

RESPONSIBLE USE OF MEDICINES IN AGRICULTURE ALLIANCE

ruma

GUIDELINES

Responsible use of vaccines and vaccinations in farm animal production

A farm health planning initiative in partnership with DEFRA

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Introduction

The Responsible use of Medicines in Agriculture Alliance (RUMA) is a coalition of organisations including agricultural, veterinary, pharmaceutical, and retail interests. This Guideline is one of a series of documents developed by RUMA. Initially RUMA came together to address issues concerning the use of antimicrobials (antibiotics) in agriculture, and it has published a summary and detailed guidance for each of the main food producing species (cattle, sheep, pigs, poultry and fish) aimed at promoting responsible use of antimicrobials (available on www.ruma.org.uk). This guidance advised that farmers should regard therapeutic antimicrobial products as complementing good management, vaccination and site hygiene. It went on to repeatedly refer to the role of vaccination in reducing the need for antimicrobial medication. It is logical therefore that RUMA should in this document go on to consider vaccines and vaccination in more detail.

A fundamental principle of good livestock keeping has always been the responsible use of medicines, and is given impetus by the encouragement of farm health planning under the Animal Health and Welfare Strategy (AHWS). This overarching strategy grew out of the post-2001 foot-and-mouth disease investigations that had highlighted inadequacies in the way in which Britain dealt with disease risk.

Farm health planning represents one of the direct ways in which the livestock sector, specifically individual producers, can be persuaded of the cost benefits of adopting on-farm health strategies. Best practice in the use of veterinary medicines must be an integral part of effective health planning, and this RUMA guideline aims to define best practice. This long Guideline is one of a series of documents and it deals with the principles of vaccination and vaccine usage in farm animals and is aimed primarily at advisers, farm managers and owners. There is also a short version of this Guideline for more general usage. Other guidelines are available each in both a short and long version and they deal with a single or group of farm animal species, namely dairy and beef cattle, sheep, pigs, poultry and fish.

Vaccination (immunisation) is a tried and tested method of assisting in the continual fight against disease in man and animals. It began in China around 1000 AD when the Chinese adopted a form of immunisation involving the inhalation of dried powders derived from the crusts of smallpox lesions. Various methods were also adopted against smallpox in other countries that involved the introduction of pus from a smallpox pustule into a scratch in a healthy person. Better known is the work of Edward Jenner, an English physician who following observations that milkmaids did not develop smallpox lesions, used cowpox inoculations to immunise his patients against smallpox. Then a hundred years later, Louis Pasteur who discovered that injection into chickens of damaged chicken cholera bacillus did not produce illness and they were protected from subsequent exposure to a fresh culture of the cholera bacillus.

Almost all people in Great Britain will have received vaccinations of one type or another during their lifetimes. Their purpose is to prevent the exposure to an infection causing signs of illness or disease. Generally their usage is recognised as being of benefit and uncontroversial, although concerns over the MMR vaccine appeared to have led to a

reduction in its usage thereby reducing overall national population or “herd” coverage and thus resulting in some children developing the infections. Generalising, all vaccines produce great benefits to the majority of people or animals, which means that they do not suffer the damaging effects, illness or death caused by the organism for which they are vaccinated. These benefits far outweigh any side-effects of vaccination which are usually transitory or a local reaction to the vaccine and occur in a small number of individual persons or animals. If this were not the case, the specific vaccines would not have been licensed for medical or veterinary usage. Many farm animals receive vaccines for the same reasons as in humans, namely, to reduce or prevent the effects of infection or illness.

All vaccines are developed for making the animal or human being immune and therefore resistant to an infection. This is vaccination or immunisation. They are used to assist in the control and prevention of a variety of infections caused by bacteria, viruses, fungi and parasites.

The Mechanisms of Infection and Immunity

Defence Mechanisms

When animals or man are exposed to a disease organism (virus, bacterium, mycoplasma, fungus, parasite etc.) and it infects them it will cause defensive reactions in the animals or man. Most of these infectious agents encountered by an animal do not penetrate the body's surface and are prevented from entry by a variety of biochemical and physical barriers. In addition the body tolerates a number of commensal micro-organisms on the surface or in the gut. These usually compete effectively with many potential pathogens. They affect the activity of pathogens by such tactics as not allowing the disease organisms to multiply – known as competitive exclusion - or by the production of chemicals which act as natural disinfectants and kill off the organisms. (These types of organisms are like probiotics or so called “good bacteria”).

Besides these anatomical and physiological defences a more complex method of body defence is the immune system. This involves non-specific (innate) and specific (active) responses to the invading organism. Innate immune responses include the ingestion and destruction of organisms by specific cells, and other inflammatory responses such as the redness, swelling and heat observed at the sites of infection.

Active or acquired immunity is a specific response to invading organisms. The reaction is to the proteins or other molecules present in the micro-organisms and/or its secretions. The protein or molecules that provoke this immunity are known as antigens and the reaction when a response is produced is in the form of an antibody. This latter is, perhaps paradoxically, also a protein. In general the appearance inside the body of a protein not recognised by the body as its own is considered a “foreign” or an alien protein. This is thus an antigen and will result in antibody being produced. While this does happen to proteins within the body, this does not always happen to all those present in the gut or respiratory system or on the skin as these are outside the body. As the antibody formation is activated by proteins, it can occur with other sources of protein that enter the body such as undigested food proteins following injections or blood transfusions.

The protein does have to be foreign to the animal as the foetal immune system is programmed to recognise its own body's protein makeup and so it does not make antibodies against itself (immunotolerance). Thus in later life, an animal very rarely makes antibodies against its own body. Should this not be the case and the animal makes antibodies against itself this is known as an autoimmune reaction. Autoimmune diseases are rare in animals.

However if any infections enter the foetus before this body protein recognition begins then they are considered by the body to be part of its own make-up. This is a "Trojan horse" type of infection and cases of this can occur with the viruses such as those causing bovine viral diarrhoea in cattle, border disease in sheep, avian leukosis and classical swine fever. The reason why immunity is not usually produced to food proteins is that they are broken down into the fundamental "building blocks" of proteins, namely amino acids. On their own these are too small to induce an immune response and so can safely be absorbed into the body. Once in the body these amino acids can then be built up into the animal's own proteins.

Normally, as a result of this exposure to a micro-organism, the animal will produce substances later on including antibodies which will make the infection less able to remain and so will mean that the animal will survive and recover from the infection's detrimental effects. Should the animal again be exposed to the same infection, following production of this reaction that is often partly in the form of active immunity it will usually not result in disease. This is because the animal will have sufficient immunity to repel the infection without causing any severe illness or, in many cases, without the animal or person being aware that they have been exposed to the infection.

Immunity

Immunity is both non-specific and specific (active). The non-specific part does not depend on previous exposure to the foreign substance. In such cases as a first line of defence, micro-organisms can be engulfed, inactivated, digested and destroyed by special types of white blood cells known as polymorphonuclear leucocytes. This occurs before specific immunity can develop.

