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A Strategic Vaccine Facility for the UK

Jacqueline M. Duggan*, Timothy J.G. Brooks

Public Health Affairs, Health Protection Agency, Porton Down, Wiltshire SP40JG, UK

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Abstract

This paper describes a proposed Strategic Vaccine Facility (SVF) to provide a capability to the UK to deal with new and emerging disease threats. It would underpin the vaccine manufacturing industry by developing expertise and technology to enable rapid manufacture of small batches of vaccines for emergency use against agents, such as bioterrorist agents and emerging diseases. It would have a rare ability to work with dangerous pathogens under containment, allowing the production of inactivated and live vaccines, which would be difficult in a conventional plant. The facility's output will include vaccine candidates and manufacturing protocols for transfer to industry, small vaccine batches for emergency use or clinical trials, and vaccine reference standards. It would also be available for manufacturing small batches of experimental and public health vaccines for the UK and the developing world, allowing clinical trials to be undertaken against key diseases. Crown Copyright © 2005 Published by Elsevier Ltd. All rights reserved.

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1. Introduction

The threat of infectious disease spread in a population, either through natural or deliberate introduction, requires that governments plan their strategies to deal with these threats to protect their nation's health. This includes plans to manufacture and stockpile medical countermeasures, such as antibiotics and vaccines. Vaccines are a key defence against infectious diseases, but industry will only manufacture vaccines against a commercial interest and has little incentive to develop vaccines on a speculative basis against a threat that may not materialise. Two parliamentary committees in the UK have identified a need for a manufacturing facility that can respond rapidly to produce vaccines against infectious diseases that pose a threat to the UK [1,2]. This paper outlines a proposal to meet this need. A Strategic Vaccine Facility (SVF) would provide the opportunity to develop production processes for a variety of experimental vaccines. These could then be tested in clinical trials and passed onto industry for production if indicated. Even if there was no immediate demand for the product, as for a vaccine against a new influenza

strain, it could still be developed to a point allowing rapid production by industry in times of need, e.g., by preparing Good Manufacturing Practice (GMP) seed banks. This would provide a strategic capability for coping with infectious diseases as a significant part of the UK preparedness plan. This paper sets out the concept for a Strategic Vaccine Facility to enhance the UK's capability to deal with new and emerging diseases.

2. What is the threat?

Pathogens capable of causing widespread disease can emerge at any time and are inherently unpredictable. We do not know when and where the next serious disease epidemic will arise and what the nature of that epidemic will be. Another notorious feature of some pathogens is their ability to spread over large areas in relatively little time. This has been further fuelled with the increase in international travel. Diseases that a few years ago would have been confined to a small, remote area can now rapidly spread world-wide in a short time span. Changes in environmental conditions, such as global warming, clearing of forestation for agriculture and widespread damming in arid regions are also factors in the emergence of disease.

* Corresponding author. Tel.: +44 1980 612913; fax: +44 1980 610848.
E-mail address: jackie.duggan@hpa.org.uk (J.M. Duggan).

Table 1
Factors affecting emergence of pathogenic organism

Factor	Effect	Example
Genetic variation		
Mutation	Organisms with altered characteristics from parent arise spontaneously	Emergence of epizootic Venezuelan equine encephalitis virus (VEEV) subtype 1C from enzootic variant 1D in 1993 and 1995
Re-assortment	Re-assortment of genes when two organisms infect same host	Pandemic influenza (re-assortment of mammalian and avian flu)
Adaptation to new species	Evolutional pressure to mutate to adapt to a new host species	Hendra (adapted to horses and humans from fruit bats) Nipah (adapted to pigs and humans from fruit bats) HIV (adapted to humans from primates)
Sharing of genetic material between organisms	Pathogenicity traits passed on through sharing plasmids, insertion sequences etc.	Enterotoxigenic <i>E. coli</i> (ETEC) due to acquisition of cholera toxin DNA <i>E. coli</i> 0157 acquired shigella toxin DNA from plasmid
Changes in animal husbandry/farming/agricultural practices		
	Exposure to pathogens not normally encountered	BSE in cattle due to feeding contaminated meat and bonemeal to cattle. Led to emergence of vCJD in humans.
New activities		
	Exposure to organisms usually limited to a niche environment	Emergence of Rift Valley Fever in Egypt due to flooding of Aswan Dam Emergence of Rocio virus in Brazil due to deforestation
Changes in human behaviour		
	Exposure to organisms not normally encountered	Ebola infection due to consumption of infected bushmeat Exposure to SARS virus from exposure to wild animals in exotic food markets/consumption of infected meat
Direct transfer of organisms from one place to another		
	Organism finds new niche in virgin population	Export of yellow fever to Caribbean/South America from Africa on slave ships West Nile virus introduced to New York
Evolution of existing pathogens		
	Pathogens may evolve to become more or less pathogenic	Disappearance of scarlet fever Evolution of H5N1 avian influenza to more virulent variant capable of infecting humans and causing morbid disease in wild birds
Veterinary pathogens		
	Veterinary pathogens of economic and public health importance are evolving and are threats to agriculture/human health	Foot and mouth virus disease in the UK in 2001 (illegal importation of infected meat) Bluetongue virus (advancing north from Africa into Europe) Death of bat handler in Scotland due to European bat lyssavirus

