GLOBAL BIOSECURITY

*Macintyre CR, Costantino V, Mohanty B, Nand D, Kunasekaran MP, Heslop DJ. Epidemic size, duration and vaccine stockpiling following a large-scale attack with smallpox. Global Biosecurity, 2019; 1(1).*

RESEARCH ARTICLES

# Epidemic size, duration and vaccine stockpiling following a large-scale attack with smallpox

C Raina MacIntyre[1], Valentina Costantino[1], Biswajit Mohanty[1], Devina Nand[2], Mohana Priya Kunasekaran[1] & David J Heslop[3]

[1]Kirby Institute, University of New South Wales, Sydney, NSW, Australia
[2]Ministry of Health and Medical Services, Suva, Fiji
[3]School of Public Health and Community Medicine, University of New South Wales, Sydney, NSW, Australia

**Abstract**

On August 16th, 2018, we held Exercise Mataika to test preparedness for a worst-case scenario of a smallpox attack which begins in the Pacific and is followed by a larger scale attack in a highly populous Asian country. The exercise was underpinned by mathematical modelling which aimed to determine the duration and magnitude of the epidemic under different scenarios, the critical threshold for epidemic control, and scenarios where the current stockpile of vaccine is adequate. We constructed a modified SEIR model for smallpox transmission. We found that time to commencing the response, rates of contact tracing and ring vaccination, and rates of case isolation are all influential factors on epidemic size and duration. Ideally, the response should commence in 20 days after the attack, corresponding to 8 days after the first symptoms appear, given an average incubation period of 12 days. Every day of delay worsens the epidemic. The WHO stockpile of vaccine of 34 million doses is adequate if rates of case isolation and ring vaccination are maintained above 60%. If rates of contact tracing, ring vaccination and case isolation fall below 53%, epidemic control is lost. In such a scenario, the epidemic persists for longer than 10 years and over a billion doses of vaccine are needed for epidemic control. There are modifiable factors which can prevent a catastrophic scenario following smallpox re-emergence. These include very rapid response time and high rates of isolation and ring vaccination. Training and capacity building, as well as pre-vaccinated teams, can also assist with rapid response. In low income countries, a smallpox epidemic could overwhelm the health system and far exceed human resource capacity, so low rates of case isolation and contact tracing is a realistic possibility. The consequences of poor epidemic control are catastrophic if rates of case isolation and ring vaccination fall below 53%, the threshold for epidemic control. Global cooperation is also critical, to ensure that vaccine and other resources are directed quickly to affected areas.

## Introduction

Smallpox was eradicated in 1980, but remains a category A bioterrorism agent [1].The only official stocks of the virus are in the United States and Russia [2], but unofficial stocks may be present elsewhere. The variola genome is fully sequenced and advances in synthetic biology have increased the likelihood of smallpox being synthesized in a laboratory [3]. Experts have previously dismissed the threat of synthetic smallpox as unlikely, but were proven wrong when in 2017 Canadian researchers synthesized an extinct pox virus and published the methods in an open access journal [4]. Smallpox or a variant thereof may re-emerge from bioterrorism or a laboratory accident [5], thus is a high priority for preparedness planning [6]. Due to ageing, advances in medical therapies, transplantation and people living with immunosuppressive conditions such as HIV, the immunological status of the population has also changed dramatically in the decades since eradication of smallpox, with almost one in five people living with immunosuppression in developed country settings [7]. A large proportion of the population today is unvaccinated and residual immunity in cohorts who were vaccinated prior to 1980 is waning [8-10]. The World Health Organization has a stockpile of 33.7 million doses of mostly second generation ACAM2000, but also some first-generation vaccine. The majority of the stockpile is pledged from member countries, with only 2.7 million doses physically held by WHO [11].