Immunity comes in two forms innate (born with) and acquired (occurs following antigen stimulation). (See Table 1)

Table 1: Components of Immunity in Animals

Innate (born with)	Acquired
Humoral (Circulating) Immunity	
Complement	Antibodies of various types
Lysozyme	Maternally Derived Antibodies (MDA)
Interferon	
Cell Mediated Immunity (CMI)	
Phagocytic Cells	T lymphocytes Activated Killer Cells Helper Cells
Natural Killer Cells	B lymphocytes
	Lymphocytes lacking T and B cell markers

Active or acquired immunity depends on the specific recognition of the foreign substance and is the usual outcome of natural infections.

Humoral (or [Blood] Circulating) Immunity

This is in two forms: **innate** and **acquired**.

Innate

These mechanisms are present before birth of the animal.

Acquired

These are acquired after birth and are in two forms: **active** and **passive**:

Active

In this form when a protein enters the body and is recognised as being foreign the animal is stimulated to produce specific antibody. This combines with the organism and helps to inactivate it as well as enhancing its removal by the white cells. This process is mimicked when undertaking vaccination.

Each antigen produces a specific protein and so it only produces a single specific antibody response (monospecific). However the causes of infections contain many proteins and so many different antigens and thus many different antibody responses (multispecific) will occur. All these responses will ultimately help in the elimination of the infection.

Passive

This is where the animal receives immunity that it has not itself produced. In some species of animals and human beings this can occur while the foetus is in the uterus. It can also occur in the newborn of some species especially ruminants because in utero antibody transfer does not occur. Thus the newborn calf and lamb as well as the piglet have been designed to be able to

absorb into their circulation and body antibodies present in the dam's first milk (colostrum). This is known as maternally derived antibody (MDA). Absorption only occurs within the first day or two of life (depending on the species) and involves various mechanisms which result in the newborn not digesting the antibody proteins within its gut and also allowing their absorption intact into the body. Without such a system the young ruminant animal would be highly susceptible to all the infections with which it was initially exposed. Birds achieve the same protection by depositing high concentrations of maternal antibody in the yolk of each egg laid.

The presence and amount of any circulating immunity in the young animal after sucking will be affected by many factors including - the efficiency of the mother to produce immunity and then transfer it into the colostrum; the ability of the offspring to take in sufficient colostrum in the first few hours of life; the management and nutrition of the mother prior to birth and the husbandry of the dam and young in the period after birth. The processes are complex and often the causes of failure are subtle. Tests are available to indicate the success or failure of this passive immune transfer.

The other way passive immunity can occur is through the administration into the body of antibodies. This is occasionally given to an animal that is ill with an infection and it will be in the form of immune serum or hyperimmune serum (obtained from animals with very high antibody levels to the infection). The most commonly used hyperimmune serum in farm animals is tetanus antitoxin (TAT).

Cell Mediated Immunity (CMI)

Innate

These are also present at birth and include :-

- Phagocytic cells (partly derived from the reticuloendothelial system) including
 - Neutrophils, macrophages – they produce several substances that kill and help digest micro-organisms and include the antigen presenting cells.
 - Natural killer (NK) cells – derived from T and B lymphocytes and are able to kill off many different target cells including virus-infected cells and tumour cells without the need for antibodies.

Acquired

This is the local immunity to micro-organisms and is produced by groups of lymphocytes (some produce cluster determinant [CD] markers) and include:-

- T lymphocytes including T helper (CD4) and cytotoxic (CD8) markers
- B lymphocytes involved in delayed-type hypersensitivity
- Other lymphocytes lacking classical T and B cell markers

The Objectives of Vaccination

There are three basic objectives in vaccination:-

- To provide immunity to the animal or group of animals (active immunity)
- To provide immunity to the offspring of an animal via vaccination of the dam (passive immunity)
- Or to provide immunity to the animal or group of animals and their offspring (active and passive immunity)

Types of Antibody

An antibody produced by exposure to an antigen is known as an immunoglobulin. There are five types of these immunoglobulins:-

- **IgA** This provides local immunity and can be found in mucus secretions in different parts of the body such as the respiratory tract, gut, mammary gland and urogenital system. They are adapted to cross the surfaces of mucosal tissues so that they can adhere to organisms in the gut, respiratory system etc. thereby preventing their attachment to the mucosal surface.
- **IgD** This is found as traces in the white cells (lymphocytes) of man and poultry. Its significance is unknown.
- **IgE** This is mainly found in parasitic infections and allergic reactions. It also contributes to mucosal defence.
- **IgG** This is the most common antibody found in the blood and the body fluids. It is the one mainly measured in blood tests when looking for infections or to monitor the response to vaccination. Its smaller size than IgM means that it can penetrate body tissues. The equivalent in birds is IgY - so called because they were first found in the egg yolk. IgY is similar in structure and function to IgG but with some biochemical differences.
- **IgM** This is found early in the immune response to an antigen and is a large protein. Its large size means that it is less able to penetrate body tissues. It encourages the white blood cells to break down the infection.

The Process of Producing an Immune Response

The process is relatively similar in mammals and fish, although fish lack bone marrow. When an infection (with its associated antigens) not previously experienced by the animal first enters the body it starts an immune response. The micro-organism will be recognised as being foreign and then cause a whole series of activities resulting in the production of immunoglobulins including IgG which can be measured in the blood. Initially complex protein molecules of a micro-organism are taken up by specialised macrophage cells called “**antigen presenting cells**”. These cells tend to be strategically sited and at them the

complex protein molecules are broken down into peptides (short amino acid chains) within these antigen presenting cells and then these are transferred to the cell's surface. If these peptides are found to be foreign then they are recognised by a special type of white cell called the T lymphocyte. Each population or clone of these T cells produces a surface molecule, a receptor. These binding sites for attachment to the individual antigens of a micro-organism and result in so-called **cell mediated immunity**.

This T cell then produces a response in other T and B lymphocyte populations. These include the production of killer cells and in the B lymphocytes the antigenic stimulus produces **memory cells**. If these are stimulated for long enough, they produce antibody against the antigen and they will remain in small numbers within the animal long after the infection has ceased. If the infection returns the memory cells are activated and produce clones and antibody rapidly increases. The antibody produced by each B-cell clone is known as a **monoclonal antibody**, collectively they are termed gammaglobulins or immunoglobulins (Ig).

This produces humoral or blood immunity. The initial rise in antibody usually takes about 10 to 14 days to start and then it will usually rise to a peak over a number of weeks (Figure 1). After this the antibody level will normally subside slowly. Should the same infection return it will stimulate an accelerated, more vigorous response by both T and B lymphocytes and the production of more antibody (**anamnestic response**) (Figure 2). In this way an environment is created which will rapidly eliminate the micro-organism. This usually means that when a second attack by the same micro-organism occurs the animal will not show signs of illness, or the signs are few or mild. Occasionally, if return of infection is a long period (usually several years) after the original exposure the reaction and antibody response might be similar to the first time. In such a case, the animals may become ill and the antibody response might be similar to the first time that the animal was exposed to the infection and will usually take about 10 to 14 days to rise.

