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Modernizing stockpiles of medical countermeasures against smallpox: Benefits, risks, and knowledge gaps

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Abstract

Objective: *New smallpox medical countermeasures are entering the marketplace, offering the opportunity to modernize existing stockpiles. However, new smallpox countermeasures are developed under the animal rule, meaning that human efficacy data are lacking, and human safety data may be limited. Also, stockpile modernization would require prioritization of increasingly limited public funds. Approaches to address these issues are needed.*

Methods: *Smallpox vaccine data were gathered by literature search. The financial value of vaccination in the face of an outbreak was evaluated using a threat-based cost/benefit analysis model, involving i) estimation of the efficacy of new smallpox vaccines based on available clinical data on virus-neutralizing seroconversion in vaccinees, ii) estimation of the likelihood for a smallpox outbreak in Denmark, and iii) estimation of the expected life-saving effects of postevent vaccination.*

Results: *The authors estimated that i) the likelihood of a smallpox outbreak in Denmark is very low (one event in 200,000 years), ii) the expected efficacy of currently available and new vaccines is 95 and 75 percent, respectively, iii) the expected frequency of serious side effects from vaccination is between 100 and 10,000 fold lower for new than for existing vaccines, depending on modes of action.*

Conclusions: *Despite the very low likelihood for a smallpox outbreak, the potentially large consequences combined with the protective effect of vaccination make maintenance of the smallpox vaccine stockpile justified and valuable. For vaccination in the face of a smallpox outbreak, a high efficacy rather than a lowered rate of adverse effects would maximize the number of lives saved.*

Key words: health security, medical countermeasures, smallpox, bioterrorism, risk/benefit assessment

Introduction

The 9/11 terrorist attacks and the anthrax letter incidents in 2001 brought biopreparedness issues to the international agenda. One of the anthrax letters was estimated to have contained in excess of a million lethal human doses,[1] illustrating the destructive potential of biological weapons. From around 2001, international biological threat preparedness activities were thus intensified, to a large extent focused on smallpox virus.

We are now beginning to see the drug development results from this effort: in 2013, a so-called third-generation (strongly attenuated) smallpox vaccine received marketing authorization in the European Union and Canada, and small-molecule antiviral drugs are expected to gain regulatory approval during the next 5 years.[2,3]

The availability of new vaccines, as well as the expected availability of new antivirals in the medium future, provides an opportunity to modernize existing stockpiles, as well as the national response plans describing stockpile use. Yet purchasing decisions for stockpile modernization involve prioritization of necessarily limited public funds, and changes to national response plans affect public health security. To support such decision making and prioritizing, we suggest here a threat-based cost/benefit analysis scheme, based on estimation of the likelihood of a smallpox

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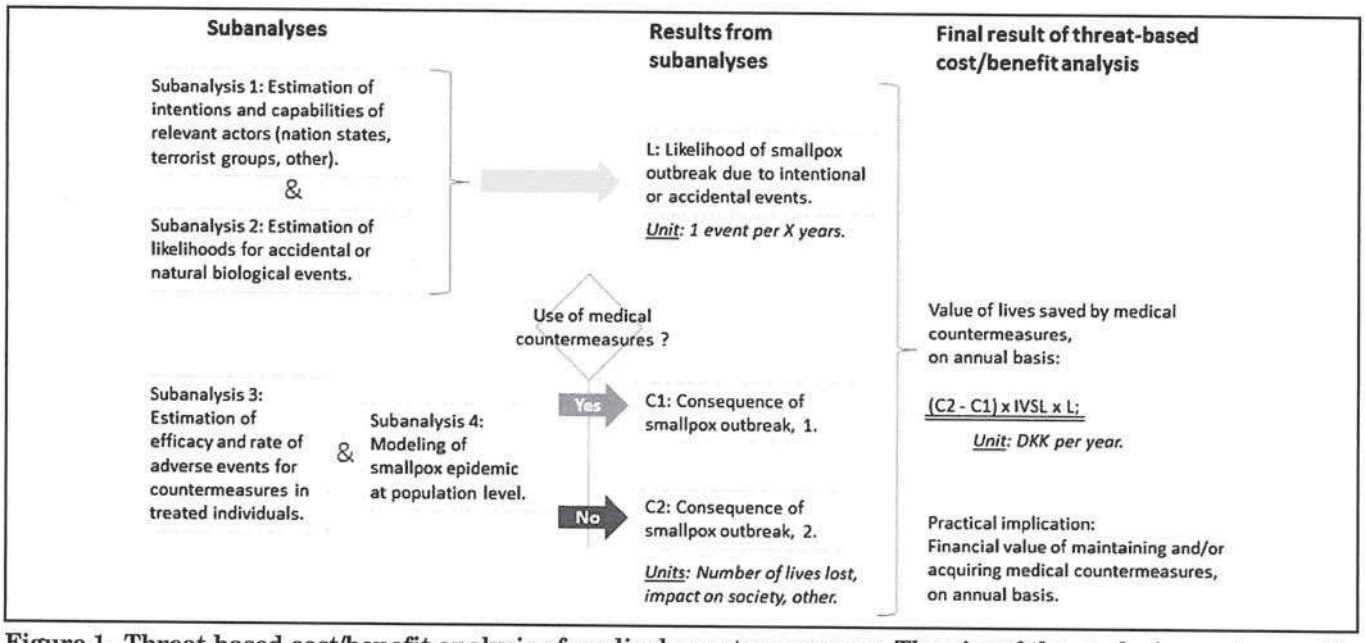