In low income countries, weak health systems and shortages of human resources for health predict a more severe impact of serious epidemics [12]. In a risk analysis model for Ebola, we showed that country factors, such as gross domestic product and ratio of physicians to population, combined with disease-specific factors can predict catastrophic epidemic impacts and the need for urgent intervention [12]. The Pacific is a uniquely vulnerable region because of widely dispersed islands, geographical and population diversity between nations, natural disasters and extensive informal maritime transport routes which can transmit infectious diseases [13]. The region also

suffers a crisis in human resources for health because of migration of skilled health workers and limited production of qualified health workers. For all these reasons, a smallpox attack in the Pacific may be difficult to control. The wider Asia-Pacific region contains highly populous low-income countries with mega-cities. Epidemics arising in Asian mega-cities may similarly be difficult to control, with greater potential for spread due to high population densities [14].

On August 16th 2018 we held *Exercise Mataika* to test preparedness for a worst-case scenario of a smallpox attack which begins in the Pacific and is followed by a larger scale attack in a highly populous Asian country [15]. The purpose of exercising a worst-case/severe scenario was to identify key vulnerabilities that can be mitigated or prevented. The exercise was underpinned by mathematical modelling which aimed to determine the duration and magnitude of the epidemic under different scenarios, the critical threshold for epidemic control, and scenarios where the current stockpile of vaccine is inadequate. This paper describes the modelling underpinning the exercise.

## Aims

We aimed to determine the influence of disease control measures (case isolation, contact tracing and vaccination) on epidemic control. We also aimed to determine the adequacy of the current global smallpox vaccine stockpile and the duration and magnitude of the epidemic under different scenarios. The objective was to inform preparedness and prioritise planning to avoid a worst-case scenario.

## Methods

We constructed a modified SEIR model for smallpox transmission based on our published model (7). We assumed that the virus was not genetically modified and that there is minimal vaccine-induced residual immunity in the world [7]. We assumed an attack in an airport in a crowded city in a de-identified, highly populous Asian country, starting the epidemic with 10,000 infected. Case fatality rates are based on expected distribution of hemorrhagic, flat, ordinary and modified smallpox [7].

### *Interventions*

We considered case isolation, contact tracing and ring vaccination (the combined intervention of contact tracing and vaccination of contacts of cases) as the key interventions for pandemic control. Only the United States has a stockpile of antivirals sufficient for the entire population, so in most cases, a ring vaccination strategy would be more feasible to ensure a rapid response. Antivirals, where available, would be given after diagnosis and isolation, so we assumed they would not add to epidemic control above the effect of isolation alone. However, antivirals would likely reduce morbidity and mortality for treated cases. Proper case isolation in suitable facilities was assumed to stop transmission of smallpox, as observed during the period of endemic smallpox [2].

Contact tracing and vaccination were assumed to be a combined intervention, with close contacts of cases traced, vaccinated and monitored for development of disease. We assumed 95% vaccine efficacy [2, 16-18]. We tested the impact of varying the following parameters on the epidemic:

1. Size of the initial attack (50, 100, 1000, 10,000).
2. Time from attack to initiating the response (20, 30 and 40 days).
3. Percentage of infectious cases isolated (30, 50, 70 and 90%).
4. Percentage of contacts traced and vaccinated (30, 50, 70 and 90%).

Key outputs were the size and duration of the epidemic under different scenarios when 1-4 above were varied.

### *Mathematical Model*

The SEIR model uses ordinary differential equations, to transfer people between epidemiological states related to their smallpox infectious status. For age-specific force of infection, we used Euler's approximation to make discrete contact rates using data from the contact matrix for the specific affected Asian country (which remains anonymous for this paper) for 100 days. We simulated an outbreak starting in this highly populated country using the projected age-specific contact matrix for that country [19]. However, in order to simulate the infection spreading globally, after 100 days we changed the contact matrix to better represent the entire world population contact patterns. To do this, we estimated the world contact matrix [19] as an average between the rates from the 10 highest most populated countries [20].

Residual smallpox vaccine immunity in the population was based on our previous estimates [7, 21, 22]. We multiplied the force of infection by a parameter ($\alpha_1$, $\alpha_2$, $\alpha_3$, $\alpha_4$) to account for different population susceptibility levels. Disease parameters and their estimation, as well as different grades of infectivity, were estimated as previously described [7]. Table 1 shows the model parameters.