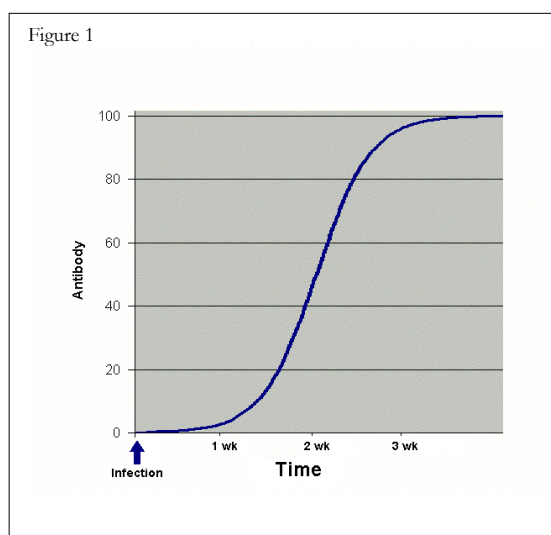


Figure 1. Diagrammatic representation of immunity following exposure of a naïve animal to a new infection. (Diagram - A. H. Andrews)

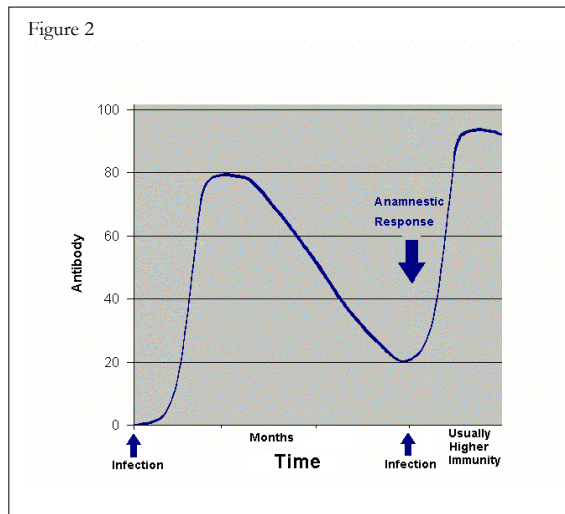


Figure 2. Diagrammatic representation of immunity following entry of an infection in a naïve animal and later re-exposure to the same infection. (Diagram - A. H. Andrews)

The specific immune responses also coordinate with non-specific defence mechanisms such as the complement system. This is a protein system designed to eliminate antigens inactivated by specific antibodies and to recruit cell populations that kill micro-organisms.

Vaccines

In many ways these are processed in the same way as if they were infectious organisms. The main difference is that there is a controlled exposure to the antigen (micro-organism). Most conventional vaccines are derived from a pathogen causing the disease and hence they provide specific protection against that disease. Only in a few limited cases can vaccines be produced from related species and still produce the required immunity. The Jenner vaccine using cowpox virus to vaccinate against smallpox is, perhaps, one of the few examples of this exception. Vaccines can be classified in many ways but the most important is that of them being either alive or dead (inactivated vaccine).

The text contains many generalisations to allow an understanding of the difference between live and dead vaccines. Being generalisations, they do not apply to all vaccines or in all situations within which they are used.

Live Vaccines (See Figure 3)

These are usually a modified strain of the infection in which the ability to cause disease has been reduced or removed. They often state in the Summary of Product Characteristics (SPC) – formerly the data sheet, “modified live” or “live attenuated”. Most of these descriptions are applied to viral or parasite vaccines. When presented to the animal, they act in the same way as an infection and so they multiply within the animal’s body. Thus they tend to produce a similar immune response to that seen in natural infection.

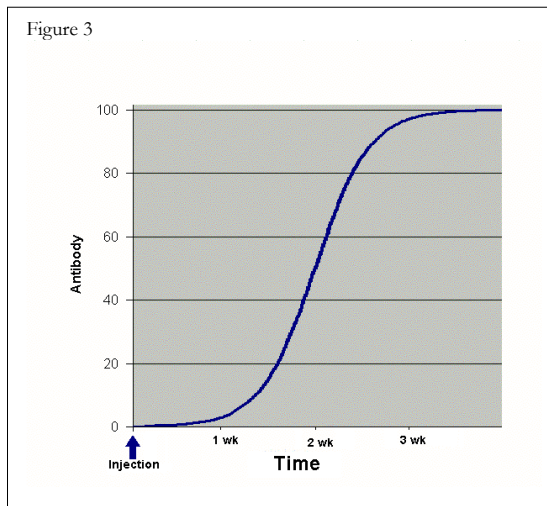


Figure 3. Diagrammatic representation of immunity following the use of most live vaccines in a naïve animal. (Diagram -A. H. Andrews)

What this means in practice is:-

- Usually only one application of the vaccine is required to produce immunity (but this does depend on the vaccine and the degree of attenuation).
- Usually the dose required to produce the antibody response is less than with a dead vaccine.
- Usually a major antibody rise occurs within about 10 to 14 days of introducing the vaccine.
- Usually these vaccines can be killed off by unsuitable storage (usually too hot, exposure to sunlight, etc.) and so they require strict observance of storage (often this means in a refrigerator).
- Usually they will have a shorter shelf life than dead vaccines. However this does depend on the specific vaccine.
- Usually once a particular vaccine vial or container is opened and/or reconstituted its efficacy will be limited.

The advantages of live vaccines include:-

- Usually the amount of the agent required is small when compared with that for a dead vaccine. This does to an extent depend on the vaccine
- The vaccines are usually less likely to produce a local reaction than a dead vaccine.
- The vaccine usually needs to be given only once and can result in less problems with compliance and less handling stress.

The disadvantages of live vaccines are:-

- Usually, but not always, the amount of the agent required is small and so its correct dose administration may be critical.
- As the vaccine organism will grow in the animal it can result in the animal being more likely to show slight general signs of illness than with a dead vaccine. However this does depend on the vaccine.

- If the animal is ill (overtly or subclinically) at the time of vaccination then this may prevent or reduce the amount of antibody production as well as cause increased expression of the intercurrent disease. Again this will vary with the vaccine.
- As the vaccine is live and multiplies within the animal's body, treatments of the animal may kill off or affect the vaccine organism i.e. live bacterial vaccines may be killed by the administration of antibiotics to the animal.
- Some vaccines may not produce a good immune response when there is still maternally derived passive immunity present in the animal from colostrum. This can also happen with some dead vaccines.
- Very occasionally infections have been introduced by contamination in the vaccine production.
- As the vaccine usually does not contain substances to reduce or stop micro-organism growth, it is more likely to become contaminated once the vial or container is opened than a dead vaccine.
- In some instances organisms can be transferred from vaccinated animals to those not vaccinated. Where this might occur precautions in the SPCs will warn not to mix vaccinated and unvaccinated animals.

