Comparison of smallpox outbreak control strategies using a spatial metapopulation model

I. M. HALL, J. R. EGAN*, I. BARRASS, R. GANI AND S. LEACH

Microbial Risk Assessment, Health Protection Agency, Centre for Emergency Preparedness and Response, Porton Down, Wiltshire, UK

SUMMARY

To determine the potential benefits of regionally targeted mass vaccination as an adjunct to other smallpox control strategies we employed a spatial metapopulation patch model based on the administrative districts of Great Britain. We counted deaths due to smallpox and to vaccination to identify strategies that minimized total deaths. Results confirm that case isolation, and the tracing, vaccination and observation of case contacts can be optimal for control but only for optimistic assumptions concerning, for example, the basic reproduction number for smallpox ($R_0 = 3$) and smaller numbers of index cases (~ 10). For a wider range of scenarios, including larger numbers of index cases and higher reproduction numbers, the addition of mass vaccination targeted only to infected districts provided an appreciable benefit (5–80 % fewer deaths depending on where the outbreak started with a trigger value of 1–10 isolated symptomatic individuals within a district).

INTRODUCTION

Given that the re-introduction of smallpox into any modern population could have profound impacts on public health many countries have developed contingency plans for such an event [1, 2]. For several countries this has included vaccine stockpiling, and the vaccination of key workers, particularly in health care and the military [3, 4]. Following the detection of smallpox in a population, contingency plans include the rapid isolation of clearly symptomatic cases and the tracing, vaccination and observation of the contacts of those cases. Supplementary to these interventions authorities may also decide to pre-emptively vaccinate some larger part of the population. Vaccination strategies for smallpox, however, are not straightforward, since most vaccines stockpiled are based on those developed during the earlier eradication programme and carry relatively high rates of adverse events, including fatality [5, 6]. Depending on the vaccine, estimates of vaccine-related fatality vary. For the Lister–Elstree vaccine used in much of Europe, fatality rates have been reported to be ~ 3–10 per million primary vaccinees [7–11] (lower in secondary vaccinees) and for the US New York Board of Health vaccine ~ 1–2 per million primary vaccinees [11–13]. Higher vaccine fatality rates than these have been reported from more localized outbreak controls [14]. Based on contemporary studies of volunteer vaccinees in the United States [3], others [15] have suggested higher vaccine fatality rates should be

* Author for correspondence: Mr J. R. Egan, Microbial Risk Assessment, Health Protection Agency, Centre for Emergency Preparedness and Response, Porton Down, Wiltshire, SP4 0JG, UK.
(Email: joseph.egan@hpa.org.uk)

applied, although the justification for this would require a high degree of conservatism, since the number of deaths (due to myocardial infarction) observed were no more than might be expected from a matched unvaccinated cohort [4, 16].

It is notable, however, in a number of the outbreaks documented from the past that more targeted approaches were occasionally supplemented by wider vaccination [17, 18]. This was usually targeted to the geographic area around the outbreak, and rarely expanded to include the whole country. We have commented previously on this expanding vaccination effort through reference to outbreak control in Edinburgh in 1902–1903 and Liverpool in 1942 [14]. A number of contemporary contingency plans also make reference to the potential for switching from more targeted approaches to wider vaccination [1, 2]. This point is raised elsewhere [19] with relation to developing criteria for switching between smallpox control options. The possibility of geographically widening vaccination efforts around cases has also been addressed very recently in an individual-based micro-simulation model [15]. The results showed that expanding vaccination efforts to include an area around each case that was of the order of 15 km radius was likely to result in a number of vaccine-related deaths (and other complications) greater than the number of deaths prevented, especially when assuming the higher adverse events rates that have been extrapolated from the recent US study [3].

We, however, posed the question whether a similar strategy targeted to populations living within administrative districts that have cases would provide an advantage over an approach based purely around targeting contacts of cases. Further, we posed the question of what might be meaningful triggers for a change between approaches, to include either district or nationwide mass vaccination. To address these questions we implemented a stochastic metapopulation framework [20] for Great Britain, in order to be able to model such controls. This has been built and parameterized in a way that is analogous with published models, with the spread of infection between districts given by known measures of population movement, which varies with geographic location. We incorporate public health controls in line with published contingency plans [1, 2] such as case reporting, finding and isolation, and contact tracing, vaccination and observation. In addition, the model also has a trigger set so that once the number of cases reaches some threshold level in any district then all of those individuals without contraindications living in that district can be pre-emptively vaccinated. The model has been run for a wide range of scenarios to determine the potential relative benefit of different values of this trigger, with extensive sensitivity analysis to take account of uncertainty regarding potential parameter assignments. For the purposes of this study we compare only deaths due to smallpox and those due to vaccination (it is recognized that this does not account for all adverse events).

METHODS

Model formulation

Here we discuss the stochastic metapopulation model [20] consisting of the 459 districts of Great Britain in 1991 (see Appendix for an explicit mathematical description). The connection between districts is given by that year's census travel to work data (www.statistics.gov.uk). This is the best available dataset to parameterize regular national population movements [15] and was varied in sensitivity analysis. For half a day people are assumed to be in their work district and for half a day they are in their home district. The probability of a case leaving a disease state over a half day time step was treated as a binomial event and disease transmission events as Poisson processes. For transmission within districts, our basis is the compartmental model formulated by Gani & Leach [21] with supplementary disease phases and extra interventions.

The non-infectious latent period of the disease is 12·0 days [22], then for 2·5 days cases have prodromal symptoms and are mildly infectious [23], while for the final 8·6 days cases are symptomatic and highly infectious [24]. Thereafter, cases have a 30 % probability of death or they recover and are immune [17]. For our baseline scenario cases infect, on average, five people [21], (i.e. $R_0 = 5$), 10 % of which are infected during the prodromal period [23, 25]. We permit R_0 to be doubled briefly until the authorities are aware of an outbreak, since in the past this doubling has frequently been observed, due largely to hospital-acquired infections [17, 21, 26]. We also allow for the fact that overtly symptomatic cases are likely to be incapacitated and unlikely to travel. Thus, we assume the movement rate of symptomatic cases between districts is reduced by 90 %. Although recent studies suggest that some protective immunity remains in the population from previous vaccination [27, 28], the

current level of immunity to infection is uncertain [21, 29] and the net effects of residual immunity are difficult to assess [19]. Given the length of time since the end of the eradication programme immunity to infection has been assumed conservatively to be zero.

