Total costs associated with replicating and non-replicating smallpox vaccines

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ABSTRACT
Routine vaccination against smallpox among the general public was discontinued more than three decades ago, resulting in a population that is increasingly susceptible to infection. Moreover, the likelihood of re-introduction of eradicated diseases, such as smallpox, increases with time primarily due to the rapid advancement of biotechnology. Our analysis outlines the relative contribution of each component to the total cost of immunisation as it compares replicating and non-replicating smallpox vaccines for the first time. We calculated the total cost of immunising one person using a replicating vaccine such as ACAM2000 was $139, while using a non-replicating vaccine (IMVAMUNE®) cost $115. Overall, the analysis indicates that the main cost component differences of replicating and non-replicating vaccines are made up of the need for screening, follow-up visit, adverse events, reimbursement and compensation when using replicating vaccines. These costs are almost perfectly balanced against the higher cost of goods, reduced productivity loss and the need for an extra vaccination visit when using a non-replicating vaccine. With the availability of a new vaccine option, preparedness planners will benefit from this analysis to support evidence-based decision-making when preparing a safe, efficacious and cost-effective stockpile and immunisation programme against smallpox.

KEYWORDS
Medical countermeasures; smallpox; stockpiling; vaccine

1. Introduction
Infectious disease threats are a continuous challenge for society and the emergency services sector, and may originate from both naturally occurring and deliberately introduced pathogens and toxins. Rare or novel pathogens pose a particular preparedness challenge for decision-makers who are faced with the question of allocating scarce public health resources to address diseases that are not a current threat.

This conundrum is epitomised by smallpox, a highly lethal disease caused by the variola virus, which is easily transmitted from person to person facilitated by a declining herd immunity. Smallpox carries a considerable morbidity and mortality (>30%) and is the most dangerous infectious disease known to mankind; killing more than 300 million people in the twentieth century. Effective licensed therapy against smallpox is not available and preparedness relies on a robust vaccination strategy.

Thus, a global vaccination campaign, initiated in 1966 under the aegis of the World Health Organization (WHO), succeeded in eradicating naturally occurring smallpox in 1977. Vaccines are made from various vaccinia virus strains, which are closely related to variola virus. Routine vaccination against smallpox among the general public was discontinued more than three decades ago, resulting in a population that is increasingly susceptible to infection. Furthermore, the likelihood of re-introduction of eradicated diseases, such as smallpox, is partly fuelled by laboratory safety transgressions and increases with time primarily due to the rapid advancement of biotechnology (Becker et al., 2008; Cello, Paul, & Wimmer, 2002; Gaudioso et al., 2011; Gibson et al., 2008). This is corroborated by a recent WHO report that concluded, ‘given the ability to recreate the variola virus using synthetic biology techniques, the destruction of the remaining stocks of variola virus at the two WHO Collaborating Centres would not irrevocably destroy the virus’ (World Health Organization [WHO], 2015).

Accordingly, some countries have re-introduced smallpox immunisation among select military and public health personnel. The traditional vaccines against smallpox involve infecting patients with replicating vaccinia virus, which can lead to severe side effects, especially in people with atopic dermatitis or other forms of eczema, as well as in people with immune deficiencies.

Recently, however, a non-replicating vaccine (IMVAMUNE®) received European and Canadian
marketing authorisation for active immunisation against smallpox for the general adult population, including people with weakened immune systems (people diagnosed with human immunodeficiency virus [HIV] or atopic dermatitis) (European Medicines Agency, 2016). Immunogenicity and safety of IMVAMUNE® were evaluated in five main studies and several supportive studies (WHO, 2013). Accordingly, in excess of 7000 individuals including HIV patients and people with atopic dermatitis have received IMVAMUNE®. These individuals are not eligible for replicating vaccines nor is it ethically feasible to conduct testing in such populations. Unlike replicating vaccines, IMVAMUNE® has been demonstrated to be safe and well tolerated with no increased risk for development of myo-/pericarditis (Elizaga et al., 2013; Zitzmann-Roth et al., 2015).