Figure 1. Threat-based cost/benefit analysis of medical countermeasures. The aim of the analysis was to provide a concrete financial estimate for the annual value of a countermeasure stockpile, which can guide decisions on expenditure on stockpile modernization or maintenance. Four subanalyses together formed the basis and provided the metrics for the final result, as indicated in the figure. The calculation example (formula on the bottom right) illustrates the calculation of the financial value of medical countermeasures using the inferred value of a saved life as sole metric. The analysis is generally applicable to any medical countermeasure. Acquisition costs and shelf life of the new countermeasures, as well as supply security and production capacity for the new countermeasures, are not relevant for and not included in the analysis. See text for details. L, likelihood of outbreak; C1, number of lives lost in outbreak with use of medical countermeasures; C2, number of lives lost in outbreak without access to medical countermeasures; IVSL, inferred (actuarial, statistical) value of a saved life; DKK, Danish kroner (currency unit).

outbreak, and estimation of the value of countermeasures applied in the face of the outbreak.

Methods

Threat-based cost/benefit analysis

The threat-based cost/benefit analysis was performed to support decision making regarding modernization of the Danish national stockpile of smallpox vaccine. The aim was that the analysis i) should be evidence based, ii) should as far as possible provide simple, numerical results, iii) should be as transparent as possible, and iv) should be clearly structured, thereby to a) allow review, challenge, and reproduction and b) facilitate use of the results in decision making.

The model used for the analysis is outlined in Figure 1; it involved estimation of the likelihood of a smallpox outbreak in Denmark and estimation of the value of different countermeasures applied in the face of the outbreak (Figure 1). To perform the analysis outlined in Figure 1, we used an expert group consensus-based process. The group was selected from personnel at the Danish Centre for Biosecurity and Biopreparedness, to cover the relevant expertises involved in the analysis.

To evaluate the likelihood of a smallpox outbreak in Denmark, the group first listed events that could lead to a smallpox outbreak in Denmark, and then assigned likelihoods to events, as well as intentions and capabilities of actors, as outlined in Figure 1. The data sources used for these assessments are listed in the notes of Table 2.

To evaluate the expected consequences of smallpox outbreaks, as well as expected effects of medical countermeasures, public-domain peer-reviewed scientific literature and public-domain regulatory documents

were used, as detailed in the references in the relevant sections in the manuscript text, combined with expert opinion (tacit knowledge) at the Danish Centre for Biosecurity and Biopreparedness, covering areas such as biopreparedness, biosecurity, drug development, assessment of medical countermeasures, and virology.

The analysis was performed over a time span of approximately 1 month, through October 2013. More information on the threat-based cost/benefit analysis is available on request from the authors.

Identification of knowledge gaps

During the threat-based cost/benefit analysis described above, several knowledge gaps of relevance for postmarketing cost/benefit analysis of new smallpox countermeasures were identified. These are detailed in the manuscript text.

