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Pacific Eclipse – A tabletop exercise on smallpox pandemic response

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ABSTRACT

Background: In December 2019, we ran Pacific Eclipse, a pandemic tabletop exercise using smallpox originating in Fiji as a case study. Pacific Eclipse brought together international stakeholders from health, defence, law enforcement, emergency management and a range of other organisations.
Aim: To review potential gaps in preparedness and identify modifiable factors which could prevent a pandemic or mitigate the impact of a pandemic.
Methods: Pacific Eclipse was held on December 9–10 in Washington DC, Phoenix and Honolulu simultaneously. The scenario began in Fiji and becomes a pandemic. Mathematical modelling of smallpox transmission was used to simulate the epidemic under different conditions and to test the effect of interventions. Live polling, using Poll Everywhere software that participants downloaded onto their smart phones, was used to gather participant decisions as the scenario unfolded. Stakeholders from state and federal government and non-government organisations from The United States, The United Kingdom, Australia, New Zealand, Canada, as well as industry and non-government organisations attended.
Results: The scenario progressed in three phases and participants were able to make decisions during each phase using live polling. The polling showed very diverse and sometimes conflicting decision making. Factors influential to pandemic severity were identified and categorised as modifiable or unmodifiable. A series of recommendations were made on the modifiable determinants of pandemic severity and how these can be incorporated into pandemic planning. These included preventing an attack through intelligence, law enforcement and legislation, improved 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) and protecting first responders.
Discussion: Pacific Eclipse illustrated the impact of a pandemic of smallpox under different response scenarios, which were validated to some extent by the COVID-19 pandemic. The framework developed from the scenario draws out modifiable determinants of pandemic severity which can inform pandemic planning for the ongoing COVID-19 pandemic and for future pandemics.

1. Introduction

The World Health organization (WHO) declared smallpox eradicated in 1980 and the virus, variola, is retained in Biosafety Level 4 laboratories in the United States and Russia [1]. Advances in synthetic biology make the synthesis of variola in a laboratory possible [2]. In 2017, Canadian scientists demonstrated they could create an orthopoxvirus at relatively low cost [3]. The experiment only came to light when the researchers notified the WHO (3). The combination of terrorist groups with stated intent for biological attacks and the technological capability to manufacture an orthopoxvirus make synthetic smallpox a greater risk today than in the decades past [2]. The world is largely non-immune to variola, given the last mass vaccination programs ceased in the 1970's and vaccine-induced immunity wanes to negligible levels after 10 years [4].

In December 2019 we ran Pacific Eclipse, a pandemic tabletop exercise using smallpox originating in Fiji as a case study. The Pacific is a challenging region for epidemic control, with informal mar-

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itime transport networks, natural disasters, rising sea levels and political conflict, as well as weak health systems and shortages of trained health workers [5].

As seen during COVID-19, a localised epidemic of a respiratory transmissible virus may spread globally if detection and reporting are delayed. Pacific Eclipse brought together international stakeholders from health, defence, law enforcement, emergency management and a range of other organisations.

1.1. Exercise aim

To review preparedness for an unnatural pandemic of a respiratory transmissible infection.

1.2. Exercise objectives

To review potential gaps in preparedness

To identify modifiable factors which could prevent a pandemic or mitigate the impact of a pandemic.

1.3. The Exercise

1.3.1. Design and facilitation

An exercise was conducted by The PLuS Alliance, in collaboration with the United States Indopacific Command. The simulation was adapted from an exercise held at UNSW Sydney in 2018 for stakeholders from the Asia-Pacific Region, which had contextual input from the Ministry of Health and Medical Services Fiji [5]. The scenario began in Fiji and was adapted for the US context. Deterministic SEIR mathematical modelling of smallpox transmission [6] using a published model was used to simulate the epidemic under different conditions and to test the effect of interventions. Live polling was used to gather participant decisions as the scenario unfolded, using Poll Everywhere software, which participants downloaded onto their smart phones. The facilitator presented questions at regular points in the unfolding scenario, providing 4–5 options and participants were able to choose responses on their smart phone using the Poll Everywhere software. The results were then presented in real time to the participants on the large screen and on their smart phones, and an interactive discussion followed. At the end of the exercise, people were shown mathematical modelling outputs of the epidemic resulting from different actions or decisions.