Dead Vaccines (See Figure 4)

Often the SPCs (data sheets) state killed in their text. They contain whole or part organisms. Many are bacterial vaccines, although some viral vaccines also are dead. Generally they consist of suspensions of "antigenic material" such as inactivated whole organisms or their products. As any organisms present are killed during the manufacturing process, they are unable to multiply within the animal's body. This means that the amount of immunity produced by the animal tends to be more dependent on the quantity of antigen present within the vaccine. Often various additives are included with these vaccines to increase the immune response and also to allow a long period of exposure to the antigen present within the vaccine. These are known as adjuvants (See below) and they allow an increase in the amount of antibody produced.

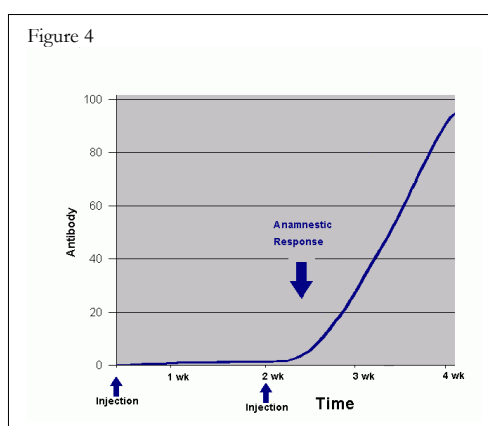


Figure 4. Diagrammatic representation of immunity following vaccination with most dead vaccines requiring two doses to produce an immune response. (Note – there is no previous background exposure to the organism.) (Diagram - A. H. Andrews)

What this means in practice is:-

- Usually, but not always, two applications of the vaccine are required to produce immunity.
- Usually the amount of antigen required to produce this antibody response is greater than with a live vaccine. However with modern vaccines this is not always the case.
- The vaccines often contain adjuvants to increase the antibody response.
- If two doses of vaccine are required to produce immunity, a time interval between the two doses will be detailed. This varies with the disease and the vaccine manufacturer and needs to be obeyed.
- Usually a major antibody rise occurs in about 10 to 14 days after the second dose of the vaccine.
- The vaccine will usually be injected and it will produce mainly IgG. Some vaccines also produce a CMI response.

The advantages of dead vaccines include:-

- The vaccine cannot cause the disease.
- Usually in a healthy animal the vaccine is less likely to cause a general illness following administration.
- It is less likely to be affected by passive immunity in a young animal than is a live vaccine. However MDA can have effects on some vaccines.
- Usually, but not always, they will have a longer shelf life than live vaccines.

The disadvantages of dead vaccines include:-

- Usually the amount of the agent required is larger than for a live vaccine.
- In some instances the volume injected will be larger than for a live vaccine. However new technologies have allowed some vaccines to reduce the volume required to be administered.
- The quantity of the immune response is mainly, but not always, dependent on the amount of antigen present in the vaccine.
- The presence of adjuvants may make such vaccines likely to produce a local reaction, some of which may remain for a long period.
- The vaccine usually needs to be given twice and can result in problems with compliance and an increase in the stress from handling.

(Toxoid Vaccines)

These are basically variations of dead vaccines but the antigens are toxins usually secreted by the micro-organism rather than whole or parts of micro-organisms. These toxins are produced by the bacterium and are responsible for the signs of illness experienced by the animal. The toxin is made safe usually by a form of chemical neutralisation and so it is not able to produce illness. The most common examples of these vaccines are the clostridial ones where neutralisation is with formalin (formaldehyde).

Combination Vaccines

While many vaccines provide specific protection for one organism or strain of an organism, others will be wider in their disease protection. This may be because they have present antigens that include different strains of the organism. Others will provide protection against a number of micro-organisms often of the same type such as in the clostridial vaccines. In other cases vaccination can be offered against different micro-organisms which result in the same types of disease such as with calf respiratory vaccines which may combine several viral antigens and also in some cases bacterial components. Other vaccines may contain completely different antigens in terms of diseases caused but they are administered together as they are important causes of infection in the species concerned or they provide required enhanced protection at certain stages in the animal's life such as with sheep clostridial/pasteurellosis vaccines.

All multiple vaccines require much expertise in their formulation to ensure that they are produced so that each component is in sufficient quantity to initiate an immune response in the animal. Such vaccines do have considerable advantages in that they reduce the number of times the animals are vaccinated with its potential stress from handling and the administration of the vaccine. Another major advantage is that it means that there are fewer dates for the owner to remember as to when to undertake initial vaccination or subsequent boosters.

Marker Vaccines

It is generally not possible to identify the difference between the immunity produced by vaccination and that from natural (wild strain) infection. This can produce difficulties when trying to diagnose the presence of infection in the individual or the national herd or flock. This sometimes can be overcome by removing part of the genetic structure of the micro-organism and making the vaccine from this (gene deleted vaccine). If immunity is due to the vaccine it can be shown that there is no antibody to the missing gene(s). Perhaps the most widely used gene deleted vaccine is a marker vaccine for infectious bovine rhinotracheitis (IBR). Its use is starting to lead to the eradication of this disease in some countries. Besides removal of antigenic material it is possible to add extra material to the vaccine. All such vaccine which allow the identification of vaccinated animals from naturally infected animals are called marker vaccines or DIVA vaccines (Differentiate Infected from Vaccinated Animals).

Recombinant Vaccines

All living cells contain in their nucleus genetic information. These genetic instructions are carried by genes on strands of deoxyribonucleic acid (DNA) within the chromosomes. More recently the genetic make-up of many organisms as well as mammals and other creatures has been defined. These sequences in all organisms are based on an arrangement of four different amino acids. This has led to the technology of identifying the role of individual genes and to determine their relative positions. Following this it is now possible to selectively remove, augment or rearrange them on the DNA strands, a process called recombination. In practice this allows desirable characteristics to be retained or enhanced and undesirable or superfluous

ones to be removed. This has the potential to deliver superior vaccines that produce enhanced immunity, have less side effects and can have additional beneficial characteristics.

Live recombinant vaccines are able to still multiply in cells and usually give an excellent immune response as they can still simulate natural infection. Identification of genes within organisms that provide disease virulence can allow their alteration or removal thereby producing safer vaccines. It is also possible to remove an essential gene which means that should it enter the environment it is unable to spread.

Subunit Vaccines

In this technology those antigens are identified that produce immunity and are separated from those that are responsible for virulence. This then allows purified antigens to be produced which create subunit vaccines. These vaccines obviously have enhanced safety. They also produce less antigenic competition as only a few components are present in the vaccine and so they may provide enhanced protection. They can also be used as marker vaccines to distinguish between immunity from vaccination and that from natural infection previous or current.

Other Vaccine Technologies

Much work is continuing to make vaccines more effective. This includes technology to introduce protective antigens from one pathogen into another pathogen and so immunise the animal against both. Another method involves vaccinating animals with only the genetic material contained within certain viruses. This then allows the animal to produce its own vaccine within its own body. This technique is often referred to as genetic immunisation or DNA immunisation.