There are a number of different factors involved in a pathogen's ability to emerge as a disease threat. The main factors are outlined in Table 1. Owing to constantly changing ecological and social factors, it is impossible to predict when and where the next emergence of a pathogen of importance to human health will be. Pathogens can disappear from niches, as well as emerge. Malaria was endemic in the UK until the 1920s when marsh drainage wiped out the main local mosquito vector (*Anopheles atroparvus*) from the UK [3]. It is a possibility that this mosquito will again find a niche in the UK and malaria will once again become endemic. Indeed, there are a number of reported "airport" malaria cases in the UK, where people living near to airports with incoming flights from malaria endemic zones are infected without having been abroad [4].

Transfer of infectious diseases through human activities such as air travel is a serious public health risk. There are over 100 cases of imported dengue virus infections into the UK each year (Dr. G. Lloyd, personal communication) and several imported cases of Lassa fever in European countries have been recorded [5]. There is the potential for these organisms to establish in a new country after importation, especially if the vector, such as mosquito species capable of transmitting infection, is present. The West Nile Virus (WNV) epidemic in the US began with the importation of virus into New York, which quickly established itself in the local mosquito population [6] and thence spread to most states in just a few years. The route of importation of the virus has not yet been established. SARS became an international problem due to rapid spread of this novel coronavirus from

China to other countries through air travel by infected passengers.

The 1918 ‘Spanish’ influenza pandemic was caused by an H1N1 strain of the influenza virus, which is thought to have arisen due to a major re-assortment, or shift, in the virus genes, resulting in changes to the major surface proteins. The ultimate result was a virus that was capable of very efficient human-to-human spread and to which the population of the time had very little pre-existing immunity. The disease spread across the world in a matter of months, killing over 20 million people. Two further, less severe, influenza pandemics also arose last century. These were the 1957 Asian Flu (H2N2) and the 1968 Hong Kong Flu (H3N2). Again, these pandemics were caused by strains thought to have arisen by genetic re-assortment between avian and human influenza viruses. Recent years have seen the emergence of an increasing number of highly pathogenic avian influenza viruses, such as H5N1 and H7N7, which have the capacity to infect humans [7,8]. None of these recent outbreaks has resulted in widespread human-to-human transmission, but the emergence of a strain of influenza with this capability may be just a matter of time.

3. Vaccination as a means to control diseases

The introduction of vaccines during the last two centuries heralded an era of disease control, culminating in the eradication of smallpox in the late 1970s. Recent advances in vaccine manufacture and increased understanding of immunology and pathogen–host interactions have expanded the repertoire of approaches that can be made to produce vaccines against individual diseases. For some diseases, vaccines are easily produced by inactivating the pathogen. An example is influenza vaccine. Vaccines against other diseases may be more difficult to produce. Vaccines against HIV still elude us, despite nearly 20 years of work by many research groups in many countries. For some emerging diseases, it would be possible to produce a vaccine based on the track record of vaccines against related strains. Other vaccine programmes may need a more sophisticated approach, with production of attenuated, sub-unit or genetically modified vector vaccines. Sophisticated vaccine development generally requires major investment and takes many years to complete.

Much of the burden of disease occurs in developing countries, with diseases such as TB, malaria, measles, HIV and parasitic diseases accounting for the majority of the morbidity and mortality due to infectious diseases. In many cases, vaccine development and manufacture has been overlooked by large pharmaceutical companies, since the high cost of developing vaccines against these diseases is not an attractive economic proposition. Such vaccine development, therefore, relies on research grants from public bodies and relief organisations, and the small research groups that take on this work do not have the necessary funding or facilities to manufacture their vaccine candidates themselves, particularly to the

quality standards demanded for use in human clinical trials. Other diseases, such as HIV and malaria have so far evaded effective vaccine development due to their complex structures and interactions with their hosts.

There are many research programmes available that are developing promising vaccine candidates. Examples of current developmental programs include vaccines for plague, Ebola and botulinum toxin [9–11]. These candidates could be taken forward into vaccine manufacture in an emergency situation. Updated information on current vaccine development work is required in order to draw quickly upon this information in an emergency. Table 2 gives the potential for vaccine development for a number of diseases that may present a risk to populations, either through natural emergence or deliberate release.