### *Sensitivity analysis*

We explored the influence of attack scenarios of 50, 100, 1000 and 10000 initial infected to determine the impact on the epidemic. The base case was a worst-case scenario of 10000 infected. Delays in diagnosis and time to obtaining laboratory confirmation could vary the time of onset of the response. We therefore varied the time of the response commencing between T=20, 30- and 40-days following virus release. Given an average incubation period of 12 days for smallpox [2], this corresponds to day 3, 8 and 18 after the onset of symptoms of the index case.

**Table 1.** Model parameters and data sources

| Definition | Value | Source |
|---|---|---|
| Duration of quarantine for traced contacts | 16.6 days | [2] |
| Duration of isolation for infectious contacts | 25 days | [2] |
| Average number of contacts per case | 11 | [21] |
| Proportion of contacts traced around an infected case | 90%; Sensitivity analysis with 70%, 50% and 30% | [2] |
| Proportion of cases that get isolated once infected and symptomatic | 90%; Sensitivity analysis on with 70%, 50% and 30% | [2] |
| Time of starting intervention | At day 20, 30 and 40 after release, corresponding to 8, 18 and 28 days after the onset of symptoms of the index case, using an average incubation period of 12 days. | [2] |
| Population of the world | 7383,008,820 | [22] |
| Initial infected | 10,000<br>Sensitivity 50, 100, 1000 | |
| Vaccine efficacy | 95% | [18] |
| Efficacy of case isolation in preventing transmission | 100% | [2] |

Given that a smallpox epidemic in a low-income country would be complicated by weak health systems and low human resources for health, a sensitivity analysis was conducted on the proportion of infectious cases isolated and contacts traced and vaccinated ("ring vaccination"). To test which of these interventions is more influential, we fixed one at 90% and varied the other between 30, 50, 70 and 90% respectively.

Given a large number of possible combinations of these proportions between the two interventions of case isolation and ring vaccination, we tested 30% (30/30), 50% (50/50), 70% (70/70) and 90% (90/90) for each of case isolation and ring vaccination to determine the impact on epidemic size and duration of differing completeness and capacity of the public health response. Time to the end of the epidemic was modelled. If the modelled epidemic did not end within 11 years (4000 days), we assumed smallpox would become endemic. We also estimated the amount of vaccine required in the differing scenarios above (based on the number of contacts to be traced and vaccinated in a ring vaccination strategy), in order to identify scenarios where the WHO stockpile is adequate or inadequate to meet disease control needs.

*Critical epidemic control threshold*

The modelling above indicated that prospect of early epidemic control was lost at the 50/50 level of contact tracing and case isolation. We therefore ran the model at varying levels between 50-60% to identify the threshold value below which epidemic control is lost.

**Results**

Figure 1 shows the epidemic without interventions for varying attack sizes from 50-10,000. Figure 2 shows the influence of time to commencing the response varying between 20, 30 and 40 days from the initial attack, with a larger epidemic resulting from each 10 days of delay.

Figure 3 shows the time to epidemic control by varying rates of case isolation and ring vaccination. If ring vaccination and isolation rates of 70% or higher each can be achieved, the epidemic will end in less than a year. If rates are 50% each, the epidemic will continue for more than 9 years. At rates less than 50% each, the modelled epidemic does not end within a decade, and smallpox becomes endemic. Supplementary Table 1 shows the matrix of modelled outputs for combinations of ring vaccination and case isolation rates by response time. Greyed out cells indicate that the epidemic did not end within 10 years in these scenarios. If ring vaccination rates are below 50%, for any prospect of epidemic control, case isolation rates must be at least 90%. We tested equal proportions of case isolation and ring vaccination in each scenario, but various permutations are shown in supplementary table 1. Supplementary figures 1 and 2 show the influence of varying rates of ring vaccination on the epidemic, keeping case isolation rates constant at 90%. Figure 4 shows the influence of varying rates of case isolation rates on the epidemic, keeping the ring vaccination rate constant at 90%. Whilst both measures are effective, case isolation is more influential than ring vaccination.