1.3.2. Participants

Stakeholders from state and federal government and non-government organisations from The United States, The United Kingdom, Australia, New Zealand, Canada, as well as industry and non-government organisations attended.

1.3.3. Exercise date and location

Pacific Eclipse was held on December 9–10 in Washington DC, Phoenix and Honolulu simultaneously.

1.3.4. Exercise format

A tabletop exercise was developed by UNSW and adapted for the US context with Arizona State University. The exercise explored clinical, public health, emergency management and societal responses, with a focus on inter-disciplinary capability, regional, national and global considerations. Modelling was used to identify the most influential factors in pandemic size and impact. Further details, model structure and assumptions of the deterministic SEIR model is available in a separate publication [6].

Participants experienced the scenario through a combination of narration and multimedia, including news reports and video footage, with interactivity and discussion throughout.

1.3.5. Scenario description

The origin and genesis of the pandemic was in Fiji, as described in Exercise Mataika in 2018 [5]. In brief, the index case of haemorrhagic smallpox in Fiji is misdiagnosed and is not identified as variola for 13 days. The scenario was based on details of the last European outbreak of smallpox, in the former Yugoslavia, including failure to diagnose haemorrhagic smallpox until a large epidemic had begun [7]. As the epidemic grows in Fiji, causing public panic and health system strain, a small team from WHO arrive in Fiji to assist with the outbreak investigation. A range of differential diagnoses including chickenpox, dengue, monkeypox and smallpox are considered. The virological diagnosis is made 13 days after the index case presented. By this stage hundreds of cases have occurred, and the common exposure of the simultaneous cases is identified as Nadi International Airport. The suspicion of a bioterrorist attack brings in law enforcement agencies and military into the response.

A limited quantity of vaccine is deployed to Fiji on day 28 after the virus release (accounting for a 12-day incubation period, meaning that the first case was not identified until day 13, and vaccine was deployed 15 days after that as the most optimistic scenario). The WHO smallpox vaccine stockpile has only 2.7 million doses of first-generation vaccine physically held in Geneva, and the remaining 31 million doses are pledged by member states, the largest quantity from the United States [8]. Protection from vaccination occurs after 7 days, so there is a delay in preparing a vaccinated responding team from WHO, who finally arrive in Fiji on day 40. The timeline is examined to show that this was the earliest possible response time, allowing 13 days to diagnosis and time for vaccination of the response team.

The strategy of ring vaccination is used, which requires contact tracing and vaccinating all of contacts who are prioritised by the closeness and degree of contact. Ring vaccination (also referred to as surveillance and containment) was used to eradicate smallpox and is the most efficient vaccination strategy to control the epidemic if vaccine supply is limited [6]. In most cases during the eradication campaign the entire village would be vaccinated if a case of smallpox was identified.

Forensic investigation confirms a biological attack occurred at Nadi International Airport, resulting in a large number of people infected simultaneously. Many potentially exposed people have since travelled to other countries or other islands on day zero. Both tourists and citizens are trapped and unable to leave Fiji. An increase in undocumented boat travel occurs as residents flee to outer islands and other surrounding Island nations.

The phylogenetics of the attack strain shows that the vaccine will be protective. The epidemic response comprises case finding, isolation, contact tracing and quarantine of contacts. Treatment of cases is supportive, as antivirals with activity against variola such as cidofivir, brincidofivir or tecovirimat (TPOXX) are not available in Fiji.

The health system is beginning to be strained and nurses go on strike because of shortages of personal protective equipment and a mounting infection and death toll among health workers. The existing bed capacity of Fiji (1753 beds) has been exhausted by day 25, with more than 2000 smallpox cases. At this point medical care for other acute conditions is compromised. There are only 2800 nurses and 873 doctors in Fiji, many of whom are infected or quarantined.