Targeted public health interventions

For the purposes of this analysis an unintentional, or covert terrorist, release of smallpox has been assumed (an overt attack would result in the prompter instigation of interventions and an outbreak that would be likely to be more readily contained). Only when a certain number of cases with the symptoms characteristic of smallpox (assumed to be four) have been reported will an alarm be raised. Once this threshold has been reached in Great Britain as a whole, the model triggers baseline interventions. We define these to be the isolation of identified cases and the tracing, vaccination and observation of their contacts. Waiting for a fixed number of symptomatic cases to appear, rather than a fixed period of time after initial infection, allows for the timing of interventions in the model to scale more reasonably with the initial number of cases, which is important for our sensitivity analysis.

For case isolation, each individual that becomes overtly symptomatic is either discovered or self-reports with some probability (0·9) and is put into an isolated state (for longer than the expected infectious period); otherwise they remain infectious in the community [21]. The isolation of symptomatic cases does not alter their probability of death (0·3), but does prevent further infections. Contacts are explicitly attributed to each case, with a probability of having been infected (0·1) [21] and a probability of being traced (0·8 in the baseline scenario). Traced contacts are vaccinated and kept under observation for longer than the sum of the expected latent and prodromal periods. Uninfected traced individuals then move either into the vaccinated group with a probability dependent on vaccine efficacy (0·975) [22] or back to the susceptible population. Infected traced individuals also enter the vaccinated group with a probability dependent on a reduced vaccine efficacy for infected cases (0·3) [17], otherwise they go on to develop the disease but are under observation. In addition, they are isolated on becoming symptomatic and assumed to cause no further infections. Untraced uninfected contacts remain susceptible and mix freely with the rest of the community; while untraced infected contacts develop the disease in the community causing infections until they are isolated as symptomatic cases.

Mass vaccination

Here we consider the mass vaccination of districts in which there was a prerequisite number of symptomatic cases in isolation, defined as Q_{delay}. This parameter has been systematically varied to determine the value of mass vaccination over baseline interventions by potentially reducing the total number of deaths (note that setting $Q_{delay} = 0$ means that nationwide mass vaccination is implemented).

All traced contacts of cases are vaccinated regardless of contraindication because of the greater potential risk from smallpox than from the vaccine. However, for mass vaccination, only a proportion of the population is offered vaccine since those contraindicated could not justifiably be vaccinated in this context and also a number might refuse. Thus, the susceptible population enters one of two states, those that can be vaccinated (assumed to be 70% [2, 5]) and those that cannot. If mass vaccination is implemented, those that can be vaccinated are removed from the susceptible population at a constant rate dependent on the time it would take to vaccinate either the whole country (7 days) or individual districts (3 days). These values are broadly consistent with current objectives in published contingency plans [2]. Changing the length of the time required to complete mass vaccination by a few days has negligible effects on the results as long as the time period remains within the order of the generation timescale of the disease. Despite excluding contraindicated individuals from vaccination, adverse reactions, including deaths, are assumed to occur at some rate. Vaccine-induced fatality has been varied around values supported by historical data during the eradication campaign, from one per million as per the US New York Board of Health vaccine [11–13] to ten per million (the upper end of values reported from the Lister–Elstree strain [7–11]).

RESULTS

Comparison of a nationwide mass vaccination strategy against baseline interventions

Starting with baseline scenario assumptions with ten initial newly latent individuals (index cases), we
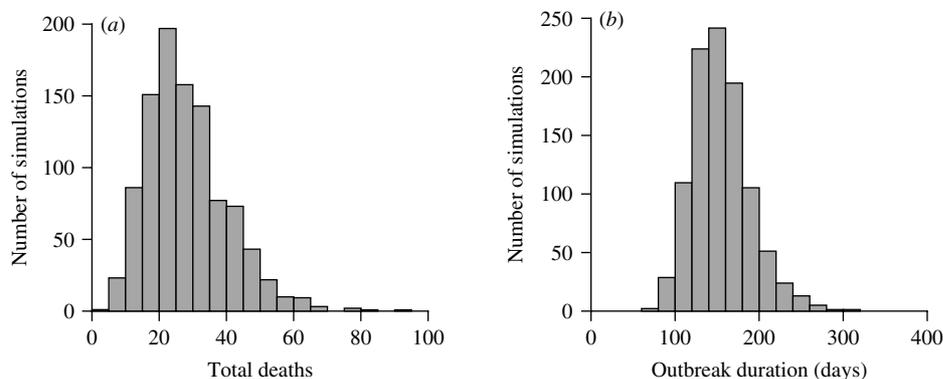
Fig. 1. Histograms of (*a*) total deaths assuming a zero vaccine fatality rate and (*b*) outbreak duration (resulting from baseline interventions for outbreaks starting in the City of London with ten index cases).
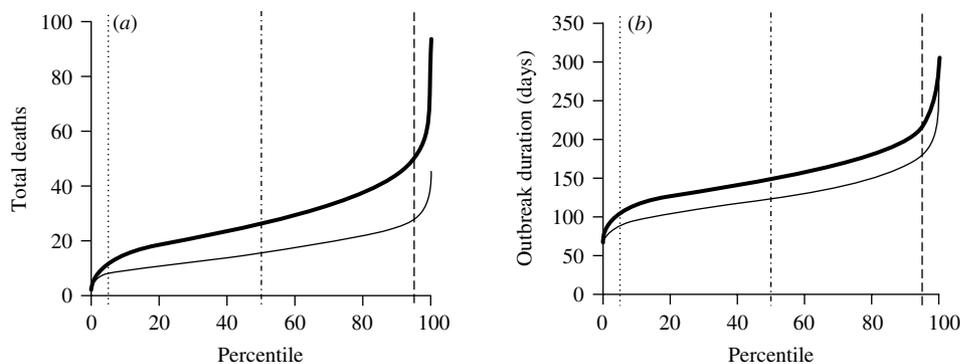
Fig. 2. Distributions of (*a*) total deaths assuming a zero vaccine fatality rate and (*b*) outbreak duration [resulting from baseline interventions (thick black line) and nationwide mass vaccination (thin black line) for outbreaks starting in the City of London with ten index cases]. Dotted line, 5th percentile; dashed line, 95th percentile; dotted/dashed line, median.