4. Maintaining the capability

Successful vaccine development and evaluation requires access to a wide range of research and evaluation techniques. In addition to fundamental skills in bacteriology and virology, these also include a wide range of molecular biology techniques, essential for many modern vaccine techniques, and a genomics programme that should contribute significantly to identifying potential vaccine candidates from new organisms. The ability to study immune responses in man and animals, and to provide satisfactory animal models are also key to new vaccine design, production and evaluation. The ability to work within the strictest mode of biological containment is critical to the operation of any proposed facility. Undertaking regular operations in the facility ensures that operators remain fully trained and have the requisite experience required to develop products under emergency situations. This requires that the facility spends its non-emergency time working with different types of micro-organisms using a range of different techniques, so that operator skills are maintained at their highest levels at all times.

In order to maintain the practical skill base and provide up to date expertise in a variety of techniques, the plant would undertake a range of small-scale production programs. This could be under contract to industry or through partnerships and collaborations with academia, public research bodies and other government departments. There is a worldwide need for new vaccines to deal with public health problems in the Third World. The SVF would be well placed to contribute to global health by developing manufacturing protocols and clinical trial batches of material for candidate vaccines in this area in conjunction with the International Aid community.

5. Facility design

The facility design needs to meet a number of varied requirements to satisfy the range of activities it could be called upon to house. These include:

Table 2
Vaccine development potential for new, emerging and old diseases

Disease	Epidemic potential	Vaccine potential	Vaccine development or availability for human use	Potential for rapid trial vaccines
Anthrax	No	Yes	Efficacious vaccine available	Extant
Bat lyssavirus (Rabies group)	No	Yes	Rabies vaccine available	Extant
Botulinum	No	Yes	Unknown degree of cross-protection Pentavalent toxoid vaccine developed in the US in the 1960s; used on a trial basis since Recombinant vaccine research under way	Basic technology can be adapted
Henipaviruses (Hendra and Nipah viruses)	Possible	Possible	No vaccine available; vaccine production may be possible, based on vaccines against related viruses	Extensive development work required
Influenza	Yes	Yes	Vaccine available against currently circulating strains; pandemic vaccine would depend on strain	Rapid vaccine development possible. Lead time is ~6 months even in an emergency.
Plague	Yes	Yes	No currently licensed vaccine; new subunit vaccines being produced but not available yet	Process for experimental vaccines can be reproduced if required
SARS	Yes	Possible	No vaccine available; number of groups working on vaccine development	Simple vaccine technology unlikely to work, based on experience with animal vaccines to other coronaviruses
Smallpox	Yes	Yes	Live vaccine available but in limited supply; new vaccines under development	Vaccine based on previous technology can be produced quickly in an emergency
West Nile	Yes	Yes	No vaccine currently available; new vaccines under development	Simple inactivated vaccines likely to be successful

1. A contained area operating under negative pressure for culture of highly pathogenic micro-organisms, protecting the workers and the environment.
2. A shell operating under positive pressure to provide a clean environment for working to Good Manufacturing Practice, protecting the product.
3. The necessary services to support GMP, such as purified water supplies and systems to monitor the environment and equipment.
4. The ability to accommodate different production methods, such as cell culture and egg culture for viruses, and fermentation processes for vaccines based on bacterial and expressed protein products.
5. An effluent treatment plant and suitable autoclaves for dealing with contaminated waste.
6. Equipment and space for downstream processes such as purification and fill and finish if these are to be completed in-house.
7. Access to quality control laboratories, media preparation laboratories, equipment preparation services, goods ordering and stores services and engineering support.
8. The ability to support more than one manufacturing process at once, so that a wide skill base can be sustained, and maintenance of the facility can be scheduled so as to allow operations to continue in other parts whilst it is undertaken.

9. Each production unit should be scaled to allow production of batch sizes suitable for clinical trials up to and including phase 3. The exact number of vaccine doses per batch would depend on the nature of the process.
10. The entire plant should be capable of rapid cleaning and turn-around so that all parts can operate in parallel to produce larger quantities of material in an emergency.

A modular facility based on separate small production units housed in a shell maintained to GMP standards is being considered as a likely candidate for the facility design. Each unit would essentially be a group of rooms with services, into which equipment can be brought as needed. Whenever possible disposable units would be used for fermenters, centrifugation vessels, containment units and so on, minimising the validation and cleaning procedures necessary before and after each production run. Disposable facilities also mean that much of the GMP quality assurance and paperwork can be duplicated between different products. Careful design should allow a disposable element such as the containment shell to be interfaced to high-cost components such as air handling systems in a way that allows rapid cleaning between processes and improves the turn-around of the facility.

6. Conclusions

Owing to the threat from bioterrorism and emerging diseases, we are proposing a Strategic Vaccine Facility for the UK to mitigate the threat. The facility must be able to work at the highest containment levels and conform to GMP standards. In order to maintain a capability base, it is envisaged that the facility would be used to manufacture small-scale GMP batches of vaccines for clinical trials and niche markets. One possible role of a SVF will be to develop vaccines against key public health diseases, such as those affecting Third World Nations, with a view to transfer the manufacturing processes to vaccine manufacturing industries in these countries. Provision of a SVF in the UK would enhance the nation's vaccine manufacturing capability and would place the UK in a strong position to fight against bioterrorism and emerging infections.

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