Results

Safety and efficacy of first- through third-generation smallpox vaccines

The smallpox vaccines used in the World Health Organization (WHO) eradication campaign were live vaccines based on vaccinia virus, a virus sufficiently related to smallpox virus (variola virus) to induce strong cross-protective immunity. The vaccines were mainly produced in the skin of sheep, cattle, or other ruminants.[4,5] Vaccination with these vaccines was done by dermal scarification using a bifurcated needle or other transdermal techniques. Local replication of the vaccine virus led to development of a Jennerian pustule (dermal "take" reaction), and subsequently a small vaccination scar.

According to WHO potency standards, these vaccines were required to contain 10^8 (100 million) plaque-forming units per milliliter and cause "take" skin reactions, a marker of vaccination success, in 95 percent of primary vaccinees and 90 percent of those vaccinated 10 or more years ago.[4,5] In individuals without pre-existing immunity to vaccinia virus, protective immunity developed within 10-14 days following a single vaccine application,[6,7] and protection rate (efficacy) was estimated to be between 91 and 98 percent.[4] Immunity was long lasting, at least 5-10 years,[8-10] although revaccination was recommended at three- to five-year intervals.[11] Even if given up to 3 days after infection with smallpox, due to the high immunogenicity and rapid action, these vaccines are assumed to provide 80-90 percent protection or reduction of disease severity.[4,12]

The abovementioned efficacy and speed came at a cost: during the WHO smallpox eradication campaign, severe side effects of vaccination were described, such as postvaccination encephalitis, progressive vaccinia (vaccinia necrosum or gangrenosum), and eczema vaccinatum. The New York City Board of Health (NYCBH) strain was reported to cause approximately one to two vaccine-related deaths per million primary vaccinees (all vaccine-related adverse effects included),[13] with the adverse effect frequency being at least 10-fold lower in revaccinees.[14] For higher pathogenicity vaccine strains, the level of vaccine-related deaths may have been as high as 55 per million primary vaccinees.[13]

In the early-mid-2000s, Acambis developed a plaque-purified (clonal) vaccine based on the NYCBH strain (Dryvax, Wyeth), using a cell culture-based serum-free manufacturing process. The resulting vaccine is supplied in freeze-dried form and is termed "second generation" (ACAM2000).[15,16]

ACAM2000 proved not to have an improved safety profile,[15,16] and therefore there is at present still a need for smallpox vaccines with better safety profiles. Current third-generation vaccines are based on attenuated vaccinia viruses, such as modified vaccinia Ankara (MVA) (Table 1).[2,17-19] Third-generation vaccines are known to have a lower rate of adverse events than first- and second-generation smallpox vaccines.[2,18] However, clinical data on safety as well as efficacy biomarkers for such vaccines are very limited.[2,18] Also, the need for prime-boosting (two vaccine injections separated by 4 weeks, with full immunity 2 weeks after the second dose, ie, 6 weeks after the start of vaccination) has raised concern regarding the value of MVA-based vaccines in outbreak scenarios.[22,23]

In addition to the smallpox vaccines summarized in Table 1, other attenuated third-generation vaccines are being pursued, and subunit (fourth-generation)

Table 1. Smallpox vaccines

Vaccine name	Virus	Vaccine type	Manufacture process	Form of vaccine	Vaccination procedure	Vaccination causes cutaneous "take" (Jennerian pustule) reaction?	Shedding of live vaccine virus from vaccinees?*	Approval status
Wetvax (Sanofi Aventis)	Vaccinia virus, New York City Board of Health strain	First generation Live, replicating in humans	Bovine skin	Liquid	Skin scratch on a single occasion	Yes	Yes	Investigational new drug status at the FDA
ACAM2000 (Acambis, now Sanofi Pasteur)	Vaccinia virus, New York City Board of Health strain, plaque-purified	Second generation Live, replicating in humans	Serum-free conditions, Vero cells	Lyophilized	Skin scratch on a single occasion	Yes	Yes	Licensed in the United States by the FDA August 31, 2007
Imvanex, Imvamune (Bavarian Nordic)	Vaccinia virus, modified vaccinia Ankara (MVA) strain	Third generation Live, restricted in ability to replicate in humans	Serum-free conditions in primary chick embryo fibroblast	Liquid	Two subcutaneous injections given at least 28 d apart	No	No	Marketing authorization in 28 EU states, Iceland, Liectenstein, and Norway in 2013 (Imvanex). Approval in Canada 2013 (Imvamune) Investigational new drug status at the FDA
LC16m8	Vaccinia virus, attenuated form of parental Lister strain	Second-Third generation Live, restricted in ability to replicate in humans	Cell culture	Lyophilized	Skin scratch on a single occasion	Yes (mild)	Yes	Licensed in Japan from 1975 Investigational new drug status at the FDA