Variola is spread by the airborne route [9] and spreads rapidly because the population in Fiji and the world is largely non-immune [10]. Smallpox has a basic reproductive number (R0) that may be as high as 4–5 [10] and is more infectious than influenza (R0 $\sim$ 2) [11]. The R0 is also similar to SARS-COV-2, which is also spread by the respiratory route [12]. In this deliberate attack it is possible hundreds or more people were infected on day zero. This

makes epidemic control much more difficult than epidemics arising from a single case zero [6].

Cases infected at the airport have dispersed globally and outbreaks are occurring in many countries. Intelligence investigations identify planning on the Dark Web for other, larger attacks. As the epidemic spreads, airlines cancel flights to and from Fiji. Residents and tourists try any means to leave Fiji, including by illegal and irregular maritime travel. These boats and cruise ships with infected passengers are denied entry into multiple countries, leaving them short of supplies and stranded. One such boat approaches the shores of Hawaii.

Support for Fiji from other countries is lacking, although telephone advice is provided and air drops of medical supplies are made. Other countries are now focused on epidemic control domestically and have limited capacity to assist overseas. Leaders in the United States are risk averse and protectionist due to upcoming elections in 2020. WHO calls for public health teams to respond, but there are few offers and some volunteers have contra-indications to smallpox vaccine. A relatively small team of responders, some semi-skilled or inexperienced, are prepared by WHO for deployment to Fiji. The US CDC cannot spare many people as they are overwhelmed with their own domestic response.

It appears that over 1000 people were infected during the attack in Fiji, resulting in rapid epidemic growth. Contact tracing has become difficult because of the ministry has over 100,000 contacts to trace, but only 50 trained but unvaccinated public health staff. Hospital beds are in short supply and the location of quarantine is debated, with selection of specific quarantine sites and community mobilization.

The WHO send 32,000 doses of vaccine to Fiji, but at that time a larger attack occurs in a mega-city in Asia, catching the world off guard and diverting all resources there. Fiji is left with a small supply of vaccines and minimal assistance. There are delays in the response because the first responders need to be vaccinated and vaccinators require training in vaccination procedures. In addition to the health system being over capacity, other industries are affected by staff absenteeism due to high rates of illness. Control of the epidemic depends on case isolation, contact tracing, ring vaccination, and speed of response.

Personnel and dedicated spaces and makeshift buildings to isolate cases are in short supply, and poorly coordinated attempts at community engagement and mobilisation begin. Crisis communication is not adequate. We estimate that at the peak of the pandemic, realistically only 50% of smallpox cases are isolated and only 50% of contacts are traced and vaccinated. Modelling shows that this exceeds the critical epidemic threshold and causes a catastrophic blow-out in the epidemic [6]. In this worst-case scenario, it will take at least 2 billion doses and almost five years to stop the epidemic [6]. Another problem is unwillingness of countries to provide pledged vaccine doses to WHO, which holds less than 10% of doses [6]. There is a delay of 12–18 months for vaccine manufacture, with 300 million doses that could be produced in this timeframe by existing manufacturers of smallpox vaccines.

The United States initially identifies 24 cases which are mostly travel related, except for 3 cases in the community around Emory Hospital who have no travel history. This raises the question of long-range airborne transmission of variola [9]. The initial outcome is that four cases are deceased and 20 are isolated and receive excellent care. The US stockpile has enough doses for mass vaccination, but the vaccine program roll out is slow. Only health workers, military, first responders and close contacts of cases are vaccinated so far. The government decides to only provide vaccines to US citizens, and not to undocumented people or people on temporary visas in the US. The media are calling for mass vaccination. The US stockpile is the largest contributor to the WHO global stockpile and there is political pressure to withhold pledged doses to WHO. Meanwhile, an uncontrolled epidemic spirals out of control in a low income, densely populated Asian country which has no stockpile. The ‘‘America First” agenda, active campaigning by politicians and media pressure are powerful in dictating that the US does not release the stockpile to WHO. Conspiracy theories and anti-vaccination groups are also active on social media.