**Figure 1.** Epidemic curve without intervention by initial number of infected people

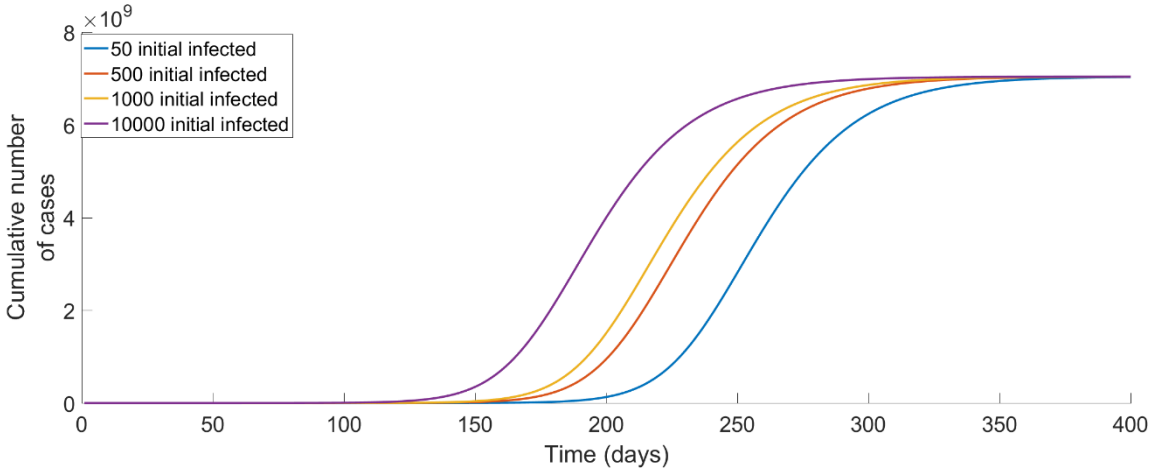



**Figure 2.** Influence of time to commencing the response, for 10000 initial infected with 90% ring vaccination and 90% of cases isolated

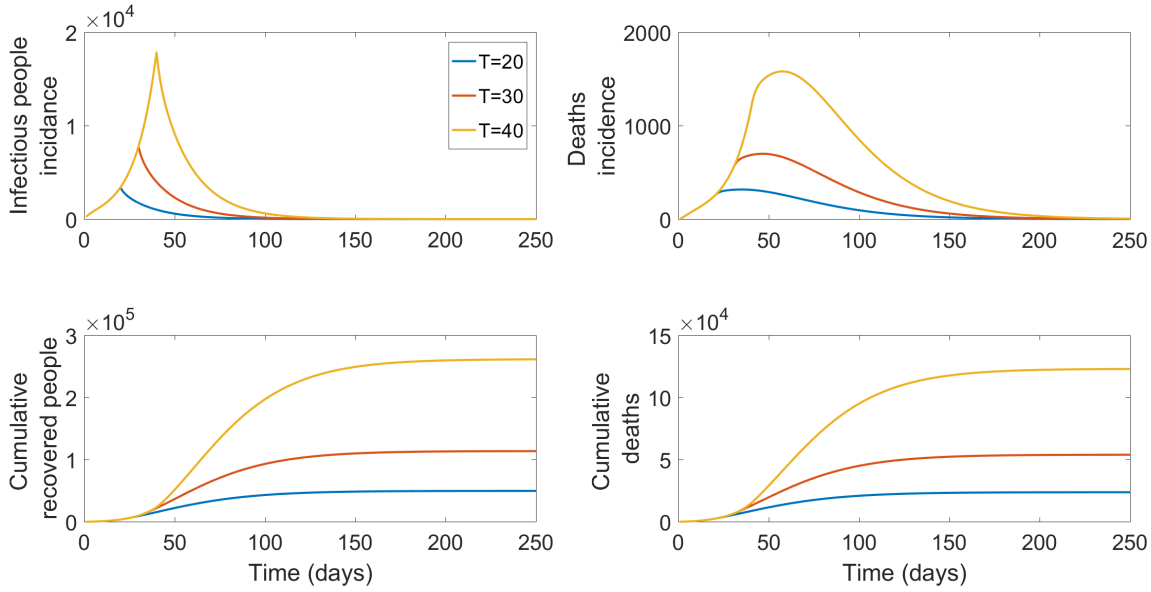



**Figure 3.** Time to epidemic control (days) by response time and percentage of cases isolated and percentage of ring vaccination of contacts.