simulated 1000 smallpox epidemics starting in the City of London implementing baseline interventions alone. Outbreaks varied considerably in both the distribution of total deaths, D_∞ (median 27, range 3–93), assuming a zero vaccine fatality rate and the distribution of outbreak duration, X_∞ (median 151 days, range 67–305), but were generally quite small (Fig. 1).

We simulated a further 1000 smallpox epidemics with the addition of nationwide mass vaccination ($Q_{delay} = 0$). Still assuming a zero vaccine fatality rate we derived the distribution of total deaths, D_0 and the distribution of outbreak duration, X_0. Comparing the two strategies (Fig. 2) we observe from the 5th and 95th percentiles that implementing a nationwide mass vaccination strategy as an adjunct to baseline interventions is likely to save a further 4–22 lives (median 11, 41% reduction in total deaths) and reduce outbreak duration by between 18 and 36 days (median 27). We assume here that comparing percentiles of the distributions corresponds with comparing analogous epidemics.

However, deaths are likely to occur due to the vaccine and so we investigated non-zero vaccine

fatality rates. The relative reduction in total deaths by implementing nationwide mass vaccination over baseline interventions alone is given by:

$$\Lambda(p, \delta_v) = 1 - \frac{D_0(p, \delta_v)}{D_\infty(p, \delta_v)}, \qquad (1)$$

where δ_v is the vaccine fatality rate per million and p is the percentile. In practice, we are interested in the average behaviour of the system and so consider the median value of each distribution, Λ_{median}. We also consider the minimum value within the 5th and 95th percentiles, $\Lambda_{minimum}$, a standardized measure of the worst case relative reduction in deaths that might be expected from each strategy.

Table 1 shows $\Lambda_{minimum}$ and Λ_{median} with eight initial infection sites (starting districts) chosen to be representative of Great Britain. Four of the starting districts are well connected via commuter movement (City of London, Manchester, Birmingham and Glasgow) and four are less well connected (Cambridge, Salisbury, Worcester and North Cornwall). If the vaccine fatality rate were zero then the total deaths would be expected to decrease by

Table 1. *Relative reduction in total deaths by implementing nationwide mass vaccination over baseline interventions alone, $\Lambda_{minimum}$ and Λ_{median}, assuming various vaccine fatality rates, δ_v per million, for outbreaks starting in different districts†*

Starting district	$\Lambda_{minimum}$ (%)					Λ_{median} (%)				
	δ_v					δ_v				
	0	1	2	5	10	0	1	2	5	10
City of London	30·8	−241·7	−525·0	−1391·7	−2900·0	40·9	−100·0	−240·7	−663·0	−1355·6
Manchester	33·3	−280·0	−640·0	−1670·0	−3470·0	40·7	−136·4	−313·6	−818·2	−1677·3
Birmingham	33·3	−272·7	−581·8	−1527·3	−3163·6	41·2	−116·7	−275·0	−737·5	−1512·5
Glasgow	33·3	−272·7	−581·8	−1527·3	−3163·6	41·2	−116·7	−275·0	−737·5	−1512·5
Cambridge	30·0	−362·5	−787·5	−2112·5	−4350·0	37·5	−172·2	−383·3	−1011·1	−2055·6
Salisbury	27·3	−442·9	−914·3	−2400·0	−4957·1	35·7	−220·0	−466·7	−1220·0	−2460·0
Worcester	22·2	−428·6	−914·3	−2442·9	−5000·0	33·3	−213·3	−466·7	−1213·3	−2460·0
North Cornwall	22·2	−428·6	−928·6	−2414·3	−4971·4	35·0	−220·0	−460·0	−1206·7	−2453·3

† Each value is based on 1000 realizations of the corresponding scenario. Outbreaks initiated with ten index cases. Negative values indicate a relative increase in total deaths.
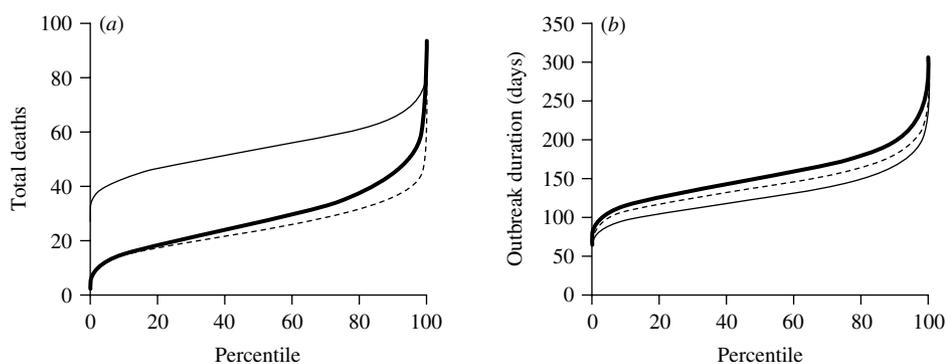
Fig. 3. Distributions of (*a*) total deaths assuming a vaccine fatality rate of one per million and (*b*) outbreak duration [resulting from baseline interventions (thick black line), nationwide mass vaccination (thin black line) and district mass vaccination with $Q_{delay} = 1$ (dashed line) for outbreaks starting in the City of London with ten index cases].