Attenuation

This is often referred to within the description of a vaccine, which is live. It involves the reduction in the virulence of a pathogenic micro-organism. The word means that the organism has been weakened and so it is less able, or unable, to produce signs of illness or disease. In some instances this may have involved isolating the organism from a species where it was less pathogenic. Otherwise it can be done in many different ways and can include using an organism strain which has minimal, or no, virulence. Growing the organism in cells within the laboratory so that over many generations a reduction in virulence is achieved. More recently the use of genetic engineering has also provided another way of producing attenuation in the laboratory.

Adjuvants

The art of vaccine production is to ensure the maximum protection of the animal with the minimum disruption by vaccination. The positive benefits of vaccination in part depend on the vaccine formulation and the additives present besides the antigens themselves. These are of varying type. Some known as adjuvants enhance the immune response of the animal to the antigen. Many are concerned with producing a “depot effect”, they include aluminium

hydroxide which is often used in clostridial vaccines. Mineral oils are also used to reduce the speed of adjuvant removal thereby increasing exposure time within the animal to the vaccine.

Other Additives

In dead vaccines it is possible to include antibacterial preservatives such as thiomersal, a mercury-based organic substance and formalin.

Reactivation of the Immune Response

Natural Infection

When an antigen (say a micro-organism) enters an animal for the first time, provided the infection is not immediately killed off, it allows the complex interaction between different sets of cells to occur, with the immune mechanisms described above being initiated. The antibody level in the blood can be measured. Initially there will be no specific antibody or immunity, but it starts to rise after 10 to 14 days (Figure 1). This may be slower or not at all if the infection is immunosuppressive or if the animal is compromised in its immune response. The antibody rise will continue and reach a peak usually weeks after the initial entry of the micro-organism before starting to fall. Often if the micro-organism is no longer present in the animal's associates or the environment the level may fall to almost zero. However usually the memory cells are still present. Thus provided the period without exposure is not too long, if the micro-organism eventually reappears then the memory cells become active and produce a very rapid (a few days) rise in the antibody level (Figure 2). This is often called an "anamnesic response". Again the degree of this response may be altered by the micro-organism or the animal. However often the antibody level produced will be higher than that initially produced.

On occasions such as:

- if the period separating exposures is too long
- the infection level is too high
- the micro-organism is immunosuppressive
- the animal is immunosuppressed
- the animal is suffering from other concurrent infections
- nutritional/metabolic problems
- the animal is acutely or chronically stressed
- other factors are present

illness and disease can occur (See Figure 6). The severity of this may be similar to that when the animal was first exposed to the micro-organism.

Booster Vaccination

Vaccines in most ways mimic infections and so their response is usually similar. However the detail of the response varies and partly depends on whether or not the vaccine is live or dead. With a live vaccine, the development and multiplication of the organism within the animal causes a similar immune response to the infection. Thus usually there is a time lag of

about 10 to 14 days before the rise in antibody levels (Figure 3). In the case of a dead vaccine there will be a minimal antibody response to the first dose of the injection and the rise in antibody may not be seen until about 10 to 14 days after the second injection of the vaccine (Figure 4).

In most vaccines, revaccination or a **booster dose** is suggested or required after a given time, often a few months or a year or more (See Figure 5). This has the effect of acting to produce the accelerated or anamnestic response with antibody levels rapidly rising and often they will be higher than from the initial vaccine response.

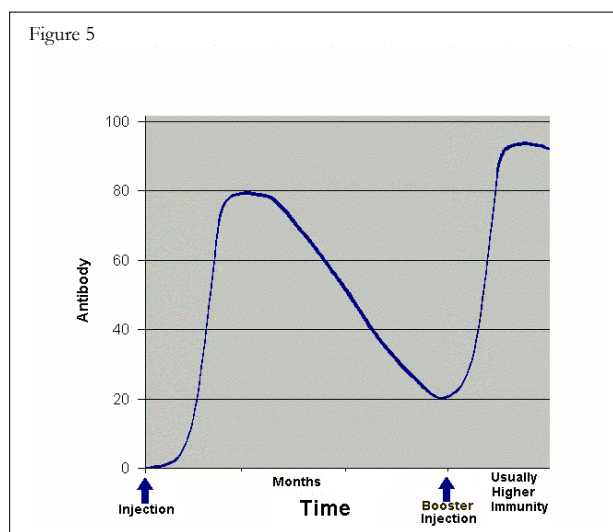


Figure 5. Diagrammatic representation of immunity following the use of a booster vaccination. (Note – no previous background expose to the organism before vaccination.)
(Diagram - A. H. Andrews)

Again, as with natural infection, if there is too long a period between vaccination and the exposure to the micro-organism, disease and illness may occur (Figure 6). When there has been a long period without vaccination then unless blood testing is undertaken, it is often best to assume that the animal is no longer immune to the infection. In consequence the full initial vaccination programme should be instituted, just as if the animal had not previously been vaccinated.

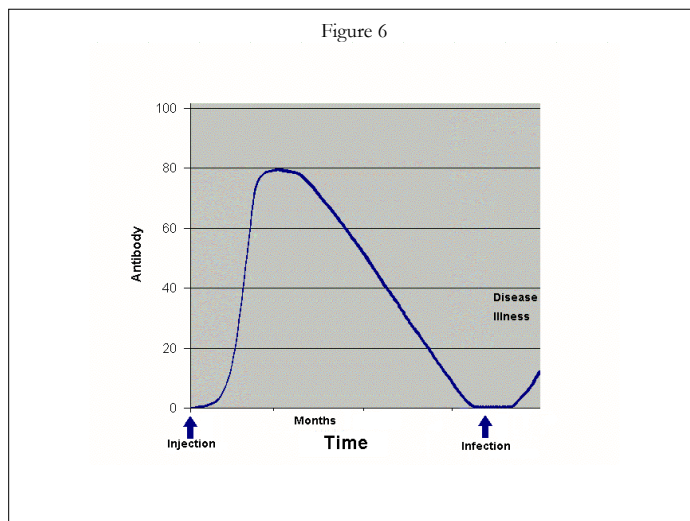


Figure 6. Diagrammatic representation of immunity following use of a vaccine and then too long a period before exposure to the infection. (Diagram - A. H. Andrews)

Immunity in the Young Animal

The young farm animal is able to produce an immune response but this ability is less well developed than in the older animal. This makes the animal very susceptible to infections when exposed in early life and is the reason why it is essential that all calves, lambs and pigs receive an adequate level of colostrum as early as possible after birth. This allows entry of the immunoglobulins (MDA) into the body circulation and these will assist in the survival of the young animal until it has had time to produce its own antibodies. The amount of uptake of this passive immunity will depend on the quality of the colostrum produced by the dam, as well as the quantity ingested and how soon it is taken in after birth. Feeding after the first day of life allows antibodies to be present in the gut. Thus in calves it is not until around 30 days old that the immune system can respond effectively to most antigens. The other problem can be that because of maternally derived passive immunity obtained from the colostrum there may be interference with antibody production following vaccination, and this may be worse with live vaccines. It is therefore essential that vaccines are administered at the ages indicated by the SPC (formerly the data sheet).