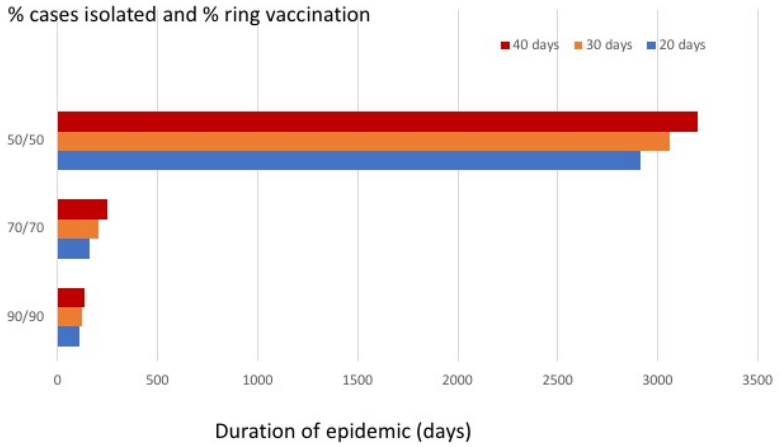


**Figure 4.** Epidemic control at values of 53-56% each of case isolation and ring vaccination

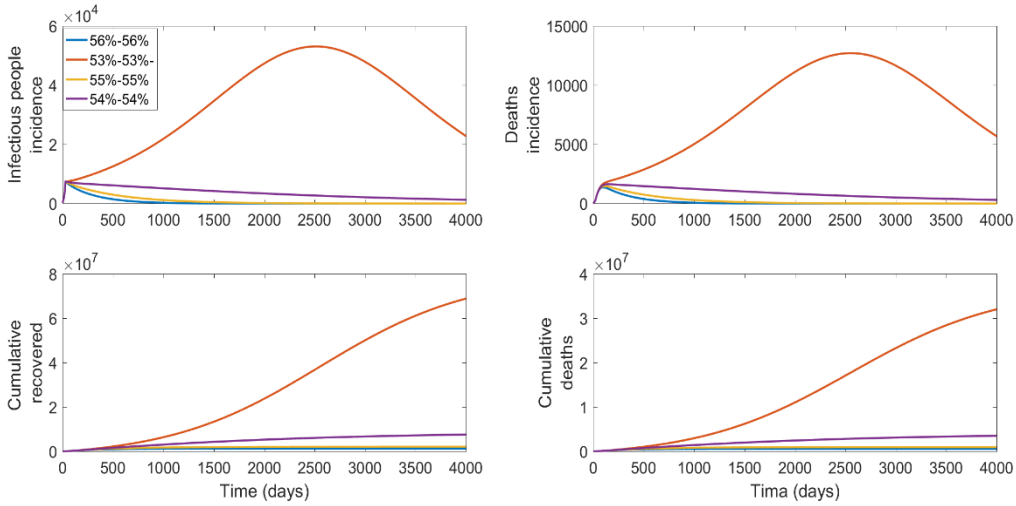
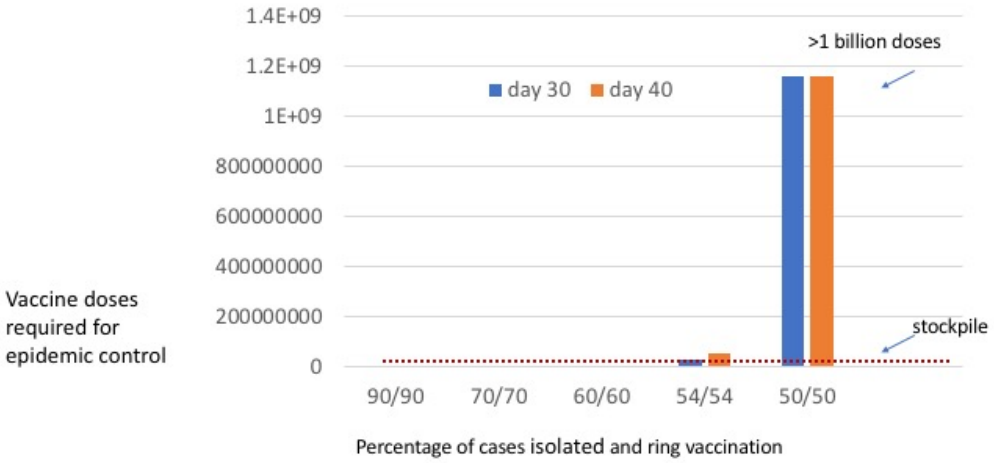



**Figure 5.** Vaccine doses required for epidemic control under varying proportions of case isolation and ring vaccination.