In addition to the vaccines listed in the table, individual countries stockpile live attenuated smallpox vaccines that can be used in emergency conditions.[20]

*Dermal vaccination with replicating smallpox vaccines leads to local replication of vaccine virus at the vaccination site. Vaccinees in fact shed live vaccinia virus from the dermal vaccination site, and transfer of vaccinia virus to contacts with skin conditions such as eczema can cause eczema vaccinatum, a generalized skin infection with vaccinia virus, which is usually self-limiting, but can in some cases be serious. Even under optimal conditions of hygiene of the skin vaccination site and counterscreening against individuals with skin conditions in the household of vaccinees, transfer of vaccinia virus to susceptible contacts occurs at a rate of 8-75 cases per million vaccinees.[21]

Table 2. Evaluating the likelihood of a smallpox outbreak in Denmark

Events that might lead to a smallpox outbreak in Denmark	Likelihood of event in one year	Likelihood of having the intention to use smallpox as a biological weapon*	Likelihood of having the capability to use smallpox as a biological weapon*	Likelihood of event affecting Denmark
Nonintentional				
Accidental escape from one of the two official smallpox repositories†	0.0002	NA	NA	0.01
Accidental escape from a clandestine laboratory or from a forgotten virus storage‡	0.00001	NA	NA	0.01
Introduction from historical/archeological sources‡	0	NA	NA	0.01
Re-emergence of smallpox virus from an animal reservoir§	0	NA	NA	0.01
*Intentional**				
National actor possessing clandestine virus stocks or recreating smallpox virus by de novo DNA synthesis	0.02	0.0005	0.25	1
National actor stealing virus from one of two official smallpox repositories	0.0001	0.000001	0.25	1
Terror group possessing clandestine virus stocks or recreating smallpox virus by de novo DNA synthesis	0.000001	0.001	0.05	1
Terror group stealing virus from one of two official smallpox repositories	0.00001	0.00001	0.05	1

All likelihoods in the table represent consensus-based expert opinions. Likelihoods of 0 represent events that are essentially not thought possible to happen. Likelihoods of 1 represent events that are thought essentially certain to happen.
The likelihood of a smallpox outbreak in Denmark was calculated by multiplying the likelihoods in the eight table rows and adding the products: $(0.0002 \times 0.01) + (0.00001 \times 0.01) + (0.02 \times 0.0005 \times 0.25) + (0.0001 \times 0.000001 \times 0.25) + (0.000001 \times 0.001 \times 0.05) + (0.00001 \times 0.00001 \times 0.05)$ = one event in 200,000 years (result rounded).
NA, not applicable. See text for additional details.
*Likelihoods for intentions and capabilities were estimated based on public-domain sources, intelligence assessments, and expert opinion and tacit knowledge by the Danish Centre for Biosecurity and Biopreparedness. The term "capability" covers technical expertise and infrastructure to manufacture, weaponize, and deliver the virus at a significant scale (infecting at least 100 people).
†The likelihood for this event was estimated based on publicly available historical laboratory biosafety track records.[25,26]
‡For example, it is a hypothetical possibility that individuals or laboratories working with smallpox before the disease was eradicated may have kept material that contains live virus. Also, it has been discussed whether live variola virus may be present in biological material that has survived from before the disease was eradicated, such as scab material, or bodies in the permafrost. The likelihoods for such events were estimated based on public-domain scientific literature.[27-29]
§The likelihood for this event was evaluated based on an assessment of the evolution and public health relevance of monkeypoxvirus.[30-38]

vaccines are also being explored. However, these are in less advanced stages of development. For excellent, recent reviews of the global smallpox vaccine development pipeline, see refs. 17,21, and 24.

