Can one size fit all? Towards a universal anthrax vaccine

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“A large-scale bioterrorist attack with *Bacillus anthracis* ... would result in considerable morbidity and mortality.”

A large-scale bioterrorist attack with *Bacillus anthracis*, the causative agent of anthrax, against an unprotected population would result in considerable morbidity and mortality. Strategies to mitigate the impact of such an event need to be developed urgently. While pre-exposure immunization would significantly reduce the impact of a covert attack, the implementation of an effective universal vaccination program would face many challenges, notably the identification of a vaccine capable of protecting all sectors of society. Any future vaccine for the general population is likely to be just one component of a multilayered integrated response to the threat.

B. anthracis is a Gram-positive spore-forming member of the *Bacillus cereus* group. It owes its pathogenicity to the production of two principal virulence factors, a tripartite toxin and an antiphagocytic capsule [1]. Both factors are plasmid encoded: the toxin genes are located on pXO1, while the genes encoding the peptide capsule are carried on pXO2. Both plasmids can be transferred into other members of the *B. cereus* group leading to the suggestion that *B. anthracis* is simply an extremely aggressive form of *B. cereus* [2].

The threat posed by anthrax depends on where in the world you live. In regions where animal husbandry is the primary focus of economic activity, and veterinary services are minimal, the disease still represents a significant burden to animal and human health [3]. However, in economically developed countries where the animal form of the disease has largely been eliminated, concern centers around the use of the pathogen as an agent of bioterrorism. Indeed, it is the ability of the bacterium to form resistant spores capable of surviving explosive dissemination and infecting via the lungs that has resulted in its development as a biological weapon [4]. The technology required to produce and handle *B. anthracis* spores is relatively simple

compared with that needed to manipulate nuclear material; this could make the pathogen an attractive option to terrorist organizations [5]. The simultaneous infection of large numbers of individuals could overwhelm the healthcare resources of even the most economically developed societies [6].

Indeed, the ability of even a small-scale release to cause harm and disruption was amply demonstrated during the US mail attacks in 2001, which resulted in the infection of 22 individuals, five of whom died. It was estimated that during this relatively small-scale attack, more than 30,000 individuals were given ciprofloxacin prophylaxis for over 60 days at an estimated cost of over US\$2 billion [7].

Antibiotic treatment is effective providing it is started early and the bacterium is susceptible. Unfortunately, as infection progresses it reaches a stage at which antibiotics are no longer effective owing to the accumulation of lethal concentrations of toxin [3]. In addition, strains of the pathogen that are resistant to multiple antibiotics have been reported [8]. A more effective means of mitigating the impact of a surprise terrorist attack, therefore, could be to immunize the general public in advance. While immunization is widely recognized as the most cost-effective form of protection against infectious disease, it is not clear whether the current vaccines would be able to protect all sectors of society, particularly the young, pregnant mothers, the immunocompromised and the elderly [3,9].

Human vaccines against anthrax have been developed and are currently given to military personnel and occupational groups at risk of exposure to the pathogen [3]. They can be divided into two groups: live-attenuated spores and nonliving subunit vaccines; the vaccine received will depend upon where in the world an individual lives. The live-attenuated spore vaccines employed in the Republic of Georgia,

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Russia and China are similar to animal vaccines in that they consist of a bacterial strain that has lost the ability to form a capsule due to the elimination of the pXO2 plasmid. Thus, while the bacterium can no longer initiate active infection in healthy individuals, it is still able to replicate for a limited period during which it releases protective immunogens, such as the components of the tripartite anthrax toxin. This toxin comprises two biologically active subunits, lethal factor (LF; a metalloprotease) and edema factor (EF; a cyclic AMP modulator), together with a third nontoxic, cell-binding component called protective antigen (PA), whose role is to transport LF and EF into susceptible host cells [3].

In the 1960s, concerns over the residual virulence of attenuated spore vaccines led to the development in the USA and UK of nonliving subunit vaccines, in which the culture supernatant of pXO2-deficient strains is combined with an aluminum adjuvant [3]. The licensed US vaccine is known as anthrax vaccine absorbed (AVA), as the supernatant fraction containing PA is adsorbed onto alhydrogel. In the UK vaccine, the PA-containing supernatant is precipitated by the addition of aluminium sulfate and is known as anthrax vaccine precipitated.