In Figure 3, we show that epidemic control is lost at the 50% level, so we tested values between 50-60% to identify the threshold below which epidemic control is lost. This was identified as 53%. Figure 4 shows model outputs at values between 53-56% and shows that the critical epidemic control threshold is >53% each of case isolation and ring vaccination. If the proportions are 53% or less, epidemic control is lost.

Figure 5 shows the vaccine dose requirements for epidemic control at varying proportions of case isolation and ring vaccination. The stockpile is adequate up to 54% each of case isolation and ring vaccination, provided the response commences within 30 days of the attack. If it is delayed to 40 days, the stockpile is exceeded, and 57,299,000 doses are required. If, however, the epidemic threshold is crossed and rates fall to 50% case isolation and ring vaccination, over a billion doses of vaccine will be required to achieve epidemic control.

**Discussion**

In the case of a large-scale smallpox attack in a low income, highly populous country, high rates of case isolation and ring vaccination are not guaranteed. Weak health systems and lack of human resources for health may create the circumstances for a catastrophic epidemic, which would occur if case isolation and ring vaccination rates of at least 53% each are not achieved. In this case the epidemic could persist for a decade or longer, or smallpox may even become endemic, as shown by our model. Influential factors on epidemic size are the size of the initial attack, time to commencing the response, case isolation rates and ring vaccination rates. Whilst the size of an attack may not be within our control, other influential factors are modifiable and potentially within our control.

An outbreak of smallpox can be controlled with a rapid response and with high rates of case isolation and high rates of ring vaccination. The latter depends on exhaustive contact tracing, which requires a high investment in human resources, given each case on average has at least 10 contacts [21]. However, if the response is delayed to 30 days or longer from the time of the initial attack (which in practice equates to 18 days after the first symptoms occur), or if the attack infects 10000 people or more, epidemic control will be much more challenging. Rapid response time is critical, especially in the case of a large attack. Delaying the response to greater than 20 days from the virus release (which means commencing the public health response within 7 days of symptom onset, given 12 days of incubation) will result in a more severe outbreak. Whether it is feasible to commence response within the best-case scenario of 7 days after symptom onset is unknown, but unlikely, particularly when a global stockpile of vaccine pledged from donor countries needs to be deployed through a specified WHO process [23, 24]. Low income countries are at risk of more severe epidemics due to lack of resources for case isolation, contact tracing and treatment. In addition, vaccination and protection of first responder teams will add some delay to deployment for the epidemic response. A rapid response also depends on rapid diagnosis of smallpox, but clinicians are unfamiliar with the disease and may not recognise it. In fact, the last outbreak in Europe was characterised by failure to diagnose a single index case, resulting in a large outbreak in Yugoslavia [25].

Recently, the clinical diagnosis of serious emerging infectious diseases has been missed by emergency clinicians, including Ebola in Nigeria and the US, both of which occurred during a peak of media reporting of the West African epidemic, when awareness should have been high [26, 27]. A similar failure was seen with MERS Coronavirus in South Korea, with repeatedly missed diagnosis at multiple hospitals [28].

Better syndromic surveillance, point of care tests and triage protocols for high consequence outbreaks such as smallpox would help prevent a worst-case scenario. However, rapid diagnostics are useful only if the clinical diagnosis is suspected and triggers testing. Pre-vaccinating teams for emergency response would also reduce avoidable delay. In the US, following 9/11, large scale smallpox vaccination of first responders commenced but was ceased due to adverse events [29]. Given the likelihood of a smallpox epidemic is unknown, a suitable option in the non-epidemic period would be to vaccinate small teams of first responders with third generation, non-replicating vaccines, thereby reducing the risk of adverse events and improving the ability to commence a response rapidly.