2. Materials and methods

In January 2003, the US Department of Health and Human Services implemented a preparedness programme in which replicating smallpox vaccine was administered to federal, state and local first responders. The US programme is well documented and represents the single largest smallpox immunisation effort undertaken by any nation in the past 30 years (Casey et al., 2005; Poland, Grabenstein, & Neff, 2005). A total of 38,885 smallpox vaccinations were administered, with a total of 590 adverse events (AE) reported within 14 days of vaccination. AEs included multiple signs and symptoms of mild and self-limited local reactions. One hundred AEs were designated as serious, resulting in 85 hospitalisations, two permanent disabilities, 10 life-threatening illnesses and three deaths. Among the serious adverse events (SAE), 21 cases were classified as myocarditis and/or pericarditis and 10 as ischemic cardiac events. Two cases of generalised vaccinia and one case of post-vaccinal encephalitis were detected. Learnings from this campaign include the importance of setting up a more strict screening procedure, which expectedly will reduce the AE frequency. The risk of myo/pericarditis may be linked to previous smallpox immunisation, but the impact of this on future campaigns is difficult to accurately determine.

A more recent prospective study identified five cases of probable myocarditis and pericarditis among 1081 healthy individuals receiving live attenuated smallpox vaccine (Engler et al., 2015). Additionally, 31 smallpox vaccinees without specific cardiac symptoms were found to have over twofold increases in cardiac specific troponin T (>99th percentile) from baseline, thus meeting a proposed case definition for possible subclinical myocarditis.

These findings underscore that the impact of smallpox vaccination is far more complex and costly than routine immunisations because the replicating vaccine carries a greater risk of AEs and requires extensive pre-vaccination planning and post-vaccination follow-up (Ortega-Sanchez, 2003). The present analysis therefore includes both direct and indirect costs to more accurately estimate the total costs:

- Cost of vaccine
- Cost of administering vaccine including training, storage and logistics
- Cost of medical treatments of AEs
- Cost of reimbursed loss of income to vaccinated personnel experiencing AEs
- Compensation due to disability or death due to AEs

For this paper, an estimate of the individual costs for both replicating and non-replicating vaccines was obtained from a variety of sources as outlined in the Results section and Table 1. Data were primarily derived through standard literature search, citing international peer-reviewed journals and renowned institutions with no limitations as to geography and time. In addition, data were obtained from manufacturers, public statistics and budget estimates and published financial reports (American Medical Association, 2015; Candrilli & Mauskopf, 2006; Chalom, Raphaely, & Costarino, 1999; Dasta, McLaughlin, Mody, & Piech, 2005; Edwards, Rivanis, Kun, Caughey, & Keens, 2011).

Moreover, a literature review of the implementation costs and resource use associated with the 2003 US Civilian Smallpox Vaccination Program was conducted. This yielded an economic analysis on frequency and cost of cardiovascular events (Ortega-Sanchez, Sniadack, & Mootrey, 2008). Moreover, to illustrate the potential costs of treating SAEs, an in-depth analysis was performed of the costs associated with treating eczema vaccinatum (Vora et al., 2008) and progressive vaccinia (Lederman et al., 2012), two rare SAEs associated with the use of replicating smallpox vaccines. Taken together, these data were then compiled to perform an economic analysis of the comparative costs of using the replicating smallpox vaccine vs. a novel non-replicating smallpox vaccine.

2.1. Costs of treating cases of eczema vaccinatum and progressive vaccinia

The rare and multi-component nature of the published cases of eczema vaccinatum and progressive vaccinia prevented the ability to cost each case using a ‘top-down’ approach based on bundled payments or aggregate costs assigned to a diagnosis-related group, procedure or diagnosis using US-based sources like Centers for Medicare and Medicaid Services or Healthcare Cost and Utilization Project. Consequently, the approach taken in this paper...
was to outline the course of care for each case to the extent possible based on the published case reports and then to cost each element of care using a ‘bottom-up’ approach. US-based costing sources were utilised, supplemented by literature where necessary. Without access to each patient’s chart or medical coders, precise estimates of the true cost of each individual case were impossible. In light of this, educated and conservative assumptions were used where necessary, and efforts were taken not to over-estimate the cost of each case. All assumptions and cost sources were documented. In mapping out the course of care for each case, all care components were separated into four primary categories: hospitalisation days, laboratory tests, drugs and procedures.