Administering the Vaccine

Vaccination should only be undertaken in healthy animals which are not compromised by poor nutritional or husbandry conditions or in other ways. The animals should not be stressed either by the environment in which they are living or from being handled or from the administration of the vaccine. Stressed animals are less likely to produce a good immune response. Also if conditions are too hot or too cold then immunity may not be as good, but this is rare in the UK. It is important to ensure that all the flock or herd is vaccinated simultaneously as otherwise those which have been missed may act as carriers of disease and incubate the infection. Such animals can remain a latent threat to the others and as the

vaccinated animals immunity wanes they may produce an overwhelming challenge to these latter animals. This is particularly a problem with range cattle and hill sheep.

Reasons for Immunity not Developing or being Reduced

Usually modern vaccines, properly administered, will achieve a high level of protection regardless of the husbandry system in which the animal is kept.

There are a few animal diseases, usually inherited, in which the animal is unable to make a proper immune response. These are very uncommon and are usually self-limiting because, if the animal is born alive, it will soon die on exposure to infection. However in animals of all ages there may be reasons for the ability of the animal to make immunity (immunocompetence) being reduced (immunosuppressed) or taking longer to develop (immunocompromised) or absent (immunodeficient).

Besides the above, vaccination will be unlikely to work if the natural infection has entered the animal before the vaccine. Equally vaccination may not stop the infection or disease when challenge is very heavy or the animal's health is compromised in other ways.

Reasons for producing a poor immunity to an infection can include:-

- The Infection Itself – a number of infections suppress immunity and these particularly include some viruses and mycoplasma
- Stress – this comes in many different forms for an animal
- Nutrition – an inadequate overall diet may suppress immunity
- Deficiency in individual feed ingredients – especially proteins, vitamin A and E, selenium, etc.
- The Production Status of the Animal – immune response is often less in the mother close to birth
- Age of Animal – very young or old are often immunosuppressed
- Other Diseases – especially cancer, metabolic diseases (e.g. pregnancy toxaemia in sheep, fatty liver in cattle)
- Vaccination Process – insufficient vaccine given, out-of-date, stored incorrectly, not administered by correct route, period too long from making up vaccine to its administration.

Methods of Administration

The routes of vaccine administration will depend on various factors including the easiest method of introducing the antigen to a particular species, the labour involvement, the type of immunity required (i.e. circulating or local [mucosal]), whether the vaccine is live or dead, any adjuvants present that will alter the duration of exposure. The ease of administration is a very important practical consideration of their usefulness. At one time most inactivated vaccines were given by injection. However it is now possible to administer some of them by mouth via the food or water, as a spray or through the skin.

Injections

Most injected vaccines are given either subcutaneously (sc) or intramuscularly (im). The former will usually remain at site longer than the latter. They are the usual form of application in ruminants and produce mainly IgG. Intraperitoneal (ip) injections are the most common routes of vaccination in fish which are sedated or anaesthetised to aid the procedure.

Intra-dermal injections

This method of application is unusual and is mainly used in contagious pustular dermatitis (orf) in sheep. The application probably results in cell-mediated immunity. A modification of this technique for fowlpox is the wing web puncture or feather follicles.

Oral

A common route of application and it is used in particular with parasitic infections such as lungworm in cattle and coccidiosis in poultry. Many live viral poultry vaccines are placed in the water.

Aerosol (nebulisation or fogging)

Mainly used for mass poultry vaccination of young birds. The vaccines tend to be live and viral. They are quickly absorbed and produce both local and circulating immunity. In poultry, coarse sprayer cabinets are used in hatcheries as well as a range of coarse sprayers on farms. Finer, more uniform, sprays are also used to produce aerosol or controlled droplet administration (CDA).

Intranasal

This is undertaken for respiratory diseases in cattle. This produces a relatively high IgA level. The vaccines are live viral. Some can be used to vaccinate animals against viruses in the face of disease. This is because of the rapid formation of non-specific interferon which assists in viral destruction and then the production of local IgA within a few days.

Eye Drop

Sometimes used on young birds with a live viral vaccine. They are rapidly absorbed and allow both local and systemic immunity to develop.

Water Application

This provides vaccination for fish using their environment to distribute the vaccine. This is the equivalent to aerosol vaccination in poultry. However drinking water application is commonly used in poultry where the target organ is the gut or, less frequently, the respiratory system.

Feed Application

Occasionally vaccines are used in the feed of pigs (not currently in the UK), poultry and sometimes fish. The main problems are ensuring adequate stability of the vaccine and its even distribution and uptake by the animals. In poultry administration is by spray onto the feed and is usually applied by a mechanical sprayer.

Egg (In-ovo) Injection

Some vaccines are injected into the egg on the transfer into the hatchery to allow the chick shortly after birth to have some specific immunity to the infection.

Vaccine Registration

In Europe the manufacture of vaccines is very strictly registered. All medicines are regulated by European Union Directives (Directive 2001/82/EC as amended by Directive 2004/28/EC). These have had to be brought into force by all Member States. In the United Kingdom the appropriate legislation is the Veterinary Medicines Regulations and these are revised annually. Before any new vaccine can be registered it must obtain a Marketing Authorisation (MA). Such a Marketing Authorisation can be obtained at a national level in the UK from the Veterinary Medicines Directorate (VMD) or via the centralised procedure of the European Medicines Agency (EMA). An application for a MA involves the submission by the manufacturer of data concerning the vaccine that are stringently reviewed by the regulatory authorities. The review ensures that the vaccine is of high quality, it is efficacious and that it is safe for the consumer, the user, the animal and the environment.

The registration process may take several years. A MA is initially valid for five years after which the company can apply for a renewal. The decision to authorise renewal is mainly dependent on the pharmacovigilance records. These records are collected from veterinary surgeons, MA holders and animal owners concerning adverse reactions and lack of efficacy arising from the use of the product. After the renewal process, the MA is not under any time restriction. However the authorities can review the vaccine's safety and risk-benefit balance at any time. The company must notify the VMD if any serious adverse reaction occurs and also it is obliged to continue to submit summary reports of all recorded incidents.

Other Authorisation Routes for Vaccine Usage

If for a particular disease there is no UK vaccine but there is a vaccine available in another country, it is possible for a veterinary surgeon to apply to the VMD for a certificate to import and use the product in the UK. The application is for a Special Import Certificate (SIC) if it is licensed in another EU country, or if from another country a Special Treatment Certificate (STC).

It is also possible to grow a micro-organism from a disease on farm and then make a dead vaccine from it. This is known as an autogenous vaccine. Again an authorisation has to be obtained and use of the vaccine is restricted to the holding from where the infection was isolated or to other holdings with an epidemiological association with the farm. Very occasionally where outbreaks of serious epidemic disease occur the legislation allows the use of a vaccine without a MA. The provision has been very rarely used.