Other areas to reduce delay could involve pre-planned and pre-designated facilities for isolation of cases and surge capacity for contact tracing. Epidemic control is sensitive to both ring vaccination and case isolation rates, which need to be maintained at high levels. Having plans for rapidly deployable physical space and human resources to ensure rapid and thorough case finding, isolation, contact tracing, vaccination and quarantine are key for preparedness planning. Clinical and public health workforce requirements should be estimated and surge capacity planned for. This may necessitate the use of community volunteers, especially for contact tracing, as there will be at least an order of magnitude higher in contact numbers compared to cases [21]. During eradication of smallpox, community volunteers were provided financial incentives to assist with case finding [30]. Plans for incentivising community members should be considered as part of pandemic planning, given the importance of a rapid response. A global response is also required, to ensure resources are directed to areas of the greatest epidemic intensity rather than being retained in high income countries with low epidemic intensity.

In Exercise Mataika, we considered a worst-case scenario to identify critical weak points, prioritise the most influential factors and then plan how severe impacts can be avoided.

This research provides a framework for disease control targets in the event of a smallpox epidemic. It illustrates the importance of not allowing control measures to fall below the threshold for epidemic control, which appears to be 53%. In low income countries, a smallpox epidemic could overwhelm the health system and far exceed human resource capacity, so that low rates of case isolation and contact tracing modelled in this study are a realistic possibility. The consequences of poor epidemic control are catastrophic if only 50% of cases are isolated and 50% of contacts traced and vaccinated. Not only does the duration of the epidemic blow out to a decade or longer, but smallpox may become endemic and vaccination requirements will far exceed the available WHO stockpile. In the less severe scenarios, the WHO vaccine stockpile is adequate for epidemic control, but stockpiling provides a limited duration of supply, and the epidemic may run for 3000 days or more, depending on the scenario. Vaccine manufacturing capacity in the world is limited and the time lag for scaled up production is 12-18 months. Available vaccine could be diluted in the event of a shortage [31]. If vaccine is not available, all efforts must focus on case isolation, contact tracing and surveillance as effective interventions for epidemic control. However, these require planning for surge capacity in physical space and human resources, as well as global coordination of response in the most severely affected areas. Other modifiable factors which are influential, such as rapid response, must be factored into planning to ensure a worst-case scenario is avoided. Training and capacity building, as well as pre-vaccinated teams, can also assist with rapid response, as every day of delay worsens epidemic control. Global cooperation is also critical to this

planning, so that resources are directed quickly to affected areas.

**Supplementary Information**

Supplemental information as referenced in the text (PDF).

**Competing Interests**

Authors CR MacIntyre and DJ Heslop ran Exercise Mataika through the NHMRC Centre for Research Excellence, Integrated Systems for Epidemic Response. The exercise event received sponsorship from manufacturers of smallpox vaccines Emergent Biosolutions and Bavarian Nordic, to cover catering, venue hire and travel for participants. Sponsors did not have input into the Exercise content. The modelling was conducted independently under the direction of CR MacIntyre prior to the Exercise and funded by the NHMRC Centre for Research Excellence and her NHMRC Principal Research Fellowship. 