∼ 33–41 %. As the assumed vaccine fatality rate is increased $\Lambda_{minimum}$ and Λ_{median} become negative, showing that the addition of nationwide mass vaccination is likely to increase the total deaths. For example, for a smallpox outbreak beginning in the City of London and assuming, conservatively, $\delta_v = 1$, then Λ_{median} suggests that twice as many deaths will result from implementing nationwide mass vaccination over baseline interventions alone (and could be much worse still with $\Lambda_{minimum}$ and/or higher vaccine fatality rates).

Comparison of district mass vaccination strategies against baseline interventions

For each value of Q_{delay} (the number of cases in isolation in a district before mass vaccination is

implemented in that district) between 1 and 10, we simulated 1000 epidemics starting in the City of London to derive a distribution of epidemics arising from the baseline scenario with ten index cases. Generalizing equation (1):

$$\Lambda(p, \delta_v, Q_{delay}) = 1 - \frac{D_{Q_{delay}}(p, \delta_v)}{D_\infty(p, \delta_v)}, \quad (2)$$

$\Lambda_{minimum}$ and Λ_{median} are defined as before. Figure 3 shows the advantages of district mass vaccination over baseline interventions by reducing the total deaths in the vast majority of simulations; however, the outbreak duration is decreased by only about half of that achieved with nationwide mass vaccination.

Examining the effect of changing Q_{delay} (Table 2), we observe that for $Q_{delay} > 5$ district mass vaccination is

Table 2. *Relative reduction in total deaths by implementing district mass vaccination with different Q_{delay} over baseline interventions alone, $\Lambda_{minimum}$ and Λ_{median}, assuming various vaccine fatality rates, δ_v per million, for outbreaks starting in the City of London*†

| | $\Lambda_{minimum}$ (%) | | | | | Λ_{median} (%) | | | | |
| | δ_v | | | | | δ_v | | | | |
Q_{delay}	0	1	2	5	10	0	1	2	5	10
1	8·3	0·0	−8·3	−50·0	−116·7	22·2	12·0	2·8	−28·6	−77·8
2	7·7	7·1	0·0	0·0	−15·4	19·1	17·2	14·3	8·0	−3·3
3	13·0	11·1	11·1	7·7	4·4	16·7	16·1	15·4	13·0	10·0
5	7·1	7·1	7·1	7·1	6·7	14·3	13·9	13·6	13·2	12·5
10	0·0	0·0	0·0	0·0	0·0	9·1	9·1	9·1	9·1	9·1

† Each value is based on 1000 realizations of the corresponding scenario. Outbreaks initiated with ten index cases. Negative values indicate a relative increase in total deaths. Q_{delay} is defined as the required number of symptomatic cases in isolation in a district before district mass vaccination is implemented within that district.

Table 3. *Optimal value of Q_{delay}, Q^*_{delay}, assuming various vaccine fatality rates, δ_v per million, for outbreaks starting in different districts*†

	Q^*_{delay}									
	$\Lambda_{minimum}$					Λ_{median}				
	δ_v					δ_v				
Starting district	0	1	2	5	10	0	1	2	5	10
City of London	0	3	3	3	5	0	2	3	5	5
Manchester	0	2	2	—	—	0	2	2	4	4
Birmingham	0	1, 2	—	—	—	0	1	1, 2	4	—
Glasgow	0	1	3	—	—	0	1	1	2	—
Cambridge	0	1	1	2, 3	3, 4	0	1	1	3	3
Salisbury	0	3	3	2, 3	2, 3	0	1	1, 2, 3	2, 3	3
Worcester	0	1, 2	2	2	2	0	1	2	2	2
North Cornwall	0, 1	1	1	1	1, 2	0, 1	1	1	1	1

† Outbreaks initiated with ten index cases. Q_{delay} is defined as the required number of symptomatic cases in isolation in a district before district mass vaccination is implemented within that district.

not always implemented since baseline interventions alone can control the epidemic before Q_{delay} is reached. This is reflected by the row of zeros with $\Lambda_{minimum}$ with $Q_{delay} = 10$. The other values of zero in Table 2 are a result of the fewer smallpox-related deaths balancing the extra vaccine-related deaths that occur when district mass vaccination is implemented. The vaccine fatality rates considered often allow a range of beneficial Q_{delay} values which forces the question of what Q_{delay} maximizes the reduction in total deaths. Table 2 suggests that for the baseline scenario, taking $Q_{delay} = 3$ ($\Lambda_{minimum}$) or $Q_{delay} = 2$ (Λ_{median}) would be most beneficial for $\delta_v = 1$.

We also examined the effect of outbreak origin. Table 3 summarizes the optimal value of Q_{delay}, Q^*_{delay}, for each of the starting districts (note that

Table 4. *Optimal value of Q_{delay}, Q^*_{delay}, and the relative reduction in total deaths by implementing district mass vaccination over baseline interventions, $\Lambda_{minimum}$ and Λ_{median}, assuming various vaccine fatality rates, δ_v per million, with different numbers of index cases†*

		Baseline ($R_0 = 5$, contact tracing efficiency $= 0·8$)				Worst case ($R_0 = 7$, contact tracing efficiency $= 0·5$)			
		Q^*_{delay}		$\Lambda_{minimum}$ (%)		Q^*_{delay}		$\Lambda_{minimum}$ (%)	
		δ_v		δ_v		δ_v		δ_v	
	Index cases	1	10	1	10	1	10	1	10
Well-connected starting districts	10	1–3	—	5–15	0	1	2–5	40–60	20–40
	100	1–3	5–10	20–30	10–20	0–1	1–4	55–70	40–65
	250	1	1–5	20–35	10–30	0–1	1–2	65–75	40–75
	1000	0–1	1–3	25–40	10–35	0–1	1–2	65–80	50–80
Less well-connected starting districts	10	1–3	2–4	15–20	5–15	1	2–4	40–50	30–45
	100	1–3	2–4	25–30	20–30	1	2–4	55–60	50–55
	250	1–2	2–4	30	25–30	1	2–3	55–60	55–60
	1000	1	2–4	30	25–30	1	2–3	55–60	55–60

† Note that the blank entry indicates that baseline interventions alone is the optimal strategy. Q_{delay} is defined as the required number of symptomatic cases in isolation in a district before district mass vaccination is implemented within that district.