Finally, it should be mentioned that new small-molecule anti-poxviral compounds such as Arestyvyr (Tecovirmat, ST-246) and others must be seen as potentially important supplements to smallpox vaccines.[3,17,22] However, the potential role and use of new small-molecule drugs in outbreak scenarios are as yet not well defined, and such drugs are therefore outside the scope of this article.

The likelihood of a smallpox outbreak in Denmark

In estimating the likelihood of a smallpox outbreak in Denmark, we used a threat-based approach (Figure 1). First, we listed events that could lead to a smallpox outbreak in Denmark. Such events were grouped in the main categories of "nonintentional" (accidental) and "intentional" (bioweapon use of smallpox). The events are listed in Table 2.

Second, for all events, we assigned likelihoods, using a scale where "very unlikely," "unlikely," "likely to a limited extent," "likely," and "very likely" events would be expected to occur once in a 100,000, 10,000, 1,000, 100, and 10 years, respectively (Table 2, column labeled "Likelihood of event in 1 year").

Third, for intentional events, we assigned likelihoods to intentions as well as capabilities of relevant actors such as nation states or terrorist groups to develop and use smallpox as a biological weapon (Table 2, columns labeled intention and capability, respectively, of the use of smallpox as a biological weapon). We defined "capability" as technical expertise and infrastructure to manufacture, weaponize, and deliver the virus at a significant scale (infecting at least 100 people).

Fourth, the likelihood was estimated that the smallpox outbreak would affect Denmark, intentionally (Denmark being the target of the attack) or accidentally (Denmark importing smallpox due to travel).

In estimating the abovementioned likelihoods, we calibrated them against one another, using for example the following rules of thumb: The likelihood of having the intention to use smallpox as a biological weapon was set higher for terror groups than for national actors. Conversely, the likelihood of having the capability to manufacture and deliver the virus was set lower for terror groups than for national actors. Nonintentional events were assumed by their nature to be unlikely to occur in Denmark but could reach Denmark by traveling activity. Intentional events were assigned a likelihood of 1 of affecting Denmark, because such events were assumed likely to target a large population at source of attack (and hence carry a high likelihood of spread to Denmark), and/or because such events were assumed more likely to target Denmark directly (see likelihood values in Table 2).

Finally, to calculate the current likelihood of a smallpox outbreak in Denmark, we multiplied the likelihood values in each of the eight rows in Table 2, and then added together the resulting eight separate products, reaching the conclusion that the current likelihood of a smallpox outbreak in Denmark is one event in 200,000 years (Table 2). Thus, an outbreak of smallpox in Denmark can be classed as "very unlikely."

Knowledge gaps in modeling the potential risks and benefits of new countermeasures

The epidemic spread of smallpox in today's susceptible populations can be modeled in silico, using parameters for disease development (such as duration of incubation period, time through the disease course when patients are infectious, and person-to-person transmission rate) obtained from epidemiological studies from before smallpox was eradicated.

Highly simplified, such computer modeling studies generally support that i) search and containment (contact tracing) is a powerful intervention, able to curtail and maybe even completely stamp out smaller smallpox outbreaks without vaccination and ii) vaccination with replicating smallpox vaccine has additional value in stamping out smallpox outbreaks, and the value is largest with targeted vaccination of individuals with known smallpox exposures (ring vaccination) and first responders.[39-44]

Yet not a single study has to our knowledge modeled vaccination with new, more highly attenuated

smallpox vaccines. One challenge here is to estimate the expected efficacy in humans, because smallpox as a natural disease is extinct, and clinical efficacy trials in humans are not possible. Instead, under Food and Drug Administration (FDA) guidance which is commonly known as the "animal rule," marketing approval may be obtained based on a combination of efficacy studies in animals and evaluation of surrogate efficacy markers in clinical trials.[45] Verifying that animal efficacy data translate to humans is particularly relevant for new smallpox vaccines, as variola virus naturally only infects humans, and even primate models with orthopoxviruses closely related to variola do not fully recapitulate human disease. Therefore, it is expected that approval of new smallpox vaccines, in addition to animal efficacy data, will be conditional on noninferiority clinical studies in humans, comparing the antigenicity of the new vaccine with the antigenicity of replicating smallpox vaccine identical or similar to the type of vaccine used during the WHO eradication campaign.[15] On one hand, it is not known whether antiviral antibodies, cell-mediated immune responses, or a combination of the two determines protection against smallpox in vaccinees. On the other hand, there is evidence to suggest that development of antibodies able to neutralize virus is important for protection against smallpox and may in fact be sufficient to protect against smallpox.[15,46-48] Thus, in practice, the development of virus-neutralizing antibody in human vaccinees is an important efficacy biomarker in the clinical testing of new smallpox vaccines.[2,15,46]