As the pandemic takes hold, critical infrastructure and supply chains are compromised, and there are shortages of medical equipment, masks, respirators, antivirals and vaccines in the US. International aid is greatly reduced because the US needs their resources and personnel for their own epidemic control. Crisis communication is an issue, and not done well. Civil unrest and riots occur in many cities, requiring law enforcement and military response, but shortages of personal protective equipment have police striking. The upcoming federal election in 2020 also becomes a factor, with politicisation of the pandemic response and nationalism. Banning of mass gatherings such as concerts and sporting events becomes contentious, as does border control, with black market travel and limited ability to patrol borders. ICE detention centres are affected by epidemics, and staff abandon several detention centres. Mexico has an uncontrolled epidemic and border disputes with Mexico are occurring. Large outbreaks begin in California and Arizona and the disease spreads more widely. Absenteeism in the workforce is affecting the economy severely. Dead bodies outside hospitals are piling up and disposal of medical waste is in crisis, as funeral homes are full or refusing service and transport companies refuse medical waste.

Basic services and critical infrastructure are affected, with California affected by power grid failures. Nefarious actors take advantage of the chaos in the US to launch cyber-attacks on government systems. A number of terrorist organisations have claimed responsibility for the smallpox attacks but none are known to have capacity for developing this kind of attack method. The population is confused, further reducing trust in authority and government. Local factions see an opportunity, raising concerns of potential coup d’état. Security is increased for key government officials

Key modern systems become unreliable, including wireless and data communications, economy and banking (cash supply), replacement parts and manufactured items, processed food, medications, waste management and contracted service capacity and availability. 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 diminished. Legitimate attempts at information husbandry by authorities are viewed with suspicion and fuel conspiracy theories.

In the worst case scenario, the end of the pandemic is greater than 8 years and results in 522 million cases, despite the vaccine being highly effective, largely because the stockpile not deployed to the area of greatest need, which are low income countries with weak health systems and inability to trace contacts or deliver vaccination programs efficiently. This was modelled on India, the last stronghold of smallpox in the world, where mass vaccination could not be achieved, prompting the switch to ring vaccination during the more than decade long eradication campaign. Even during COVID-19, India, despite having the largest vaccine manufacturing capacity in the world, was unable to cope with the second wave or with vaccine supply in 2021, with supplies interrupted for other countries in Asia and Africa which were depending on Indian supplies. In the modelled pandemic, globally, only 50% of cases are iso-

lated and only 50% of contacts vaccinated, which reflects a possible scenario in low income countries on the background of an immunologically naïve population, thus causing a blow-out of the pandemic [6]. We show that poor control results in higher case numbers and greater requirement for vaccine doses [6].

Globally, large cities are the worst affected and rural areas with subsistence mechanisms are more resilient and able to provide primary healthcare. After the pandemic is over, societal recovery begins, but from a lower baseline than pre-pandemic because of severe economic, logistic, development and social impacts. The majority of the world enters a period of economic and social depression.

1.3.6. Analysis of polling

We used Poll Everywhere software and presented participants in Pacific Eclipse with discussion points and trigger questions about key decisions during the unfolding scenario. The data from the live polling from both the Australian Exercise Mataika [5] and US Pacific Eclipse, both of which had international participants, were combined and analysed using descriptive epidemiology.

2. Results

A total of 157 of over 300 attendees who participated in the exercise completed the polling, comprising 51 in 2018 and 106 in 2019. Among the attendees that completed the polling, 88 (56.1%) were from North America, 51 (32.5%) from Asia-Pacific including Australia, 16 (10.2%) from Europe and 2 (1.3%) from other areas. The countries accounting for most attendees are the United States (n = 88, 52.9%) and Australia (n = 40, 25.5%).

Among the attendees, 29 (25.2%) work in public health; 26 (22.6%) in military or other defence-related areas; 16 (13.9%) in academia; 16 (13.9%) in emergency response or management; and 28 (17.8%) in other areas (healthcare, private sector). The scenario progressed in three phases and participants were able to make decisions during each phase. The first was about an undiagnosed emerging epidemic, diagnosis, early public health management and communication. The second phase was focused on global responses during an established pandemic, and the third phase on critical infrastructure, disaster response and recovery. Detailed responses to polling are shown in Appendix B, and a selection below.