table entries containing more than one value correspond to indistinguishably beneficial strategies). It is important to highlight the blank entries which indicate that for some scenarios mass vaccination with any value of Q_{delay} is not beneficial. This occurs because the increase in vaccine-related deaths outweighs the decrease in smallpox deaths for any strategy that results in mass vaccination. In these cases, which tended to be for the worst case relative reduction in deaths that might be expected ($\Lambda_{minimum}$) and for outbreaks that started in well-connected districts with the higher assumed vaccine fatality rates, baseline interventions alone are the optimal strategy for controlling an outbreak. It is clear from Table 3 that if the vaccine fatality rate were zero, then nationwide mass vaccination would be the optimal strategy. However, as δ_v increases and vaccine-related deaths become more significant, there is a trend for Q^*_{delay} to increase. Although the impact on smallpox-related deaths is reduced as Q_{delay} increases, on average there will be fewer vaccines administered since fewer districts will reach Q_{delay}. At some point the resulting fall in vaccine-related deaths outweighs the rise in smallpox-related deaths giving the values we see in Table 3. For most low values regarding the vaccine fatality rate ($\delta_v = 1$, 2) in the scenarios considered here, district mass vaccination with Q_{delay} equal to 1, 2 or 3 is usually better than baseline interventions alone.

Sensitivity analysis

Extensive sensitivity analysis, focused on identifying the more risk averse strategies, $\Lambda_{minimum}$ (see Appendix), was conducted by varying the number of index cases and key model parameters. Poorer contact tracing efficiencies (0·5), higher values of R_0 (up to 7), and larger numbers of index cases (up to several thousand) all tended to reinforce the benefits of district mass vaccination, with trigger values of Q_{delay} in the range 1–10, the higher values with the higher assumed vaccine fatality rates (Table 4). Conversely, baseline interventions alone were favoured when R_0 was low ($R_0 = 3$), particularly for outbreaks starting in well-connected districts. Adjusting the proportion of infections caused during the prodromal period (2·5–20%) had little effect on the results. Neither did doubling the extent of population movement between patches, except for the case of outbreaks starting in the City of London, where baseline interventions alone were optimal.

DISCUSSION

The simulations discussed in this paper indicate that for smallpox outbreaks, already being tackled by the most targeted approaches (finding and isolating symptomatic cases and tracing, vaccinating and

observing contacts), fewer total deaths can often be achieved by the addition of district mass vaccination. Previous studies argued that either large-scale mass vaccination would be necessary for adequate control, especially if resources are limited [29–31], or more targeted strategies would be sufficient [15, 29], especially for outbreaks with few index cases. Some of the reasons for these different conclusions have been discussed in depth elsewhere [19, 32, 33]. The question has remained, however, under what, if any, circumstances might targeted approaches be usefully switched to include vaccination of some larger section(s) of the population [1, 2, 19, 29]. In our simulations we have confirmed that the addition of nationwide mass vaccination would be suboptimal for outbreaks with smaller numbers of index cases [33]. We have also confirmed that for outbreaks with few index cases targeted approaches employing case isolation and contact tracing could control a smallpox outbreak [19, 29, 33]. Most significantly we have demonstrated for the first time by using a demographically realistic metapopulation patch model that for most of the scenarios examined, a superior strategy was to supplement the basic targeted approaches with district mass vaccination waiting until a district has a small number of cases. Across a wide range of scenarios, this trigger only varied between 1 and 10 isolated cases, and was close to 1 for many scenarios. Only in a limited number of scenarios (smaller numbers of index cases, low estimates for R_0 and more optimistic contact tracing efficiencies) was the addition of district mass vaccination suboptimal. Nationwide mass vaccination was optimal only if the outbreak started in the City of London district with of the order of 100 ('worst case scenario') or 1000 (baseline scenario) index cases, with conservative assumptions regarding the vaccine fatality rate.

We have considered neither the logistical constraints of delivering control strategies nor their interaction with the disease process. This parsimonious approach was taken to make the model more computationally tractable, allowing extensive sensitivity analysis. The disease dynamics were modelled more 'phenomenologically' than by Kretzschmar et al. [19] and Riley & Ferguson [15], with a fixed rate of case contacts and a time invariant infectiousness and probability of diagnosis. Kretzschmar et al.'s stochastic branching model and Riley & Ferguson's individual-based micro-simulation model both had more realistic parameterization of these aspects, but similarly showed, with assumptions that closely resemble the baseline interventions in our model, that these can be successful in containing a smallpox outbreak. We have also more formally compared model results by re-parameterizing our model to account for differences in assumptions between studies. These simulations gave results similar to those of Kretzschmar et al. and Riley & Ferguson where regionally targeted mass vaccination was not considered, with some variation in our results dependent on whether outbreaks started in well- or less well-connected districts. However, whilst we agree that for less severe scenarios targeted controls are often better, there are a wide range of starting assumptions, such as large numbers of index cases, where the addition of district mass vaccination provides appreciable benefits (5–80% fewer total deaths).

Differences between studies probably arise because of how regional mass vaccination and other interventions have been implemented. Riley & Ferguson assume that no interventions will be implemented until 21 days after the index cases have become infectious. This seems somewhat pessimistic, since all of these cases will have essentially been outside of any form of isolation for most of their symptomatic infectious period, whilst also most probably in a sick and disabled state. Further, this assumption would not have scaled well with numbers of index cases in our sensitivity analysis; it seems unreasonable to assume that 100 or more cases would reach 21 days from the beginning of their infectious period before public health authorities became aware. We assumed that baseline interventions would be implemented once there are four symptomatic cases in the community. This is a more optimistic assumption and results in less transmission before the implementation of interventions. We have, however, examined scenarios broadly similar to those of Riley & Ferguson and still find some benefit of district mass vaccination. Direct comparison shows that by waiting until there were only four symptomatic cases in the community only 2–3 million vaccines were administered in total, whilst waiting for 21 days after the index cases became infectious 8–9 million vaccines in total were used. This is still somewhat lower than the 13 to 14 million doses of vaccine observed by Riley & Ferguson under similar parameter assumptions (policy seven and higher transmission scenario C). This approximately 50% increase in vaccines administered is probably a result of the arguably wider extent of the regionally targeted vaccination policy used by Riley & Ferguson. A major advantage of this study is that we have been

able to demonstrate that there are potentially rational triggers for implementing beneficial regional mass vaccination strategies and that this depends to some degree on where the index cases are geographically located. This was possible since our model parameterized the longer range movements of individuals directly on the census movement data that captured the specific peculiarities of regional movement rather than on a generalized movement kernel.