Using development of virus-neutralizing antibody as a surrogate efficacy parameter, and based on the clinical data in the public assessment report,[2] we estimate the upper bound for the efficacy of the new Imvamune (Imvanex) vaccine in healthy and vaccinia-naive individuals, following two prime-boost vaccine injections separated by 28 days,[49,50] to be approximately 75 percent. This estimate is based on the reported clinical neutralizing antibody seroconversion rates in vaccinia-naive individuals of 77-90 percent,[2] and the assumption that 90 percent of individuals exhibiting seroconversion would be protected.

Another challenge is to estimate safety, as clinical trials for new smallpox vaccines may be limited. Our approach here has been to separate known severe adverse effects to smallpox vaccination into those that require active replication of vaccine virus (eczema vaccinatum and progressive vaccinia), and those where autoimmune mechanisms cannot be ruled out (myocarditis/epicarditis and possibly postvaccine encephalitis). For the former type of adverse effect, we in our work currently assume that highly attenuated as well as subunit smallpox vaccines carry zero risk. For the latter type of adverse effects, we in our work currently assume that highly attenuated and maybe even subunit smallpox vaccines may have some risk, but that the frequency of adverse effects can be expected to be lower than with replicating vaccines, by a factor we currently assign sizes of between 100 and 10,000. These modeling assumptions are obviously temporary, pending more clinical data to elucidate these issues. For example, cardiac safety data are lacking for MVA-based vaccines.[2,51]

In summary, despite the inherent uncertainties in estimating efficacy as well as safety of new smallpox vaccines outlined above, we suggest that computer modeling of their use in the field in the face of outbreaks is possible as well as meaningful, and we suggest that such modeling studies would provide valuable data toward decision making on modernizing smallpox vaccine stockpiles. Finally, it should be mentioned that small-molecule antivirals provide potentially valuable alternatives or supplements to smallpox vaccines. However, the potential role of small-molecule drugs in smallpox preparedness has as yet only been examined in a single study.[22]

Estimating the potential value of vaccines in the face of a smallpox outbreak

In our estimation of the consequences of a smallpox outbreak in Denmark (population size 5.6 million), one "worst case" scenario considered was a coordinated attack involving relatively minor releases of smallpox virus in four major cities. Our current assumption, based on published modeling studies from other countries, is that the epidemic, if using only a search and containment strategy without any vaccination, could affect up to approximately 3 percent of the population,[39-44] that

is, 157,000 individuals, causing 30,000 deaths due to smallpox disease, assuming a 19 percent case fatality rate, reflecting residual immunity in the part of the population having received smallpox vaccination in childhood.

In the context of such a massive smallpox attack, a nationwide vaccination appears warranted. The current Danish smallpox vaccine stockpile consists of first-generation, replicating vaccine.[52] On the basis of the efficacy and adverse effect profile of such vaccines reported from the WHO eradication campaign (95 percent efficacy, 1-30 vaccination-related deaths per million vaccinees, depending on vaccine strain), we currently estimate that a nationwide vaccination campaign would result in a total of between nine and 180 vaccine-related deaths (total mortality for all vaccine-related adverse effects taking into account that up to 25 percent of individuals may have underlying conditions such as eczema predisposing to vaccination side effects).

For comparison, a mass vaccination of the US population with replicating smallpox vaccine was reported to be expected to cause approximately between 125 and 800 vaccine-related deaths; at the time of these estimates, the population size was approximately 280 million.[53,54]

Conversely, on the basis of the published modeling studies from other countries, we estimate that a nationwide Danish mass vaccination campaign with a replicating vaccine with 95 percent efficacy would reduce the number of smallpox cases from 157,000 to 40,000 or less, that is, the number of smallpox-related deaths in a mass vaccination scenario would be reduced from 30,000 to 7,000 or less.[39-44]