### Table 1. Total costs (2012 USD) of replicating and non-replicating smallpox vaccines.

| Vaccine | Replicating | Non-replicating | Cost to budget holder per vaccine $ |
|---------|-------------|-----------------|-------------------------------------|
|         | Replicating | Non-replicating |                                      |
|         | $4.85       | $57.00          | 1                                   |
|         | $28.50      |                 | 2                                   |
| Administering vaccine | $28.61 | $28.61 | 3 |
| Training (per day) | $0.001 | $0.29 | 2 |
| Screening | 105% | 0.00 | 4 |
| Vaccination visit | $28.61 | $28.61 | 5 |
| Vaccination site care | 1 | 0.29 | 6 |
| Follow-up visit | $28.61 | $28.61 | 7 |
| Revaccination | $60.07 | $2.76 | 8 |
| Medical treatments of AEs | $10,000 | $0.80 | 9 |
| Eczema, progressive vaccinia, severe generalised vaccinia, inadvertent inoculation | $0.00008 | $0.80 | 10 |
| Cardiac AE | N/A | $14.13 | 11 |
| Non-cardiac SAE | $42.93 | $4.24 | 12 |
| Non-serious AE | $109.86 | $1.10 | 13 |
| Reimbursed loss of income due to death | $349,911 | $8.75 | 14 |
| Compensation due to death | 25 per mill. | $8.75 | 15 |
| Total cost | $138.87 | $114.77 | 16 |

Notes: 1. Available pricing quotes of ACAM2000 (replicating, single dose needed) and Imvamune (non-replicating, 2 doses needed). ACAM 2000 cost per dose calculated from contract total (http://www.fiercebiotech.com/press-releases/425m-ten-year-acam2000-smallpox-vaccine-contract-awarded) assuming: 9 million vaccines/year over 8 years; 2/3 of contract ($425MM) relates to delivery of doses. Imvamune cost per dose (Edison ADR update 24 September 2014, exhibit 4). 2. A full day of training is assumed prior to managing a replicating vaccine. Each vaccinator then immunises 1000 individuals on average. Federal Bureau of Labor Statistics. Labor Rate SOC code 29-0000 Healthcare Practitioners and Technical Occupations. Mean hourly wage $35.93. 3–4, 6. Assumes the same hourly wage cost regardless of procedure (first and second vaccination visit, follow-up and revaccination). Current Procedure Terminology (CPT) 90471 Immunisation administration for vaccines $25.39 and CPT 95144 Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy $2.22, total $28.61. http://www.nd.gov/dhs/services. An assumed 4% of patients need revaccination. Dressing was changed every 3rd day for 30 days; 5 by 7 cm Polyskin II transparent dressing; Kendall box with 100 pcs. $69.99 (ref americandiabeteswholesale.com). 5: Dressing was changed every 3rd day for 30 days; 5 by 7 cm Polyskin II transparent dressing; Kendall box with 100 pcs. $69.99 (ref americandiabeteswholesale.com). 6. Assumes the same hourly wage cost regardless of procedure (first and second vaccination visit, follow-up and revaccination). Current Procedure Terminology (CPT) 90471 Immunisation administration for vaccines $25.39 and CPT 95144 Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy $2.22, total $28.61. http://www.nd.gov/dhs/services. An assumed 4% of patients need revaccination. 7: Only applies to replicating vaccine: unit cost is the sum of cost for vaccination visit, vaccination site care and follow-up visit. Assumes 100% take on re-vaccination. 8: 2.5 dosages of 42 ml (70 kg bodyweight) VIG used in 33 cases per million vaccines. Source: Chemical Biological Defence Program. Fiscal year 2009 budget estimates. 9+11: based on calculations from ortega-Sanchez et al. (2008) and from casey et al. (2005). No cases of myocarditis have been linked to IMVAMUNE®. WHO (2013), Summary report on first, second and third generation smallpox vaccines and elizaga et al. (2013). In contrast, the cost of a replicating vaccine (Dryvax, ACAM2000 or LC16m8) was $5 (Fierce Biotech, 2008) per dose, and should be administered in a single procedure of scarification, which necessitates initial screening, specialised training of staff, prolonged dressing and subsequent clinical inspection of a ‘tack’ (scab formation) to ensure adequate protection, followed by revaccination in 4% of cases (Nalca & Zumbrun, 2010). In contrast, the cost of a non-replicating vaccine dose (IMVAMUNE) was $29 (USA Spending.Gov, 2014), and should be administered twice as an intramuscular injection with no need for

