, Hughes SM, Karwowski MP, Chevalier MS, Hall E, Joyner SN, et al. Addressing needs of contacts of Ebola patients during an investigation of an Ebola cluster in the United States-Dallas, Texas, 2014. MMWR Morbidity and mortality weekly report. 2015;64(5):121-3.
28. Fasina FO, Shittu A, Lazarus D, Tomori O, Simonsen L, Viboud C, et al. Transmission dynamics and control of Ebola virus disease outbreak in Nigeria, July to September 2014. Eurosurveillance. 2014;19(40):20920. DOI: https://doi.org/10.2807/1560-7917.ES2014.19.40.20920
29. Kim S, Yang T, Jeong Y, Park J, Lee K, Kim K. Middle East respiratory syndrome coronavirus outbreak in the Republic of Korea, 2015. Osong Public Health Res Perspect. 2016;6(4):269-78.
30. MacIntyre CR, Zhang Y, Chughtai AA, Seale H, Zhang D, Chu Y, et al. Cluster randomised controlled trial to examine medical mask use as source control for people with respiratory illness. BMJ open. 2016;6(12):e012330. DOI: https://doi.org/10.1136/bmjopen-2016-012330
31. Eichner M. Case isolation and contact tracing can prevent the spread of smallpox. American journal of epidemiology. 2003;158(2):118-28. DOI: https://doi.org/10.1093/aje/kwg104
32. Igonoh A. Through the Valley of the Shadow of Death.Dr. Ada Igonoh survived Ebola – This is

her Story: BellaNaija.com. 2014 [updated 15 September 2014; cited 2018 August 26]. Available from: https://www.bellanaija.com/2014/09/must-read-through-the-valley-of-the-shadow-of-death-dr-ada-igonoh-survived-ebola-this-is-her-story/.

33. Nevin RL, Anderson JN. The timeliness of the US military response to the 2014 Ebola disaster: a critical review. Medicine, Conflict and Survival. 2016;32(1):40-69. DOI: https://doi.org/10.1080/13623699.2016.1212491

34. Kim SH, Yeo SG, Jang HC, Park WB, Lee CS, Lee KD, et al. Clinical responses to smallpox vaccine in vaccinia-naive and previously vaccinated populations: undiluted and diluted Lancy-Vaxina vaccine in a single-blind, randomized, prospective trial. The Journal of infectious diseases. 2005;192(6):1066-70. DOI: https://doi.org/10.1086/432765

35. Couch RB, Winokur P, Edwards KM, Black S, Atmar RL, Stapleton JT, et al. Reducing the dose of smallpox vaccine reduces vaccine-associated morbidity without reducing vaccination success rates or immune responses. The Journal of infectious diseases. 2007;195(6):826-32. DOI: https://doi.org/10.1086/511828

36. Prem K, Cook AR, Jit M. Projecting social contact matrices in 152 countries using contact surveys and demographic data. PLoS computational biology. 2017;13(9):e1005697. DOI: https://doi.org/10.1371/journal.pcbi.1005697

37. Grigg C, Waziri NE, Olayinka AT, Vertefeuille JF. Use of group quarantine in Ebola control—Nigeria, 2014. MMWR Morbidity and mortality weekly report. 2015;64(5):124.

38. McLeod MA, Baker M, Wilson N, Kelly H, Kiedrzynski T, Kool JL. Protective effect of maritime quarantine in South Pacific jurisdictions, 1918–19 influenza pandemic. Emerging infectious diseases. 2008;14(3):468. DOI: https://doi.org/10.3201/eid1403.070927

39. Boyd M, Baker MG, Mansoor OD, Kvizhinadze G, Wilson N. Protecting an island nation from extreme pandemic threats: Proof-of-concept around border closure as an intervention. PloS one. 2017;12(6):e0178732. DOI: https://doi.org/10.1371/journal.pone.0178732

40. Boyd M, Mansoor OD, Baker MG, Wilson N. Economic evaluation of border closure for a generic severe pandemic threat using New Zealand Treasury methods. Australian and New Zealand journal of public health. 2018;42(5):444-6. DOI: https://doi.org/10.1111/1753-6405.12818

41. Nishiura H. Determination of the appropriate quarantine period following smallpox exposure: an objective approach using the incubation period distribution. International journal of hygiene and environmental health. 2009;212(1):97-104. DOI: https://doi.org/10.1016/j.ijheh.2007.10.003

42. Ministry of Health. Responding to Public Health Threats of International Concern at New Zealand Air and Sea Ports: Guidelines for public health units, border agencies and health service providers. Wellington: Ministry of Health. 2016 [cited 2018 Sept 27]. Available from: https://www.health.govt.nz/system/files/documents/publications/responding-public-health-threats-international-concern-nz-air-sea-ports-aug16.pdf.

43. Priest PC, Duncan AR, Jennings LC, Baker MG. Thermal image scanning for influenza border screening: results of an airport screening study. PloS one. 2011;6(1):e14490. DOI: https://doi.org/10.1371/journal.pone.0014490

44. Priest PC, Jennings LC, Duncan AR, Brunton CR, Baker MG. Effectiveness of border screening for detecting influenza in arriving airline travelers. American journal of public health. 2013;103(8):1412-8. DOI: https://doi.org/10.2105/AJPH.2012.300761

45. MacIntyre C, Chughtai, AA, Seale H, Richards, GA, Davidson, PM. Respiratory protection for healthcare workers treating ebola virus disease (evd): are facemasks sufficient to meet occupational health and safety obligations? International Journal of Nursing Studies. 2014;51(11):1421-6. DOI: https://doi.org/10.1016/j.ijnurstu.2014.09.002

46. Wade N. New smallpox case seems lab-caused. Science. 1978;201(4359):893-. DOI: https://doi.org/10.1126/science.684414

47. Thomas G. Air sampling of smallpox virus. Epidemiology & Infection. 1974;73(1):1-8. DOI: https://doi.org/10.1017/S0950268800001060

48. Meiklejohn G, Kempe C, Downie A, Berge T, Vincent LS, Rao A. Air sampling to recover variola virus in the environment of a smallpox hospital. Bulletin of the World Health Organization. 1961;25(1):63.

49. Tak S, Jareb A, Choi S, Sikes M, Choi YH, Boo H-w. Enhancing 'Whole-of-Government'Response to Biological Events in Korea: Able Response 2014. Osong public health and research perspectives. 2018;9(1):32. DOI: https://doi.org/10.24171/j.phrp.2018.9.1.06

50. MacIntyre CR, Seccull A, Lane JM, Plant A. Development of a risk-priority score for category A bioterrorism agents as an aid for public health policy. Military medicine. 2006;171(7):589-94. DOI: https://doi.org/10.7205/MILMED.171.7.589

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