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Interim smallpox guidelines for the United Kingdom

Developing new policies from old evidence

Last week, the Department of Health in London published interim guidelines for responding to a deliberate release of smallpox in the United Kingdom.[1 2] The guidelines describe contingency plans for diagnosis and management of the first cases, vaccination strategies before and in the event of an outbreak, and other essential measures to ensure outbreak preparedness and control. Two of us (RH and DM) have contributed to the development of the guidelines, and the aim of this editorial is to give a brief summary and highlight some of the underlying evidence. (Comments on the guidelines may be sent to smallpoxplan@doh.gsi.gov.uk before the end of this year.)

Developing policies to combat an eradicated infectious disease is difficult for two reasons. Firstly, it is impossible to balance the benefits and risks of interventions against the potential risk from disease. No one knows whether variola virus exists outside the two laboratories approved by the World Health Organization, whether it has fallen into the hands of organisations or individuals with the will and ability to use it as a weapon, or whether it can actually be disseminated in a way that would cause mass casualties. Secondly, the underlying evidence relies on historical data, which were collected in a different, now outdated context and are often incomplete. Nevertheless, analysis of historical data has provided valuable insights into the disease and the importance and effectiveness of different interventions, and several key messages have emerged that have been used to develop contingency plans.

Rapid diagnosis of the first cases is essential. Any delay in implementing control measures would substantially increase the size of an outbreak.[3] The last naturally occurring case of smallpox in the United Kingdom dates back to 1973, and most clinicians are now unfamiliar with the presenting symptoms and signs. To facilitate early diagnosis, under the United Kingdom guidelines all clinicians will be issued with a diagnostic algorithm to help them recognise and assess cases of suspicious illness. Further clinical pictures are available through the website of the Public Health Laboratory Service (www.phls.org.uk). A cadre of vaccinated doctors specialising in infectious diseases will provide diagnostic support, and emergency smallpox response teams will be established to carry out further assessment, laboratory investigation, and management of suspected cases. A small number of specialist laboratory staff will be vaccinated and trained in the laboratory diagnosis of orthopox viruses.

The most appropriate vaccine strategy remains the subject of debate. Three options might be considered: pre-emptive mass vaccination,[4] mass vaccination after a release,[5] and search and containment with tracing and vaccination only of contacts of cases.[6] Advocates of pre-emptive vaccination probably have an overly pessimistic view about the potential for disease transmission and the effectiveness of control measures. Although smallpox may be infectious from the onset of prodromal symptoms, most transmissions have occurred from patients with overt disease.[7] In addition, transmission usually required close contact with infected individuals: attack rates were highest among household members, although spread within hospitals has been documented.[8] If smallpox were to re-emerge, infected individuals would be extremely unwell by the time they were highly infectious and therefore unlikely to transmit infection extensively within the community.

Any vaccination strategy must consider the risk of adverse events. The best historical estimates of adverse event rates are from active surveillance in the United States in the 1960s,[9] when the crude death rate from vaccination was about one in a million. However, when the age and vaccination status of modern populations is taken into account, the adjusted death rate is now higher: it has been calculated that in France (population 60 million), a universal vaccination strategy would result in around 300 deaths and 18 500 serious adverse events.[10] In addition, some groups have a special risk of vaccine related complications, notably immunosuppression, eczema, and pregnancy. The emergence of HIV and the use of immunosuppressive drugs have produced a greater number of susceptible people in modern populations.

In the absence of smallpox anywhere in the world, the overriding concern must be to minimise harm. Pre-emptive vaccination in the United Kingdom will be therefore limited to a few hundred specialist healthcare workers who would be involved in the assessment and management of the first cases. They will be carefully screened for contraindications to minimise the risk of adverse events. Further essential personnel will be identified who could be vaccinated as part of a second tranche in the event of a heightened threat or a confirmed case of smallpox in the United Kingdom.

Two recent models have produced conflicting recommendations about the most appropriate vaccination strategy in the event of the re-emergence of smallpox. This is due in part to different assumptions about how populations mix. Kaplan et al assumed that

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everyone has an equal chance of contact with anyone else, and their model preferred a vaccination strategy that included large swathes of the population.[5] Halloran et al assumed that individuals mix largely within close social networks, and their results showed that a search and containment strategy, such as that recommended by WHO and used during the eradication campaign, would be preferable.[6]

The United Kingdom has opted for search and containment, with wider vaccination initiated only if an outbreak is multicentred or uncontrolled. Vaccination centres will be identified that could be operational within 24 hours if necessary. The United Kingdom's vaccination strategy will be reviewed as results from more sophisticated mathematical models emerge, and in the event of an outbreak these models will be used in real time to assess whether the adopted strategy is proving adequate to control the transmission of infection.

Vaccination alone will not control an outbreak without concurrent isolation of cases and monitoring and observation of contacts.[3 5 6] In the United Kingdom, smallpox care centres will be identified that could be used to treat patients and observe febrile contacts. In addition, the clinical and public health infrastructure required for tracing and monitoring of contacts will be identified in advance.

The United States has also published guidelines for responding to smallpox,[11] and other countries in Europe and North America are in the process of developing contingency plans and securing access to supplies of vaccine. Poorer countries have neither a public health infrastructure capable of responding rapidly to an outbreak, nor stocks of vaccine or the capability to produce vaccine. In many of these, overcrowding and a high prevalence of HIV would favour the spread of infection. This raises the question of whether and how these countries would obtain the support and resources, including supplies of vaccine that would be essential for smallpox control. A case of smallpox anywhere in the world would represent a global health emergency.

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Evaluating treatment effects reliably

Although principles are well known, they are ignored too often

The introduction, more than half a century ago, of properly randomised trials in which the treatment allocation was rigorously concealed was a watershed in the evaluation of treatment effects.[1] But this major advance did not come out of the blue: as was highlighted at a recent conference in Oxford (Beating biases in therapeutic research: historical perspectives, www.wuhmo.ox.ac.uk/docs/BeatingBiases.html), attempts to combat bias in therapeutic evaluation had in fact been made during the preceding few centuries.[2–4]

In the 18th century, the traditional practice of claiming therapeutic achievement on the basis of pathophysiological theories and anecdotal "successes" started to be challenged by medical non-conformists who wrote careful, prospective, analytical accounts of medical treatments, some of which included comparison with a control group.[4] These "arithmetic observationists and experimentalists"[4] recognised the need to avoid inappropriate inference of cause and effect in therapeutics and realised that bias may be introduced by, among other things, selecting patients for particular treatments (selection bias) and reporting only particularly successful treatments (publication bias).

One innovation aimed at reducing selection bias was to alternate patients in a consecutive series between treatment and no treatment.[1] But alternation had the major limitation that the investigator knew which treatment the next patient would receive, and this knowledge could influence whether a particular patient was considered suitable for the study.[1] In the 1930s, Bradford Hill realised that properly executed randomisation would reduce this potential for selection bias by ensuring that treatment groups were balanced with respect to both measured and unmeasured prognostic variables. This insight underpinned the first trials in which treatment allocation was randomised and rigorously concealed: a trial of immunisation against whooping cough, and a trial of streptomycin for pulmonary tuberculosis, both conducted in the late 1940s.[1]

So is bias in therapeutic evaluation beaten? Sadly not. Even though the fundamental methods for avoiding bias in therapeutic research are well established,[5 6] examples of studies with inappropriate designs still occur. Importantly, many studies of treatment effects still do not involve random allocation of the treatment under study.[5] Although in some circumstances such non-randomised observational studies can provide

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