### 3. Results

#### 3.1. Cost of vaccines

The cost of a replicating vaccine (Dryvax, ACAM2000 or LC16m8) was $5 (Fierce Biotech, 2008) per dose, and should be administered in a single procedure of scarification, which necessitates initial screening, specialised training of staff, prolonged dressing and subsequent clinical inspection of a ‘tack’ (scab formation) to ensure adequate protection, followed by revaccination in 4% of cases (Nalca & Zumbrun, 2010). In contrast, the cost of a non-replicating vaccine dose (IMVAMUNE) was $29 (USA Spending.Gov, 2014), and should be administered twice as an intramuscular injection with no need for
The total estimated costs of treating the case of eczema vaccinatum, as described in the case report, was $133,898. This consisted of hospitalisation costs of $126,158 (94%), lab costs of $3817 (3%), drug costs of $557 (0.42%) and procedure costs of $3366 (2.5%). All costs are in 2012 US$.

The total estimated costs of treating the case of progressive vaccinia, as described in the case report, was $322,165. This consisted of hospitalisation costs of $205,663 (64%), lab costs of $31,974 (10%), drug costs of $80,590 (25%) and procedure costs of $3938 (0.01%). All costs are in 2012 US$.

3.4. Cost of reimbursed loss of income to vaccinated personnel experiencing AEs

The number of days missed from work was calculated as the sum of the proportion of reported cardiovascular AEs of total public health responders vaccinated times the proportion of vaccinees absent from work due to a cardiac AE times the number of days missed from work, as reported by Ortega-Sanchez et al. (2008). The cost of time missed from work was calculated using hourly earnings reported by the US Bureau of Labor Statistics for the general population (Bureau of Labor Statistics, 2016).

3.5. Compensation due to disability or death due to AEs

This was calculated as the incidence of death among vaccinees (Casey et al., 2005) times the official compensation rate (Public Safety Officer’s Benefits Program, 2016) multiplied by the number of immunised subjects.

As referenced in Table 1, the total cost of immunising one person using a replicating vaccine such as ACAM2000 was $139, while using a non-replicating vaccine (IMVAMUNE) cost $115.

4. Discussion

Calculating the overall cost of immunisation requires adding a number of components such as cost of vaccine, staff labour, medical treatment of AEs, reimbursement, compensation and loss of productivity to provide policymakers with a fair basis for identifying the most cost-effective option.

One such example involves the US National Association of County and City Health Officials, which worked during January–March 2003 with nine diverse local public health agencies to define the costs incurred in planning and implementing the smallpox vaccination programme (Brown, Randall, & Ransom, 2013). The actual and estimated costs reported by these agencies for implementing the three key components of the programme using a
A replicating vaccine: community mobilisation and preparation; vaccination clinics; and follow-up care and surveillance ranged from $154 to $284 per person vaccinated, with a mean of $204 per person. This did not include the cost of the vaccine. As explained, some of these costs would also apply to a non-replicating vaccine.

When conducting an updated analysis comparing different vaccine candidates, it was therefore expected that the cost of each successful immunisation would come to a substantial amount, and the cost of the vaccine itself would only represent a fraction of the overall cost. This was also demonstrated in another study in which non-vaccine costs constituted the major cost component, such as monetary expenses (e.g. travel cost, over-the-counter medication, etc.) and productivity losses (e.g. temporal disability, permanent disability and premature death) (Brown et al., 2013). The present findings corroborate this observation and furthermore outline the relative contribution of each component to the total cost of immunisation as it compares replicating and non-replicating smallpox vaccines for the first time (Figure 1).