In conclusion, we have demonstrated that targeted controls are probably optimal for a number of smallpox release scenarios, particularly for small numbers of index cases and lower transmission rates with efficient interventions. Even for scenarios with higher R_0 and larger numbers of index cases we have confirmed that these controls are likely to manage outbreaks. However, we have also shown that there are a large number of scenarios where district mass vaccination would probably provide a meaningful benefit in minimizing the total numbers of lives lost. The optimum trigger varies with starting district but is generally small and under none but the most extreme of scenarios was national mass vaccination ever an optimal strategy. It would be interesting to determine the potential benefits of mass vaccination in smaller geographic areas than districts.

Ultimately, it will be critical for real-time data collection and analysis to assess which type of scenario is developing and to adapt ongoing intervention strategies accordingly. Such data would also need to give early enough warning of a 'failing'

into six classes; susceptible (S), latent (E_U), prodromal (P_U), symptomatic (I), recovered (R) and dead (D). When the population in the symptomatic class reaches I_{trigg} baseline interventions are begun. Traced contacts are divided into those that are uninfected (C) and those that are infected (E_T). Uninfected traced individuals move into the vaccinated group (V_T) or back to the susceptible population (if the vaccine failed). Infected traced individuals leave to enter either the vaccinated group (although with reduced vaccine efficacy) or develop the disease and become prodromal but under observation (P_T). Untraced uninfected contacts are ignored while untraced infected contacts (E_U) eventually enter the prodromal state (P_U) in the community. Each person that becomes symptomatic either enters isolation (Q) or remains in the community. Only a certain proportion of the population can be vaccinated and thus we divide the susceptible population in two; those that can be vaccinated (S_V) and those that cannot (S). When the population in the isolation class reaches Q_{delay} a proportion of the population that may be vaccinated, γ, is removed from S and enters S_V (i.e. $S_V = \gamma S$ with S then containing the remaining susceptible population). Following mass vaccination, those that have been vaccinated enter the vaccinated class (V_P) or back to the susceptible population (S) (if the vaccine failed).

We can write down a set of conservative equations describing the dynamics outlined above (with parameter values given in Tables A 1 and A 2):

$$
\left.\begin{aligned}
\dot{S} &= -(1-(1-\rho)(1-\phi))T+(1-\varepsilon_1)(\tau_O^{-1}C+\tau_V^{-1}S_V) \\
\dot{S}_V &= -(1-(1-\rho)(1-\phi))T_V-\tau_V^{-1}S_V \\
\dot{C} &= \rho(1-\phi)(T+T_V)-\tau_O^{-1}C \\
\dot{E}_U &= (1-\rho)\phi(T+T_V)-\tau_L^{-1}E_U \qquad \dot{E}_T = \rho\phi(T+T_V)-\tau_L^{-1}E_T \\
\dot{P}_U &= \tau_L^{-1}E_U-\tau_P^{-1}P_U \qquad\qquad\quad \dot{P}_T = (1-\varepsilon_2)\tau_L^{-1}E_T-\tau_P^{-1}P_T \\
\dot{I} &= (1-\theta)\tau_P^{-1}P_U-\tau_I^{-1}I \qquad\quad \dot{Q} = \theta\tau_P^{-1}P_U+\tau_P^{-1}P_T-\tau_O^{-1}Q \\
\dot{R} &= (\tau_I^{-1}I+\tau_Q^{-1}Q) \qquad\qquad\quad \dot{D} = \delta R+\delta_v(V_p+V_T) \\
\dot{V}_T &= \varepsilon_1\tau_O^{-1}C+\varepsilon_2\tau_L^{-1}E_T \qquad\quad \dot{V}_P = \varepsilon_1\tau_V^{-1}S_V
\end{aligned}\right\} \quad \text{(A 1)}
$$

intervention to allow intensification or de-escalation of controls sufficiently rapidly to prevent substantial excess deaths [32].

APPENDIX

Detailed model formulation

Prior to the implementation of public health intervention strategies the total population (N) is divided

with the transmission terms T and T_V given by

$$
T_{(V)}(t) = \frac{S_{(V)}(t)}{\phi N}\left[\frac{R_I I(t)}{\tau_I} + \frac{R_P P_U(t)}{\tau_P}\right], \quad \text{(A 2)}
$$

where R_P and R_I are the average number of secondary cases caused during the prodromal and symptomatic periods respectively. We complete the governing set of equations with the initial conditions, $S(0) = (1-\alpha)N-E_0$, $E_U(0)=E_0$, $R(0)=\alpha N$, with all other classes equal to zero at time zero, where E_0 is the

Table A 1. *The model disease parameters*†

Parameter	Description	Value
τ_L	Latent period (days)	12·0
τ_P	Prodromal period (days)	2·5
τ_I	Symptomatic period (days)	8·6
R_0	Reproduction number	5·0‡
R_P/R_0	Infections caused in prodromal period (%)	10·0‡
δ	Case fatality rate (%)	30·0
α	Immunity to infection (%)	0·0
ϕ	Contacts that are infected (%)	10·0
κ	Reduction in case movement when symptomatic (%)	90·0

† See text for discussion and references.
‡ Varied in sensitivity analysis.