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The principal protective immunogen of both vaccines is PA, which induces protection by stimulating the production of blocking antibodies that neutralize the translocation of LF and EF into target cells. Indeed, on the basis of animal protection studies, the magnitude of the PA-specific toxin neutralization antibody response has been proposed as a surrogate marker of protection [3]. While these subunit vaccines have been shown to be protective in animal studies, their ability to protect humans against aerosol exposure has yet to be demonstrated conclusively. In addition, there are concerns over the reactogenicity and immunogenicity of each vaccine. For the US vaccine, the current US FDA-licensed dosing schedule is 0 weeks, 4 weeks, 6 months, 12 months and 18 months, plus an annual booster. The UK vaccine schedule is slightly shorter in that doses are given at 0, 3, 6 and 32 weeks, followed by

annual boosters. Furthermore, the genetically diverse nature of the target populations (not all ethnic groups respond in a similar manner to AVA) and the ability of aggressors to use genetic engineering to produce vaccine-resistant strains has prompted researchers to investigate new vaccine approaches [10].

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Broadly speaking, those at risk of exposure to anthrax can be divided into three main groups: serving military personnel, individuals at risk of occupational exposure and members of the civilian population who could be the victims of a biological attack. In some ways military personnel are the easiest to protect, as they comprise fit and healthy individuals with access to an effective healthcare system that is able to deliver and monitor individual immunization schedules. Indeed, for some US military units, vaccination with AVA is compulsory [101]. The military also have access to warning systems, protective clothing and antibiotics to supplement the protection provided by vaccination. Groups at risk, such as veterinarians and first responders, can also be immunized prior to exposure and will have access to protective clothing and medical treatment if required. By contrast, the diverse nature of the general public, with regards to age and health and the number of individuals who could be infected by a covert attack, makes them a challenging group to protect. This is accentuated by the fact that they are unlikely to have been immunized prior to exposure: so why don't we immunize the public as we do for seasonal flu and childhood diseases?

The current UK- and US-licensed vaccines are given by injection and require an extensive priming schedule followed by annual boosters; therefore, immunization of the population of a major city the size of London would pose a considerable administrative and logistical challenge. While research is in progress to develop anthrax vaccines capable of conferring rapid protection following a single dose, we are a long way from any such product reaching the market [11,12]. Even if a vaccine is developed that is capable of protecting animals, how will we confirm that a similar level of protection can be achieved in humans? The relative scarcity of

naturally occurring cases of human inhalational anthrax would make it extremely difficult to perform robust clinical efficacy trials on any new vaccine. It was for this reason that the FDA introduced the two-animal rule, under which an anthrax vaccine could be licensed for human use providing it was capable of protecting two different animal species against infection with the pathogen [102]. This rule requires that the mechanism of protection is understood and correlates of immunity are identified that can be applied to humans. It is difficult to see how defined animal models will be able to capture the heterogeneity of the at-risk human population.

So let's suppose we employ the currently licensed vaccines on the civilian population, who would we immunize and what would we do about those groups of society for whom the vaccines are not indicated? What of the individuals who decide not to be immunized on religious grounds or owing to concerns over vaccine safety, or perhaps because they believe that an anthrax attack is not a credible threat? Given that a large-scale attack against an unprotected civilian population could result in the death of thousands, should vaccination be made compulsory as it is for some parts of the US army? Such a decision would be extremely

controversial and, I suspect, impossible to enforce in a democratic society if the response to the compulsory smallpox immunization campaigns of the 19th century are anything to go by [13]. Perhaps the only viable approach would be to immunize the willing and medicate the rest with antibiotics when an attack does occur, accepting that it will not be possible to save everyone [8].

In light of the complex issues highlighted above, it is difficult to see how science alone can formulate a medical countermeasure capable of meeting all of the challenges present by this scenario. Any future vaccine for the general population is likely to be just one component of a multilayered integrated response to the threat.

Financial & competing interests disclosure

L Baillie is a co-inventor of a second-generation anthrax vaccine based on protective antigen, which was developed while working for the UK government. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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