**References**

1. CDC. (Centers for Disease Control and Prevention). General Fact Sheets on specific bioterrorism agents. 2017 [updated Jul 12 2017. Available from: http://emergency.cdc.gov/bioterrorism/factsheets.asp.
2. Fenner F, Henderson D, Arita I, Jezek Z, Ladnyi Iea. Smallpox and its Eradication/F. Fenner ... [et al]. Geneva: World Health Organization. 1988:1469.
3. 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
4. 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
5. MacIntyre CR. Biopreparedness in the age of genetically engineered pathogens and open access science: an urgent need for a paradigm shift. Military medicine. 2015;180(9):943-9. DOI: https://doi.org/10.7205/MILMED-D-14-00482
6. 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
7. 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
8. WHO. (World Health Organisazation). Smallpox. Geneva, Switzerland: World Health Organization; 2018 [cited 2018 Mar 20]. Available from: http://www.who.int/csr/disease/smallpox/en/
9. Rao AR. Smallpox. Bombay,(India): Kothari Book Depot; 1972.
10. Parrino J, Graham BS. Smallpox vaccines: Past, present, and future. Journal of allergy and clinical immunology. 2006;118(6):1320-6. DOI: https://doi.org/10.1016/j.jaci.2006.09.037
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. Ajisegiri WS, Chughtai AA, MacIntyre CR. A Risk Analysis Approach to Prioritizing Epidemics: Ebola Virus Disease in West Africa as a Case Study. Risk Analysis. 2018;38(3):429-41. DOI: https://doi.org/10.1111/risa.12876
13. 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
14. 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
15. K R. Simulated smallpox pandemic reveals global preparedness, response challenges 2018 [updated 22 August 2018. Available from: https://homelandprepnews.com/stories/30105-simulated-smallpox-pandemic-reveals-global-preparedness-response-challenges/.
16. Gani R, Leach S. Transmission potential of smallpox in contemporary populations. Nature. 2001;414(6865):748. DOI: https://doi.org/10.1038/414748a
17. Massoudi MS, Barker L, Schwartz B. Effectiveness of postexposure vaccination for the prevention of smallpox: results of a delphi analysis. The Journal of infectious diseases. 2003;188(7):973-6. DOI: https://doi.org/10.1086/378357
18. Mack TM. Smallpox in Europe, 1950–1971. Journal of Infectious Diseases. 1972;125(2):161-9. DOI: https://doi.org/10.1093/infdis/125.2.161
19. 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

20. United States Census Bureau. U.S. Census Bureau Current Population 2018 [updated 22 November 2018. Available from: https://www.census.gov/popclock/print.php?component=counter.
21. Mossong J, Hens N, Jit M, Beutels P, Auranen K, Mikolajczyk R, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. PLoS medicine. 2008;5(3):e74. DOI: https://doi.org/10.1371/journal.pmed.0050074
22. United Nations DESA/Population Division. Data Query 2017 [Available from: https://population.un.org/wpp/DataQuery/.
23. Henderson D, Arita I. The smallpox threat: a time to reconsider global policy. Biosecurity and bioterrorism: biodefense strategy, practice, and science. 2014;12(3):117-21. DOI: https://doi.org/10.1089/bsp.2014.1509.comm
24. Checchi F, Waldman RJ, Roberts LF, Ager A, Asgary R, Benner MT, et al. World Health Organization and emergency health: if not now, when? Bmj. 2016;352:i469. DOI: https://doi.org/10.1136/bmj.i469
25. 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
26. 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
27. Upadhyay DK, Sittig DF, Singh H. Ebola US Patient Zero: lessons on misdiagnosis and effective use of electronic health records. Diagnosis. 2014;1(4):283-7. DOI: https://doi.org/10.1515/dx-2014-0064
28. Park JW, Lee KJ, Lee KH, Lee SH, Cho JR, Mo JW, et al. Hospital outbreaks of middle east respiratory syndrome, Daejeon, South Korea, 2015. Emerging infectious diseases. 2017;23(6):898. DOI: https://doi.org/10.3201/eid2306.160120
29. Nicolle L. Smallpox (Editorial). Can J Infect Dis. 2003;14(5):247-8. DOI: https://doi.org/10.1155/2003/590490
30. Henderson DA. Principles and lessons from the smallpox eradication programme. Bulletin of the World Health Organization. 1987;65(4):535.
31. Group YFW, Medicine CtAoT. Current Travel Risks: Interim Canadian recommendations for the use of a fractional dose of yellow fever vaccine during a vaccine shortage. Canada Communicable Disease Report. 2016;42(8):158. DOI: https://doi.org/10.14745/ccdr.v42i08a02

**How to cite this article**: Macintyre CR, Costantino V, Mohanty B, Nand D, Kunasekaran MP, Heslop DJ. Epidemic size, duration and vaccine stockpiling following a large-scale attack with smallpox. *Global Biosecurity*, 2019; 1(1).

**Published**: February 2019



*Global Biosecurity* is a peer-reviewed open access journal published by University of New South Wales.