CHAPTER 1.1.10.

GUIDELINES FOR INTERNATIONAL STANDARDS FOR VACCINE BANKS

INTRODUCTION

Emergency vaccination is one of several measures that may be deployed to control outbreaks of disease as it provides a valuable adjunct to the application of the essential zoosanitary measures. These include rapid diagnosis, tracing, movement control and disinfection, and may also include slaughter of infected and in-contact animals.

The terms ‘emergency vaccine’ and ‘emergency vaccination’ can have different connotations, but are usually applied to differentiate between routine, prophylactic (preventive) vaccination and emergency vaccination, the latter being applied as an immediate response to an outbreak of disease. Emergency vaccination may be applied in a number of different circumstances and in a number of different ways, including the following:

a) Against an outbreak of disease in a country that is normally free of this disease and that does not normally vaccinate against this disease. It may be applied as Ring Vaccination or Barrier Vaccination, outside of and around a focus of the disease to inhibit outward spread.

b) Against an outbreak of disease in a neighbouring country or region when emergency Barrier Vaccination may be applied along the border in the country or region that is at risk.

c) As a complimentary measure in a stamping-out policy, when emergency vaccination is applied to the animal population around an outbreak location, usually within the protection zone in which outbreaks have occurred, by so-called Suppressive or Dampening Down Vaccination. This is a form of ring vaccination that is followed by killing of the vaccinated animals.

d) Against an outbreak of disease in a country that does normally vaccinate but where emergency vaccine is applied to boost existing immunity.

e) Against an outbreak of disease in a country that does normally practice preventative vaccination, but where the vaccine(s) employed do not provide protection against the strain involved in the outbreak.

Criteria that determine the successful application of emergency vaccination include rapid access to vaccine(s) that (i) contain virus strain(s) of sufficient antigenic relatedness to the outbreak strain(s) (ii) are of the required type of vaccine formulation (iii) have acceptable safety and potency (iv) have appropriate availability, including quantity and immediacy of supply and (v) meet considerations of cost. The evident need to hold strategic reserves, or banks, of such valuable commodities is best exemplified by foot and mouth disease (FMD) vaccines. They are specified in contingency plans for use in an FMD outbreak and have led to an escalation in the establishment of national and international FMD vaccine reserves for use all over the world (3), providing assurance that vaccine would be readily available and at the disposal of the country requiring it.

Emergency FMD vaccines are normally formulated to a higher potency than its conventional counterpart and there are banks who stipulate a requirement of at least $6 \text{PD}_{50}$ (50% protective dose) per dose for cattle in contrast to the minimal statutory requirement of $3 \text{PD}_{50}$. Higher potency can be achieved by simply increasing the antigen payload per dose and its benefits can include rapidity, magnitude and duration of the protective response (1, 4). However, conventional vaccines may also be used in an emergency, particularly when vaccine of appropriate strain composition is immediately available or where revaccination might be desired in an already pre-immune population.

The concept of vaccine banks, exemplified by FMD, and the increased reliance on such banks is indicative of it being a very practical adjunct to other control measures that could usefully be
adopted for a number of other diseases such as bluetongue, classical swine fever and avian influenza.

DEFINITION OF A VACCINE BANK

Strategic reserves, or banks as they are more commonly referred, are of two types. They may hold the final end product, a ready-to-use formulated vaccine, and/or the antigen component, which can be stored for a very long time for subsequent formulation into vaccine as and when required. The latter has been more commonly adopted for FMD because of the economic benefits, and this avoids constantly replacing vaccines that exceed their shelf-life. Stockpiles of antigens, or ready-to-use vaccine, will be referred to as vaccine banks in this chapter.

TYPES OF VACCINE BANKS

A country may hold its own national bank and/or it may be part of a larger group of countries that have drawing rights and share a bank such as exemplified by the North American or European Union FMD vaccine banks. Such consortiums may share a common geographical region, or have similar disease status and approach to control. The bank may be held on the territory of one or several of its members or be retained by the manufacturer, and, if held as antigen, would be formulated for use either by the manufacturer, or in a dedicated facility maintained by the bank members. However, in the latter case, the recent increasing demands by licensing authorities to require the same standards of independent manufacturing facilities as those of the commercial sector with a marketable product, is making this option very difficult. In the case of an antigen bank, a contract between the authorities and the vaccine manufacturer (formulation and filling) has to clearly define the details of formulation of the vaccine, e.g. time between reception of order and delivery, availability of buffers and vials, etc.

The location of stored antigens is of vital importance since the need to formulate vaccine may require antigen to be returned to the original manufacturer, incurring a delay in supply. Even if the antigens are held by the commercial sector, delay following a request for the supply of emergency vaccine might still occur if the manufacturer is currently in the middle of production of a product. The time to produce the vaccine should be about 48–72 hours. Delays in the production and despatch of emergency vaccine to control an outbreak may lead to wider spread of the disease and further difficulty in its control. Formulated vaccine would of course allow for immediate access. However, beside the wasteful and uneconomic implications resulting from regular replacement of the vaccine, it may not always contain the most suitable strain to deal with an outbreak.