Legal Categories

Under the Veterinary Medicines Regulations vaccines for farm animals fall into two categories namely POM-VPS and POM-V.

POM-VPS

(Prescription-Only Medicine – Veterinarian, Pharmacist, Suitably Qualified Person)

This is a medicine for food-producing animals which must be prescribed by a veterinarian, pharmacist, or SQP (either orally or in writing) and which must be supplied by one of those groups of people in accordance with the prescription. (Formerly these were PML livestock products, MFSX products and a few P products).

POM-V

(Prescription-Only Medicine – Veterinarian)

A medicine which must be prescribed (either orally or in writing) by a veterinarian to animals under his care following a clinical assessment and which may be supplied by a veterinarian or pharmacist in accordance with the prescription (formerly POM products and a few P products).

Milk and Meat Withholding Times

Generally most vaccines do not have a withholding time for either milk or meat. However there are a few exceptions to this and so again always the manufacturer's SPC (formerly the data sheet) should be read. The most common vaccines used that have a withhold time are live ones used in sheep. Thus a vaccine for the control of toxoplasma abortion has a meat withhold time of six weeks and in some vaccines for enzootic abortion in ewes the withdrawal time is seven days. If vaccines are used off SPC usage then a standard withdrawal period should be observed.

Adverse Side-Effects from Vaccination

Considering the many millions of doses of vaccine sold annually and used in farm animals, adverse side effects are very rare. The types of reaction will vary according to the vaccine used. However it is usually live vaccines that can make the animal show a temperature rise with associated reduction or cessation of feeding, dullness and reduced milk production, if lactating. With dead vaccines the most common side effect is local and is a reaction around the site of vaccination especially if there is an adjuvant present to delay the antigen absorption. However reactions can occur in vaccines without the presence of adjuvants. It is for this reason that most vaccines which are injected will indicate the site for their administration. Usually it will be advised that the vaccine, particularly if subcutaneous, should be introduced into an area of the animal not used for human consumption such as behind the animal's ear or in the area of the chest wall behind the elbow. Then if there is any residual vaccine left or any reaction to it, there will be no involvement of an edible part of the carcass. Occasionally a relatively large volume of a cold vaccine into a small or young animal has resulted in cold shock.

Suspected Adverse Reactions and Environmental Incidents

Should a suspected adverse reaction occur such as a possible side effect, etc it should be reported to the veterinary surgeon or supplier of the vaccine and an Animal Suspected Adverse Reaction report (yellow form) completed and returned to the Veterinary Medicines Directorate. Cases of suspected lack of efficacy should also be reported. It is advisable that all suspected problems are also reported to the MA holder. In the case of a suspected Environmental Incident a blue form should be completed and again sent to the Veterinary Medicines Directorate.

Handling Vaccines and their Storage

Vaccines, particularly live ones, need to be treated with respect when handling, storing and using them. It is important to read and follow all instructions on the SPC and product literature to ensure that the vaccines will produce their maximum activity.

Many live vaccines need to be kept under a specific storage environment that may involve keeping them away from light and in cool conditions. It is important to regularly check that a refrigerator is working at the required temperature. Often once the vaccine is made up it will only be viable for a short period and again still needs to be kept in the conditions stated on the SPC. Only sufficient vaccine should be made up as can be used in the stated viability period. Other vaccine that is required to be made up later must still be kept under the required storage conditions to ensure its efficacy is maintained.

Dead vaccines usually require two doses and these should be administered at the interval indicated by the manufacturer. When live or dead vaccines need boosting then this should be done at the intervals stated by the manufacturers.

Vaccines for Notifiable Diseases

Some notifiable diseases have vaccines which can be used in the United Kingdom and a good example of these are those used for Newcastle disease. However, there are also in the United Kingdom authorised vaccines for some notifiable diseases such as foot-and-mouth disease and avian influenza. These are authorised in case of need, and the government has a contingency stockpile of some of these. However in the United Kingdom, it is illegal to use or import such vaccines without official permission.

The Economic Benefits of Vaccination

Vaccines and vaccination strategies should form an integral part of all farm/herd health planning. Some diseases that are prevalent or a constant threat should be considered in detail in such a plan as how best to control or prevent their occurrence. In such instances it would be helpful to show the cost-benefit of such control measures to that particular farm or herd/flock. Other diseases that are less common or are of less severity, should also be included in the plans in case these occur in the area or on the farm. The criteria for controlling (including vaccination strategies) the entry and/or spread of disease on that farm

should be detailed. Ideally the risk assessment and a rough cost benefit for the strategy should be included and agreed in the proposals.

In all cases where disease is likely to occur, vaccination will produce benefit to healthy animals. Usually this is in the form of preventing signs of illness when disease occurs on the farm or by reducing the severity or losses associated with the disease. Any lack of disease is taken for granted, and as such it is often hard to impress on producers the cost benefit of disease control and vaccination. Whilst the effects of disease may be all too apparent when there has been an outbreak which is then controlled or removed by vaccination, memories tend to be short. Then the use of vaccination in the control strategy may be challenged or might be discontinued.

Where disease has not apparently occurred, the financial advantages are much less easy to determine on the individual farm or to convince the farmer about, unless a detailed examination is carried out of the on-farm benefits and they are compared with the costs of disease when it occurs. Thus to most farmers the costs of calf pneumonia outbreaks appear only to be due to the result of veterinary involvement and the treatments provided. However it can be shown that the costs of such inputs and involvement in a bovine respiratory disease outbreak in suckler calves as well as those born in the dairy herd and reared for beef or heifer replacements are only about 40 % of the total costs of a disease outbreak. The other costs can include increase in management inputs, mortality, labour, growth reductions and delayed deaths. They are hidden or not costed but on all farms they provide the majority of costs. In sheep, the costs of outbreaks of pasteurellosis have been shown to result in a cost benefit in favour of vaccination of over 7:1. The problem with this disease is that outbreaks are sporadic and variable in extent. Thus often one or a few dead sheep are accepted as part of the normal farming process. This means that in individual farm problems, because of the wide variation in incidence, mortality and related disease problems in each group of sheep, the benefit over the cost of clostridial/pasteurellosis vaccination varied from 2:1 to about 40:1. Often the relationships between one disease and others not necessarily related are not recognised by those dealing with the problem.

Perhaps one of the clearest advantages of vaccination was seen in the 1990s following the introduction of pig enzootic pneumonia (EP) vaccination into herds where the disease was present. In these herds, once the vaccination regime was introduced, there was often a reduction in age of animals reaching slaughter weight of about a fortnight. Conversely removal of EP vaccination resulted in the time to slaughter lengthening by an almost equal amount.

In salmon farming, the introduction of the oil-based bacterial vaccines around the early 1990s dramatically reduced the amount of antibiotics to a fraction of that previously used.