To assess the impact of a vaccine with lower efficacy, the simplest back-of-the-envelope calculation is that mass vaccination with vaccines with for example 95 and 75 percent efficacy would leave 5 percent versus 25 percent of the population unprotected, respectively, that is, a reduction in vaccine efficacy from 95 to 75 percent would translate to a fivefold increase in the susceptible (nonprotected) population. Published studies support that a nonlinear relationship between vaccine efficacy and caseload through the course of the smallpox outbreak is expected, such that relatively modest vaccine efficacy changes at the individual level can translate to approximately threefold smallpox caseload changes at the population level.[22,39] Thus, we estimate that in the above-mentioned scenario of a smallpox bioterror attack and mass vaccination, a vaccine with a 75 percent efficacy, even with essentially zero frequency of adverse effects as may be the case for Imvanex (Imvamune), would be expected to reduce smallpox-related deaths from 30,000 to 22,000 or less, that is, in fact save far fewer lives than replicating vaccine.[22,23,39] This calculation in fact likely overestimates the effect of vaccination, as the slow induction of protective immunity (the need for two injections of MVA-based vaccine) is not taken into account. The calculations and numbers discussed above are summarized in Table 3.

Estimating a reasonable level of investment in maintaining the Danish replicating smallpox vaccine stockpile

As discussed in the paragraph above, in the face of a smallpox outbreak, the high efficacy of replicating smallpox vaccine is expected by far to outweigh vaccination-related deaths. Further, the number of lives saved justifies a certain expenditure on maintenance of the vaccine stockpile (Figure 1). Using an actuarial value of a saved life as sole metric (eg, 10 million Danish kroner, or approximately 1.7 million USD), the net financial gain from the use of replicating vaccine in the outbreak scenario discussed above can be calculated as $(30{,}000 - 7{,}000 - 180) \times 10{,}000{,}000 = 228$ billion DKK (30,000: estimated number of deaths in outbreak without access to smallpox vaccine; 7,000: estimated number of deaths in outbreak using replicating smallpox vaccine and mass vaccination; 180: number of vaccine-related deaths; see also Figure 1). The reasonable yearly level of investment in maintaining the Danish replicating smallpox vaccine stockpile can thus be estimated to be approximately 228 billion DKK/200,000 years = 1.14 million DKK per year or approximately 200,000 USD per year (200,000: the likelihood of a smallpox outbreak in Denmark is estimated as one in 200,000 years; see also Figure 1).

Table 3. Evaluating the potential value of vaccines in the face of a smallpox outbreak				
	Number of smallpox cases due to the outbreak	**Number of smallpox deaths due to the outbreak**	**Number of deaths due to severe side effects from vaccination**	**Number of lives saved compared to scenario 1**
Scenario 1: Isolation and quarantine of cases, without any vaccination	157,000	30,000	Not applicable	Not applicable
Scenario 2: Isolation and quarantine of cases combined with vaccination of the whole population with replicating vaccine	40,000	7,000	9-180	23,000
Scenario 3: Isolation and quarantine of cases combined with vaccination of the whole population with MVA-based vaccine	118,000	22,000	0	8,000

The table compares population-wide, postevent vaccination with replicating vaccine and MVA-based vaccine, following a hypothetical situation of intentional release of smallpox virus in four major Danish cities. The values for scenarios 1 and 2 were based on published data for adverse effects for replicating vaccines,[13,14] and on extrapolating published epidemiological modeling studies from other countries to Denmark.[39-44] The values for scenario 3 were generated by simple calculus, based on an estimated 75 percent third-generation vaccine efficacy, and not taking into account the slower protection by third-generation vaccines compared to replicating vaccines (4-6 wk vs 10-14 d, respectively). See text for details.

Discussion

The aim with this study was to provide a financial estimate for the reasonable level of investment in maintaining and modernizing the Danish smallpox vaccine stockpile. For this, we used a threat-based approach, that is, an approach where the likelihood of a smallpox outbreak directly influences the suggested reasonable level of annual investment in a smallpox countermeasure stockpile (Figure 1). Thus, acquisition costs and shelf life of the new countermeasures, as well as supply security and production capacity for the new countermeasures, were not relevant for and not covered by our analysis. A discussion of these issues was recently provided by Henderson.[23]