An initial clinical diagnosis of monkeypox (33.5%), smallpox (43.2%) and other diseases (23.3%) was made by participants. When asked the most important initial public health strategy, case isolation was the first choice for 62.3% of participants, followed by sourcing of PPE for the health workforce (16.4%) and active case finding (11.9%). In the absence of vaccines, more than half participants (53.3%) agreed with the strategy of contact tracing and quarantine, while 32.6% felt isolating and treating cases was the most important. After vaccine is available, half of respondents (47%) believed that case isolation is as important as contact tracing, quarantine and vaccination.

When asked about priority for vaccination, most participants agree that healthcare workers and first responders should be vaccinated first (76.6%), while 18.6% felt contacts of cases should be vaccinated first.

When the initial cluster of cases becomes an epidemic with community spread, most participants (87.3%) acknowledged the role of social contact restriction in reducing spread. Almost half (46.6%) believed law enforcement is necessary to implement travel restrictions. Most participants deemed school closure most effective if implemented early (72.3%).

When new cases emerge in US, more than half participants (52.3%) considered this an immediate and major threat, and 68.1% recommended reserving some of the pledged doses for ring vaccination of high-risk groups and contacts, while releasing the remaining doses to the WHO stockpile. Another 24.5% instead recommended holding onto the stockpile and not releasing it to WHO.

When asked to choose the hospitals designated to treat cases, 47.8% participants recommended to use all available hospitals, and 38.1% to use only a few designated hospitals. Most participants (70.7%) suggested utilizing large buildings to cope with the rising demand for hospital beds, followed by tent hospitals (15.8%). Most participants agreed that clinical staff are the priority group for PPE (64.3%), while 26.9% believed other non-health groups (military, police and government) are the priority.

In dealing with absenteeism, providing support and addressing the reasons for absenteeism is the preferred strategy (58.0%), followed by identifying second and third-line replacements for key positions (28.0%). Most participants agreed that disinformation is a potential major issue (90.5%), and clear and honest communication is key to re-establish social and community trust (83.7%). Healthcare workers are considered the most trusted members of the community by participants (65.0%).

Appendix C provides a link to the multimedia materials used during Pacific Eclipse.

3. Discussion

Pacific Eclipse was held on December 9 and 10 2019, the 40th anniversary of smallpox eradication, while the COVID-19 pandemic was emerging, unknown to the world. Whilst SARS-COV-2 is a different virus, with pre-symptomatic and asymptomatic transmission (compared to smallpox where transmission occurs only in the symptomatic phase) and a lower case-fatality rate, the long incubation period, similar R0 and predominant respiratory transmission make the two infections comparable in pandemic potential. This provided a validation of the hypothetical pandemic we had exercised and showed that many issues highlighted by Pacific Eclipse did come to pass during the COVID-19 pandemic. This included stranded cruise ships with infections on board denied entry at international ports [13], shortages of PPE [14], border closures impacts on international travel [15,16], politicisation of the pandemic response, misinformation on a significant scale [17], riots and inequity driven by nationalism in the distribution of vaccines and medical supplies.

We saw the importance of case isolation and contact tracing on pandemic control and countries that failed to recognise this lost of control of the epidemic [18]. One impact we did not fully realise was the loss of pandemic control in high income countries such as the US and UK due to poor leadership (including lack of utilization or disruption of existing pandemic plans, which assumed an influenza pandemic, and lack of standard disaster management protocols), insufficient pandemic planning, cultural factors and lack of appropriate expert advice [19]. We did exercise the impact of the 2020 federal election in the US and Brexit in the UK on the smallpox pandemic, but did not anticipate the complete failure in organised public health response in these countries at critical junctures. This was similarly not predicted by the Global Health Security Index, which ranked the US first among all countries in pandemic preparedness [20]. Therefore funding, resources and scientific expertise alone do not guarantee a successful pandemic response. Cultural factors, such as emphasis on individual freedoms in the US, impacted on the ability to use public health measures such as masks and lockdowns. In such cases, leadership could overcome cultural biases, but the combination of poor leadership and cultural factors in the US proved catastrophic.