Table A 2. *The model intervention parameters*†

Parameter	Description	Value
I_{trigg}	Number of cases required to trigger intervention strategies	4
τ_Q	Isolation period (days)	20
τ_O	Observation period (days)	15
τ_V	Vaccination period (days)	7
θ	Cases entering isolation (%)	90‡
ρ	Contacts found (%)	80‡§
ε_1	Vaccine efficacy whilst uninfected (%)	97·5
ε_2	Vaccine efficacy whilst latent (%)	30
γ	Population that may be mass vaccinated (%)	70

† See text for discussion and references.
‡ Zero prior to intervention.
§ Varied in sensitivity analysis.

number of initial latent individuals (index cases) seeded in the residential population of a district. Note that in the main text [see Results, equations (1) and (2)], D_∞, D_0 and $D_{Q_{\text{delay}}}$ refer to the cumulative number of deaths over the entire course of the epidemic.

Further to the temporal dynamics discussed above, we incorporate spatial dynamics into the model by allowing the transmission equation (A 2) to become a vector of length M,

$$T_{(V)m}(t) = \frac{S_{(V)m}(t)}{\phi N_m} C_m(t), \qquad (A\ 3)$$

where we use the subscript notation m to differentiate the events occurring over the M districts.

$$C = C_S^T \left[\frac{R_I}{\tau_I} C_I I + \frac{R_P}{\tau_P} C_S P_U \right],$$

where $C_{S/I}$ are $M \times M$ matrices representing the proportion of susceptible and symptomatic individuals that move from one district to another.

Detailed sensitivity analysis

With R_0 reduced to 3 (other parameters unchanged) epidemics starting in less well-connect districts still benefit from district mass vaccination with $Q_{\text{delay}}^* = 1$ (assuming $\delta_v = 1$) but epidemics starting in well-connect districts are optimally controlled through baseline interventions alone. Well-connect starting districts tend to have large populations (and are themselves mostly connected to other districts with large populations) which results in a large number of vaccine-related deaths. This shifts the balance in favour of baseline interventions when there are fewer smallpox deaths due to the lower R_0. For higher values of δ_v there is no additional benefit from district

mass vaccination over baseline interventions for any starting district.

Reducing R_0 to 3 and reducing contact tracing efficiency to 0·5, outbreaks started with ten index cases give results very similar to those in Table 3 when assuming $\delta_v = 1$, but lean in favour of baseline interventions alone for higher vaccine fatality rates.

Returning to baseline assumptions ($R_0 = 5$ and contact tracing efficiency = 0·8) but reducing the number of index cases to five again gives results very similar to those in Table 3 when assuming $\delta_v = 1$, but which lean in favour of baseline interventions alone with higher vaccine fatality rates. Increasing the number of index cases above ten results in progressively lower values for Q_{delay}^* indicating that implementing district mass vaccination earlier is beneficial in controlling outbreaks which have increased initial severity. With the number of index cases equal to 100, the results are similar to those in Table 3; however, the blank table entries which indicated previously that baseline interventions alone were optimal now have optimal values of Q_{delay} between 5 and 10, indicating district mass vaccination with these trigger values would be beneficial. Increasing the number of index cases to 250 and assuming $\delta_v = 1$ results in $Q_{\text{delay}}^* = 1$, with the other values remaining approximately as for 100 index cases with higher vaccine fatality rates. Increasing the number of index cases further to 1000 results in $Q_{\text{delay}}^* = 1$ (or slightly above) for all non-zero vaccine fatality rates ($\delta_v \leqslant 10$) with the exception of the City of London (see below). $Q_{\text{delay}} = 1$ is optimal for all outbreaks starting in well-connect districts (except the City of London) up to $\sim$1000 index cases and for less

well-connected districts up to $\sim 30\,000$ index cases. However, above these thresholds the difference between $Q_{\text{delay}} = 0$ and $Q_{\text{delay}} = 1$ becomes marginal and either strategy (nationwide mass vaccination or district mass vaccination) is equally advantageous, with the conservative assumption that $\delta_v = 1$. District mass vaccination with $Q_{\text{delay}} = 1$ is still optimal, however, with higher assumed vaccine fatality rates. For any of the higher vaccine fatality rates, it is only when the number of index cases exceeds $\sim 50\,000$ (where such district population sizes exist) that nationwide mass vaccination becomes optimal, but even then is only equally optimal to district mass vaccination, and this applies to outbreaks starting in both well- and less well-connected districts.

The City of London is an exception to the above. Nationwide mass vaccination becomes optimal once the number of index cases increases above ~ 1000, assuming $\delta_v = 1$. The City of London is exceptionally well connected and therefore epidemics spread out into more districts, more quickly, which means that delaying mass vaccination has a negative impact on control and total deaths. However, with the higher assumed vaccine fatality rates district mass vaccination with $Q_{\text{delay}} = 1$ would still be optimal up to ~ 1000 index cases in the City London. With ~ 2500 index cases nationwide mass vaccination is optimal, but only with a vaccine fatality rate less than or equal to three per million. District mass vaccination with $Q_{\text{delay}} = 1$ is optimal with assumed vaccine fatality rates greater than three per million.

The 'worst case scenario' that we investigated in the sensitivity analysis here was to increase R_0 to 7 (towards the upper end of the range of values that have been reliably reported [21]), and reduce the contact tracing efficiency to 0.5 (probably rather pessimistic). A similar pattern of behaviour for Q_{delay}^* to that seen with the baseline parameters in Table 3 was again observed but with the shifts to the lower values for Q_{delay}^* occurring at lower numbers of index cases. That is, particularly for outbreaks started by relatively small numbers of index cases, district mass vaccination was often the optimal approach. The most notable difference is that nationwide mass vaccination becomes optimal for outbreaks starting in the City of London with ~ 100 index cases assuming $\delta_v = 1$ and with ~ 2500 index cases with a vaccine fatality rate less than or equal to eight per million; district mass vaccination with $Q_{\text{delay}} = 1$ is optimal with higher assumed vaccine fatality rates in both scenarios.

With baseline assumptions ($R_0 = 5$ and contact tracing efficiency $= 0.8$) and ten index cases, decreasing or increasing the percentage of infections caused in the prodromal period from 10% to 2.5% or 20% respectively results in similar values to those in Table 3. Doubling the movement between districts has a marginal effect for all starting districts except for the City of London, where baseline interventions alone are the optimal strategy for all non-zero vaccine fatality rates ($\delta_v \leqslant 10$).