Estimates based on case reports of the total cost associated with care for a single case of eczema vaccinatum was ~$134,000 and progressive vaccinia was ~$322,000; both of these cases required extensive clinician involvement and significant participation by experts from the Centers for Disease Control and Prevention (CDC) as well as other public health officials. Thus, when breaking down individual cost items it might be expected that treating SAEs such as eczema vaccinatum or progressive vaccinia, each of which are very costly, would markedly skew the results in favour of non-replicating vaccines. However, seen from a broader population perspective, the contributions from treating general AEs ($0.80), cardiac AEs ($14.13), non-cardiac SAEs ($4.24) and non-serious AEs ($1.10), which are of primary concern when using replicating vaccines, only amount to approximately $20 per vaccinee (Table 1). It is important to note that in the event of a large-scale vaccination campaign it is possible that the AEs associated with the replicating smallpox vaccines will overwhelm available health care capabilities leading to greater costs and increased morbidity and mortality.

Overall, the analysis indicates that the main cost component differences (Table 1 and Figure 1) of replicating and non-replicating vaccines are made up of the need for screening ($28), follow-up visit ($28), AEs ($20), reimbursement ($9) and compensation ($9) when using replicating vaccines. These costs are almost perfectly balanced against the higher cost of goods ($57), reduced productivity loss and the need for an extra vaccination visit ($28) when using a non-replicating vaccine.

Cost-offsets, i.e. cost-saving relevant to the policy-maker due to improved health outcomes, are typical elements of the economic product value. Cost-offset due to fewer AEs of an innovative drug is one such example and will be important to the health care decision-maker, because the costs of the traditional drugs typically accrue in parallel to paying for the (additional) cost of the new drug. Moreover, treatment, including VIG, a rare and
expensive product that countries must stockpile before starting any vaccination programme, must also be considered.

The availability of a safe and efficacious non-replicating smallpox vaccine should be viewed as a supplement to existing replicating vaccine stockpiles, as the unique safety profile allows protection of the sizeable proportion (constituting 5–25% in a pre-event scenario) of the population that are not eligible for receiving replicating vaccines due to immunodeficiency, or skin disorders like eczema. According to CDC guidelines, there are no absolute contraindications to replicating vaccines in the post-exposure scenario. Most of this analysis deals with the post-exposure scenario, and pre-exposure scenarios may change use and policy implications, as well as cost estimates. Accordingly, non-replicating vaccines hold a particular operational advantage in pre-exposure settings as they may be used indiscriminately.

Thus, the composition of national smallpox vaccine stockpiles should be guided by the technical performance and operational applicability balanced against the total cost of available vaccines. Therefore, senior government leaders will be forced to weigh scientific, epidemiological and political realities and make difficult choices to reduce morbidity, mortality and public unease (Bice & Yeskey, 2015).

The prevalence of eczema, or immune deficiencies have escalated since the smallpox eradication campaign of the 1960s. For example, the current rate of atopic dermatitis is approx. 20%, up from 3% in 1960 (DaVeiga, 2012). Furthermore, the herd immunity against smallpox is significantly reduced while more people are immune-compromised leading to greater vulnerability in the population. As a result, in a modern-day scenario, significant numbers of SAEs associated with traditional replicating vaccines should be anticipated in the event of a smallpox outbreak. These SAEs will present significant practical, logistical and ethical challenges for the public health system and will result in significant morbidity and mortality throughout the population.

As outlined by this investigational paper, although the initial procurement cost of the non-replicating vaccine IMVAMUNE® is approximately 12 times higher than replicating vaccines, such as ACAM2000, the overall costs of an active immunisation programme are rather comparable, with IMVAMUNE® representing a marginally cheaper option.

5. Conclusions

Smallpox vaccination using traditional replicating smallpox vaccines is associated with significant additional expenses not reflected in the cost of the vaccine alone. These additional expenses are not associated with non-replicating smallpox vaccines and when the complete expense of an active smallpox vaccination programme is considered, product costs represent a minor component.

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