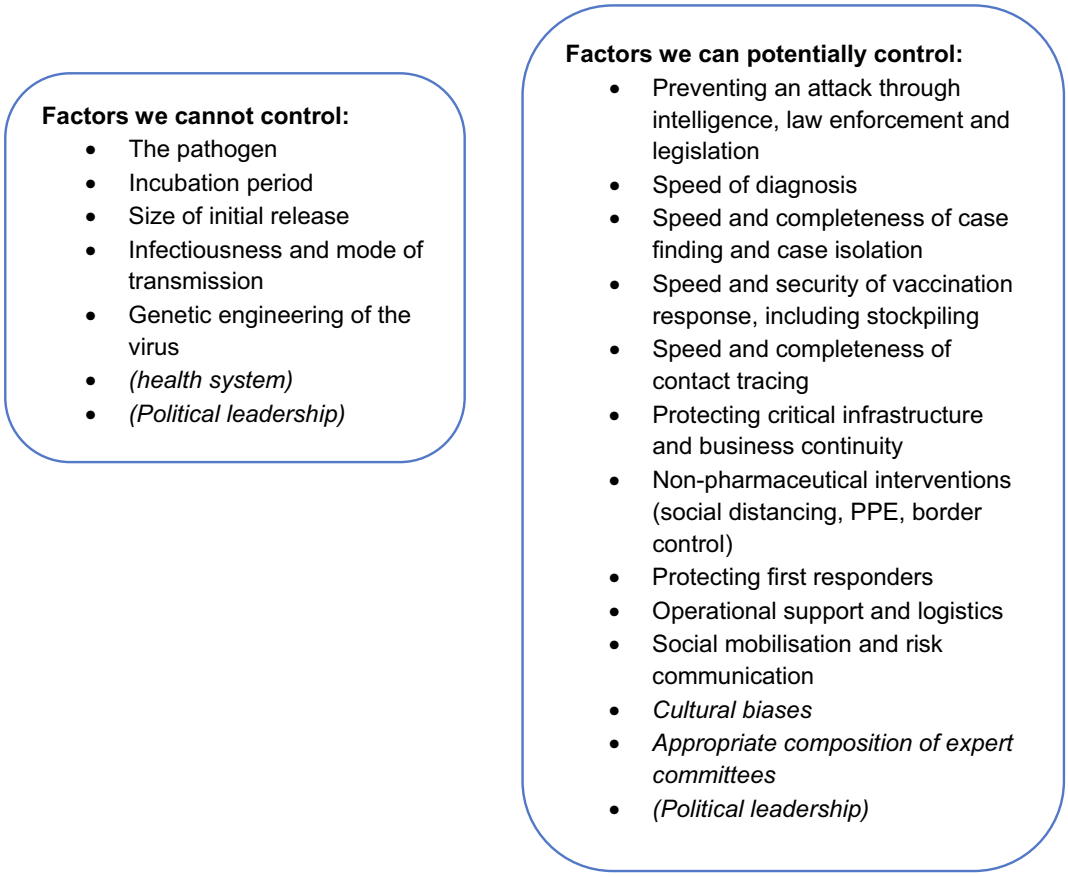

Fig. 1. Factors affecting epidemic severity which can and cannot be modified – additional factors in italics.

Although we discussed vaccine shortages in our scenario, one issue that we did not explore was the role that vaccine hesitancy plays in pandemic response. Although smallpox vaccines are not new, it is reasonable to believe that there would be hesitancy due to its unusual mode of administration. Currently, there are high levels of COVID-19 vaccine hesitancy in many countries worldwide [21–23], even in countries with adequate vaccine supplies and high disease incidence such as the US. In response, some countries have had to impose strict vaccination policies. For example, during a severe delta-strain outbreak in Fiji, the prime minister imposed a 'no jab, no job' policy that required all workers to be vaccinated against COVID-19 and and in the US, a large number of companies have imposed mandatory vaccination [24,25]. Thus, future pandemic planning should not only focus on vaccine supply and distribution, but also how to promote vaccine acceptance.