DECLARATION OF INTEREST

None.

REFERENCES

1. **Centers for Disease Control and Prevention website.** Smallpox Response Plan and Guidelines (Version 3.0) (http://www.bt.cdc.gov/agent/smallpox/response-plan). Accessed 26 November 2002.
2. **Department of Health website.** Smallpox mass vaccination: An operational planning framework (http://www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4114017&chk=gG5D7t). Accessed 24 June 2005.
3. **Casey CG, et al.** Adverse events associated with smallpox vaccination in the United States, January–October 2003. *Journal of the American Medical Association* 2005; **294**: 2734–2743.
4. **Poland GA, Grabenstein JD, Neff JM.** The US smallpox vaccination program: a review of a large modern era smallpox vaccination implementation program. *Vaccine* 2005; **23**: 2078–2081.
5. **Kemper AR, Davis MM, Freed GL.** Expected adverse events in a mass smallpox vaccination campaign. *Effective Clinical Practice* 2002; **5**: 98–99.
6. **Lane JM, Goldstein J.** Evaluation of 21st-century risks of smallpox vaccination and policy options. *Annals of Internal Medicine* 2003; **138**: 488–493.
7. **Conybeare E.** Illness attributed to smallpox vaccination during 1951–60. *Monthly Bulletin of the Ministry of Health Laboratory Service* 1964; **23**: 126–133. 150–159.

8. **Dick G.** Smallpox: a reconsideration of public health policies. *Progress in Medical Virology* 1966; **8**: 1–29.

9. **Dick G.** Complications of smallpox vaccination in the United Kingdom. International Symposium on Smallpox Vaccine, Bilthoven 1972; *Symposia Series in Immunobiological Standardization* 1973; **19**: 205–215.

10. **Martin-Bouyer C, *et al.*** Deaths due to smallpox vaccination in France, 1968–1977 [in French]. *Archives Françaises de Pédiatrie* 1980; **37**: 199–206.

11. **Kretzschmar M, *et al.*** Frequency of adverse events after vaccination with different vaccinia strains. *PLoS Medicine* 2006; **3**: e272.

12. **Lane J, *et al.*** Complications of smallpox vaccination, 1968. National surveillance in the United States. *New England Journal of Medicine* 1969; **281**: 1201–1208.

13. **Lane J, *et al.*** Complications of smallpox vaccination, 1968. Results of ten statewide surveys. *Journal of Infectious Diseases* 1970; **122**: 303–309.

14. **Kerrod E, *et al.*** Surveillance and control measures during smallpox outbreaks. *Emerging Infectious Diseases* 2005; **11**: 291–297.

15. **Riley S, Ferguson NM.** Smallpox transmission and control: spatial dynamics in Great Britain. *Proceedings of the National Academy of Sciences USA* 2006; **103**: 12637–12642.

16. **World Health Organization.** Cardiac adverse events following smallpox vaccination – United *States 2003*. *Morbidity and Mortality Weekly Report* 2003; **52**: 248–250.

17. **Fenner F, *et al.*** *Smallpox and its Eradication*. Geneva, Switzerland: World Health Organization, 1988.

18. **Ström J, Zetterberg B.** Smallpox outbreak and vaccination problems in Stockholm, Sweden 1963. *Acta Medica Scandinavica, Supplementum* 1966; **464**: 1–171.

19. **Kretzschmar M, *et al.*** Ring vaccination and smallpox control. *Emerging Infectious Diseases* 2004; **10**: 832–841.

20. **Keeling MJ, Bjornstad ON, Grenfell BT.** Metapopulation dynamics of infectious diseases. In: Hanski I, Gaggiotti O, eds. *Ecology, Genetics, and Evolution of Metapopulations*. San Diego: Elsevier, 2004, pp. 415–445.

21. **Gani R, Leach S.** Transmission potential of smallpox in contemporary populations. *Nature* 2001; **414**: 748–751.

22. **Mack T.** Smallpox in Europe, 1950–1971. *Journal of Infectious Diseases* 1972; **125**: 161–169.

23. **Eichner M, Dietz K.** Transmission potential of smallpox: estimates based on detailed data from an outbreak. *American Journal of Epidemiology* 2003; **158**: 110–117.

24. **Koplan J, Azizullah M, Foster S.** Urban hospital and rural village smallpox in Bangladesh. *Tropical Geographical Medicine* 1978; **30**: 355–358.

25. **Fraser C, *et al.*** Factors that make an infectious disease outbreak controllable. *Proceedings of the National Academy of Sciences USA* 2003; **101**: 6146–6151.

26. **Wehrle P, *et al.*** An airborne outbreak of smallpox in a german hospital and its significance with respect to other recent outbreaks in Europe. *Bulletin of the World Health Organization* 1970; **43**: 669–679.

27. **Hammarlund E, *et al.*** Duration of antiviral immunity after smallpox vaccination. *Nature Medicine* 2003; **9**: 1115–1116.

28. **Nishiura H, Schwehm M, Eichner M.** Still protected against smallpox?: estimation of the duration of vaccine-induced immunity against smallpox. *Epidemiology* 2006; **17**: 576–581.

29. **Bozzette SA, *et al.*** A model for a smallpox-vaccination policy. *New England Journal of Medicine* 2003; **348**: 416–425.

30. **Halloran ME, *et al.*** Containing bioterrorist smallpox. *Science* 2002; **298**: 1428–1432.

31. **Kaplan EH, Craft DL, Wein LM.** Emergency response to a smallpox attack: the case for mass vaccination. *Proceedings of the National Academy of Sciences USA* 2002; **99**: 10935–10940.

32. **Ferguson NM, *et al.*** Planning for smallpox outbreaks. *Nature* 2003; **425**: 681–685.

33. **Eichner M.** Case isolation and contact tracing can prevent the spread of smallpox. *American Journal of Epidemiology* 2003; **158**: 118–128.