The economic benefits of sharing a bank are obvious, but they also provide potential to stockpile greater doses and a wider number of vaccine strains, and reduce the problem of deciding on the introduction of narrow spectrum vaccine strains. Collaboration between vaccine banks would also be an economic way of increasing the amount of emergency vaccine available. Care would be required to ensure that collaborating banks operate to the same standards that drawing rights were clearly defined and that regular contact was maintained between banks to confirm the safety, efficacy and availability of the vaccines. Issues related to regulatory compliance would also need to be addressed at an early stage to ensure that vaccine produced from the bank would be authorised for use in any of the participating countries.

SELECTION OF VACCINES FOR A BANK

Depending on the disease and the likely contingency requirements, a range of vaccine strains may be required. Disease control authorities in consultation with the vaccine bank administrators must decide upon the vaccine strains that should be held and on what basis they should be stored (i.e. as a separate antigen component for subsequent formulation, or as a ready to use formulation). The value of any vaccine bank is very much dependant upon the appropriateness of what it holds for field application, particularly in respect to diseases that are made up of several serotypes and have wider strain variation. The potential of an outbreak not adequately covered by a banked vaccine must be alleviated by continuous monitoring of the global disease situation and recognition that additional vaccine strains may need to be included in the banks portfolio or, in the case where no suitable vaccine strain is available, developed speedily for subsequent inclusion.

The world as an interdependent community that encompasses rapid and extensive movement of people, animals and animal products and the increasing awareness of the potential to deliberately introduce disease through bio-terrorism heightens the risk of an incursion and makes prediction of specific threat difficult. To improve the process of vaccine selection, a continuous exchange of information and increased co-operation and collaboration between different international, regional and national laboratories, vaccine manufacturers and the vaccine/antigen banks authorities should be encouraged. Risk analysis studies should be done to classify the virus strains to be stored with the priority level of high, medium and low. Close liaison with national and international reference
laboratories is therefore recommended as some laboratories already provide periodic recommendations on strains that should be included in FMD vaccine banks. In the context of the risk of bio-terrorism, disease control authorities may consider it pertinent to restrict the information released relating to the storage of specific stockpiles of antigens and/or vaccines.

**QUANTITIES OF VACCINE REQUIRED IN A BANK**

The decision as to how many doses of vaccine are required is complex and problematic, embracing questions of serotypes, strains, use of mono or polyvalent vaccines, and type of formulation. Factors bearing on the decision include the type of disease, the different circumstances and ways of applying emergency vaccination (items a to e) described in the introduction), number, species and location of livestock that are to be protected, geographical considerations, knowledge of the current and predicted global epidemiological situation, and the analyses of risks of introduction and spread of disease, together with cost–benefit studies. In determining the supply of emergency vaccines, decisions on the quantity of the product inevitably involve a compromise between the cost of purchase and the likely number of doses required. The minimum vaccine requirement might therefore be based on the number of doses that could be distributed and applied in the first week of vaccination, the expectation would be that additional supplies could by then have been procured, either from other banks or from commercial sources. For example, 500,000 bovine doses of different FMD vaccine strains were routinely maintained by the International FMD Vaccine Bank (IVB), and drawing rights by member countries varied from 100,000 to 500,000 bovine doses. Nevertheless, this would soon be exhausted if used in an area of high livestock density.

**ACQUISITION OF VACCINES FOR A BANK**

According to both the type of vaccine bank and the disease concerned, the acquisition of the appropriate vaccine(s) or antigen(s) will depend on whether they are available from the commercial sector or government institutions or produced in-house.

Regulatory concerns on existing, or potential, immunological veterinary medicinal products (IVMPs) and the advisability to use approved, authorised medicines, will predispose a bank to acquire, or maintain, its vaccines and antigens selectively. It is recommended that appropriately licensed manufacturers that have the necessary Marketing Authorisation (MA) and internationally accepted standards of Good Manufacturing Practice (GMP), modern quality assurance (QA) and Qualified Person (QP) product release should be used as authorised sources.

This has certainly been exemplified in recent years by FMD vaccine banks in which there has been a strong preference for purchasing and holding antigens/vaccines within the commercial manufacturing sector and thus avoiding the expense and difficulties of maintaining a dedicated ‘licensed’ facility compliant with GMP for the purpose of formulation in an emergency.

Disease control authorities should consider the option of requesting a tender for antigens/vaccine from more than one supplier, particularly where regulatory considerations are of paramount importance, and they may wish to seek advice from appropriate licensing authorities on the necessary standards required. Request for tenders can then ensure not only a competitive price but a veterinary medicinal product manufactured to an acceptable level of quality. It should also establish suppliers that can produce the desired vaccines/antigens and dose amounts within a specified time period that meet necessary, or indeed mandatory, tests of compliance such as safety and efficacy.

Where the requirement is to hold antigens/vaccines at a site other than at the principle site of manufacture, disease control authorities may wish to consider only accepting them after they have been shown to have passed the necessary acceptance testing procedures such as safety and/or efficacy. Alternatively, if the antigen/vaccine has to be located in the bank prior to completion of any acceptance testing, then the antigen/vaccine should be stored apart and labelled as quarantined material until the testing shows full compliance to the vaccine banks requirements.