The polling data showed that stakeholders had different perspectives and had a quite wide range of competing and sometimes conflicting solutions to problem solving and decision making. This partially reflects the broad, cross-sectoral and international stakeholder group involved, but also the uncertainty around many issues during an emerging pandemic. Cross-sectoral collaboration is critical for good pandemic planning to ensure that the best decisions can be made rapidly and with consensus. We did not include formal economic analyses in the exercise, but this is also an important consideration for competing pandemic control options.

A framework for planning, preparing and responding to a pandemic of a serious respiratory pathogen was previously devised following Exercise Mataika, [5] which is further refined and modified below with learnings from Pacific Eclipse and the COVID-19 pandemic (Fig. 1). The principle for pandemic planning is that factors affecting pandemic severity are divided into modifiable and non-modifiable ones, and the focus of planning is those which can be modified. New additions or modifications to the original recommendations in italics. Fig. 1 shows the influential factors on epidemic severity that can and cannot be modified, with political leadership falling into both categories, as some aspects may be modifiable, whilst others may not. The Pacific Eclipse scenario and the COVID-19 pandemic highlighted some additional factors which were not accounted for in the original Exercise Mataika, including health system (such as universal access to healthcare) as a factor that cannot be controlled acutely during a pandemic, political leadership as a factor we may or may not be able to control. Added factors that may be controlled were cultural bias and composition of expert committees. The recommendations arising from the workshop are summarised in Appendix A in Boxes 2–11.

4. Conclusion

Pacific Eclipse illustrated the impact of a pandemic of smallpox under different response scenarios, which were validated to some extent by the COVID-19 pandemic, which saw cultural factors, lack of universal healthcare and political leadership impact on pandemic control. The framework provided above, which draws out modifiable determinants of pandemic severity, can inform pandemic planning for the ongoing COVID-19 pandemic and for future pandemics. We showed that vaccination provides an effective exit strategy to a pandemic, and that this requires high and rapid coverage, as well as vaccine to be supplied to the areas of greatest need [6]. Countries that cannot achieve high coverage due to lack of access or hesitancy, will determine the duration of the pandemic and the level of global disruption, which may extend to many years in some hot spots [6].

Pacific Eclipse enabled inter-disciplinary expert input into many aspects of a smallpox pandemic and took a wider view of pandemics than the traditional health-centric view, by also including many first responder sectors, culture, politics, community and critical infrastructure. We engaged experts from many different sectors and looked at all phases from pre-attack to societal recovery. The importance of cross-disciplinary international dialogue between heath, law enforcement, military, emergency management and other sectors was highlighted. The exercise identified critical weak points that can be mitigated with prior planning, such as intelligence gathering, response, recovery, physical infrastructure and human resources requirements. We showed that global pandemic control matters for all countries, and that global interest must overcome national interests toward this end. While this exercise focused on smallpox and used a SEIR model, a wide range of disease models, including agent-based models, could be utilized to explore different scenarios and further inform pandemic planning. An inclusive, collaborative approach with all relevant sectors globally is important, rather than a health-centric, solely nationalised approach.

CRediT authorship contribution statement

C. Raina MacIntyre: Conceptualization, Methodology, Investigation, Writing – original draft. **David J. Heslop:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Phi Nguyen:** Formal analysis, Writing – original draft. **Dillon Adam:** Investigation, Methodology, Writing – review & editing. **Mallory Trent:** Investigation, Methodology, Writing – review & editing. **Brian J. Gerber:** Conceptualization, Investigation, Methodology, Writing – review & editing.

Declaration of Competing Interest

Pacific Eclipse received funding for venue hire, participant travel and accomodation from Emergent Biosolutions, Bavarian Nordic, Siga and Meridien Medical Technologies. The sponsors did not have any input or role in the design of the exercise.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.10.081.

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