We focused on smallpox vaccines, and excluded from analysis new small-molecule anti-poxviral compounds such as Arestyvyr (Tecovirmat, ST-246) and others, which must be seen as potentially important supplements to smallpox vaccines.[3,17,22] However, essentially no consensus as yet exists on the use of anti-poxviral compounds in smallpox outbreak scenarios, for example, whether such drugs are relevant for large-scale prophylactic use similar to vaccines, or would be limited to select indications (eg, therapeutic use in smallpox patients, or therapeutic use in individuals experiencing serious adverse effects of replicating smallpox vaccine). In our opinion, such unknowns currently made it impossible to include these drugs in our analysis. In any case, in contrast to third-generation vaccines, no small-molecule anti-poxviral compound has as yet obtained EU marketing authorization. It can be hoped that the unknowns mentioned above will be resolved as the drugs approach market.

To our knowledge, this is the first publication to propose strategies to assign efficacy and safety values to MVA-based smallpox vaccines. Even though new smallpox countermeasures are developed under the animal rule (see main text), it is clear that estimates of

smallpox vaccine efficacy in humans cannot rest solely on animal data but must include efficacy-related endpoints (biomarkers) from clinical trials. Using reported seroconversion rates in virus-neutralization assays in clinical trials[2] as a surrogate efficacy parameter, and assuming that 90 percent of individuals seroconverting in virus-neutralizing assays following vaccination would be protected, we estimate that in healthy individuals without preexisting immunity to vaccinia virus, the upper bound for the efficacy of the new Imvamune (Imvanex) vaccine following two prime-boost vaccine injections separated by 28 days to be approximately 75 percent. Based on limited clinical data from human immunodeficiency virus-positive patients with CD4 counts in the range 200-750,[2] efficacy estimated by reported seroconversion rates in virus-neutralization assays could be as low as 57 percent. Many uncertainties are inherent in such efficacy estimates, for example, whether protective immunity in humans is mediated by antibody, cell-mediated responses, or a combination of both. Also, the levels of virus-neutralizing antibody required to provide protection against smallpox in humans is not known; however, titers of>32 (1:32 dilution of plasma giving a 50 percent reduction in plaque-forming units) have been suggested to be likely to be protective.[15] Imvamune was administered side-by-side with Dryvax (a replicating vaccine used during the WHO eradication campaign) in a clinical phase I trial.[55] However, study limitations did not allow conclusions to be drawn regarding whether the virus-neutralizing antibody responses induced by Imvamune were comparable to those induced by Dryvax, and a key phase III noninferiority study with Imvamune and ACAM2000 is planned.[2] Finally, it should be mentioned that after the submission of this manuscript, an updated clinical guidance for smallpox vaccine use in a postevent scenario was published by the CDC.[56] However, the guidance does not contain concrete estimates for the expected efficacy of third-generation smallpox vaccines.

As explained in the text, we currently estimate that in an outbreak scenario, high efficacy and rapid effect of smallpox vaccines are likely to be paramount in terms of saving lives. This estimate is based on a simple calculus where published epidemiological modeling studies from other countries were extrapolated to Denmark (see section "Estimating the potential value of vaccines in the face of a smallpox outbreak"). Thus, this estimate should be refined using more advanced modeling approaches. For more advanced modeling approaches, we believe the strategies to assign efficacy and safety values to third-generation smallpox vaccines described in this article should be valuable. Also, modeling studies are needed of the value of vaccines requiring two prime-boost injections in the face of an outbreak. However, it should be mentioned that our conclusions are in line with other studies.[23]

The estimation of the likelihood of a smallpox outbreak in Denmark was based on an expert group consensus-based process, which we believe are commonly accepted for risk evaluation, and essentially the only possible approach in this case.[57] Such approaches are unavoidably subjective. Yet our estimate that the likelihood of such an event is one in 200,000 years (Table 2) is essentially in agreement with similar estimates for the United States.[58]

Finally, the reasonable level of investment in maintaining the Danish smallpox vaccine stockpile was calculated from the subresults discussed above, using a threat-based cost/benefit, which we believe is applicable to any medical countermeasure approach (Figure 1). The reasonable level of investment in maintaining the Danish smallpox vaccine stockpile calculated here likely underestimates the value of stockpile maintenance and modernization, as the actuarial value of a saved life was used as sole metric, and other costs associated with a large smallpox outbreak were not included in our example calculation.

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