**REGULATORY STANDARDS - SAFETY, EFFICACY AND QUALITY**

Regulatory requirements for a veterinary medicinal product must be considered by any country wishing to have the necessary authorisation to use emergency vaccine in an outbreak situation. For example, all veterinary medicinal products that are placed on the market in the European Union (EU) must hold a marketing authorisation and the EU lays down the requirements for such authorisations. The EU also has emergency provisions under Articles 7 and 8 that permit release of a vaccine without an authorisation in the country requiring it. However, a more recent EU Directive 2003/85/EC on current and future policy on control of FMD places more emphasis on
the use of vaccines as part of a vaccinate-to-live policy. This makes the issue of an authorised product even more essential, particularly where vaccinated animals are intended for the food chain and require the support of agencies responsible for human health. Therefore, it is important that licensed products be used; unlicensed products are very much a last resort.

Quality, safety and efficacy are therefore all the more important and these will vary depending on the disease. Where particular immunologicals are covered by individual monographs in official Pharmacopoeias (e.g. FMD vaccine in the European Pharmacopoeia – Monograph 63) then the standards for Safety, Efficacy, Sterility and Quality are laid down. For the other case where the immunologics comes under the Pharmacopoeia general section on Vaccines for Veterinary Use then those minimum standards should apply, and disease control authorities may wish to add, to the minimum standards, other individual requirements. These standards might include antigen strain identity, freedom from adventitious agents, innocuity, absence of toxicity, quantity of antigen payload per dose, safety, potency and sterility, and manufacture in officially approved quality assured (QA) good manufacturing practice (GMP) premises.

Any adjuvant or pharmaceutically active ingredient used in a formulation must also conform to the necessary guideline requirements including residues in food-producing species.

Differentiating between animals that have been vaccinated and animals that have either recovered from infection or that have acquired sub-clinical infection post-vaccination may also be an important issue, as is the case for FMD. The detection of antibodies to non-structural polyproteins (NSPs) such as 3ABC of FMDV has been shown to be a sensitive and specific method to differentiate between infection and vaccination. This relies on manufacturing methods whereby the NSP component can be reduced to a level that will not cause detectable sero-conversion following vaccination making purity of vaccine an important consideration.

**STORAGE OF VACCINES/ANTIGENS IN A BANK**

It is important that the areas of storage chosen to hold emergency antigens/vaccines are suitable in the context of the required national or internationally accepted standards of GMP. This is usually covered when a bank is held in a ‘licensed’ and routinely inspected vaccine plant. However, if the bank is located outside a nominated vaccine formulation facility, regulatory considerations again may be of paramount importance and Disease Control Authorities may wish to seek advice from appropriate licensing authorities on the necessary standards required.

If the vaccine bank is associated with a laboratory, or other facility, where pathogens are handled, this should be completely independent of the bank storage facilities, and maintenance and monitoring personnel should obey a quarantine period before entering the bank.

Appropriate storage of antigens/vaccines in an emergency reserve will be very much dependent on the disease to which they are targeted to. The antigen may be a chemically inactivated or killed virus, for example such as that used in FMD vaccines, or it may be an attenuated vaccine such as that exemplified by Bluetongue vaccines. The antigens themselves may be concentrated and held at ultra-low temperature, over liquid nitrogen for example, or may be a freeze dried commodity where low temperature is not necessarily important. Whatever the method of storage, it is vitally important that they are optimally maintained and routinely monitored in order to have some assurance that they will be efficacious when needed. Managers of vaccine banks should therefore ensure that the necessary arrangements are in place to monitor their reserves on a routine basis and to include, where necessary and at appropriate time intervals, a testing regime to ensure integrity of the antigen component or acceptable potency of the final product. For example, 24-hour storage temperature may be recorded as well as periodic inspection of the bottles containing the antigen for cracks or leakage. In this context, managers may wish to also consider the possibility of independent testing, or of greater reliance on overseeing/auditing of the manufacturer’s test procedures.

The need for routine testing of stocks for stability is evident, and therefore depositories of antigens/vaccines should include a large number of small samples that are representative of the larger stock for such purposes stored side by side with it.

Whilst not directly related to the establishment, storage and operation of vaccine or antigen banks, Countries should nevertheless recognise the importance of contingency planning to ensure that the stored vaccine, if required, is distributed and administered in an efficient and prompt manner. They should make certain that the necessary cold-chain facilities are available, that vaccination protocols are defined in advance, that vaccination teams are established and trained appropriately and that all the other necessary documentation, equipment, reagents and clothing is stockpiled to sufficient levels to support any potential vaccination campaign. Therein the benefits of also performing periodic exercises and simulations should not be overlooked.
It would be advisable for member countries to monitor the literature published on important advances that are being made in subjects relating to vaccine bank technology. Ongoing research does lead to improvements of product, equipment, manufacture and distribution and therein more efficient and practical use of Banks. In this context there has been a recent study examining methods of prolonging the storage of fully formulated vaccine by a novel formulation procedure (2).

REFERENCES


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