VACCINATING – THE DOS AND DON'TS

Basic

ALWAYS READ THE MARKETING AUTHORISATION SUMMARY OF PRODUCT CHARACTERISTICS (SPC) (FORMERLY THE DATA SHEET)

This applies even when the same vaccine is being used frequently as it reminds you of some unusual circumstances which might arise during vaccination and not previously seen by yourself. It also informs you of any changes concerning instructions, usage or efficacy.

Storage

Ensure all vaccines are stored correctly before use.

Many vaccines require cool storage – ideally have a dedicated refrigerator for vaccines and medicines that can be secured.

Any vaccine not requiring refrigeration should be stored in a dedicated vaccine store or otherwise the medicines cabinet or store. These must be lockable.

Keep all vaccines away from children.

Keep all medicine cabinets, stores and refrigerators clean.

Where similar vaccines are kept with different expiry dates ensure those with the shortest expiry time are at the front.

Many vaccines only have a short shelf-life, ensure you only use vaccines in date. When ordering vaccines ensure only sufficient is ordered to meet the requirements at that time.

Safety of those Vaccinating

All those vaccinating animals should be adequately trained.

Check any precautions about those who can handle and use the vaccine.

Some vaccines do have marked reactions following self injection and always be aware of this and keep easy access to the SPC (data sheet) in case an accident occurs.

If self injection occurs, then you should seek immediate medical advice and take the SPC or package insert with you.

While most injections will not cause any harm to the injected person, do not assume that a small injection will be harmless without taking professional advice.

Ensure that there is sufficient labour available to allow vaccination to be undertaken with minimal stress to both animals and handlers and thereby making vaccination safer.

Animals to be Vaccinated

Only vaccinate fit and healthy animals.

Do not vaccinate stressed animals.

Do not vaccinate exhausted animals.

Do not vaccinate animals in very late pregnancy.

Do not vaccinate animals younger than the age given by the vaccine manufacturers without taking advice.

Elderly animals may not respond in their immunity as well as younger ones.

Do not vaccinate animals that are nutritionally deprived or starved.

Do not vaccinate animals that are deficient in nutrients including vitamins and minerals.

Do not vaccinate animals soon after they have been ill without taking advice from the manufacturers.

Do not vaccinate animals too close to service or in the service period unless it is stated that this is acceptable.

Do not vaccinate animals that are immunosuppressed.

When injecting vaccines ensure that the site of injection is clean and dry.

If animals have had an immunosuppressive disease or illness wait as long as possible before vaccination. Where possible take advice from the manufacturers.

Do not use more than one vaccine at the same time unless authorised.

If different vaccines for different diseases need to be given to the same animal, there must be an adequate interval in between each vaccine to ensure that they all produce a satisfactory immune response.

Do not administer other treatments or do other procedures at the same time as vaccination without taking advice from the manufacturer.

If other procedures or treatments are of necessity to be given for management purposes as well as vaccination, undertake a risk assessment of the likely effects on efficacy.

Ensure when feed or water is the vehicle for providing vaccination then it has been correctly prepared so that the vaccine is not negatively affected by the vehicle. Manufacturers provide instructions as how to prepare feed and water appropriately.

If vaccines are to be given orally via water or feed, manage the animals to ensure all will be able to receive their appropriate amount of the treated feed or water.

Vaccine Courses and Booster Dosing

Where the vaccine regime involves giving more than one dose, ensure that the second dose is given at the required interval.

Where a second dose is used, ensure the correct dose is given.

Ensure it is known how long after the vaccine course immunity will have developed.

When booster vaccinations are required, ensure that they are given at the correct intervals.

If the time lapse for booster vaccinations will be for some reason too short or too long then take advice.

If the time interval before a booster vaccination is longer than authorised it will usually be necessary to assume that the animal has lost its immune memory and a new initial vaccination course may be required. Advice should be sought on this matter.

Preparing the Vaccine

FOLLOW ALL THE ADVICE PROVIDED ON THE SPC OR PACKAGE INSERT

Check the dose or dilution rate.

Ensure that the tops of all vials and bottles of diluent are sterile.

Ensure with injectable vaccines a sterile needle is used to enter both vaccine vial and diluent.

If the vial contains multiple doses and a single injection syringe is to be used, ensure a sterile needle remains in the vial top.

The type of swab to be used to clean and sterilise the top needs to be determined as some sterilants such as alcohol may denature or kill live antigen.

Ensure that any syringes etc. are clean and sterile and do not contain any extraneous material such as disinfectants etc. that might kill off or denature the vaccine.

If having to reconstitute the vaccine always use the correct type of diluent or water.

If reconstituting is required always use the correct volume of diluent or water.

If the vaccine to be used is applied via the drinking water or by air as a coarse or fine spray ensure that the water used will not affect the efficacy of the vaccine.

If reconstituting is required, it probably means that it is a live vaccine and check how long it is viable after reconstitution.

With live vaccines only make up sufficient volume that can be easily used within the designated time.

Ensure all vaccines when in use are kept as required i.e. some must not be exposed to high temperatures or to direct sunlight etc.

When a multidose syringe is used ensure the correct volume is being injected.

With all types of syringes ensure that the needle is changed at frequent intervals so as to ensure it is not blunt or causing contamination.

If a vaccine vial is broached but not completely used at the time, check on the SPC (data sheet) the length of its in-use shelf-life and do not use after that period.

Vaccinating an Animal

Ensure that the animal is competently and adequately restrained before vaccination.

Do not vaccinate animals that are inadequately restrained or when “playing up” as this may lead to injury to people or the animal, or placing the vaccine in the wrong place or missing the animal all together

Place the vaccine into a clean area as aseptically as possible.

If the animal is dirty find a clean area or sometimes clipping will allow somewhere cleaner to be used.

If animals are too dirty do not vaccinate until they are cleaner.

Where possible do not inject in the rain as this can lead to more contamination at the sites used for injection.

Check in the manufacturer’s literature if any particular parts or areas of the body should be used.

Give the vaccine by the correct route.

If more than one route can be used take advice to determine the one best to use, probably it should be based more on the rate at which immunity develops or the type of immunity produced rather than just on the ease of administration.

Recording Vaccination

An animals medicines record book must be kept, copies of relevant regulations and of good practice should be available.

Accurate information must be kept of the animals vaccinated, the date of vaccination, the batch number, the amount used, the expiry date of the vaccine, and the withdrawal period that must be observed.

The medicines record book must be kept for five years even when all the animals have died or been slaughtered.

Information of all vaccines in use should be available to all stock keepers and should be kept on file.

Any suspect adverse reaction including apparent non-efficacy should be reported to the

Veterinary Medicines Directorate (VMD) and the supplier. The report can be made via the prescribing veterinary surgeon or supplier.

In the case of a suspected adverse reaction, forms can be found on the VMD website:
<http://www.vmd.gov.uk>

Disposal of Vaccines and Containers

Read the SPC (data sheet) and dispose of according to their recommendations and those of the regulatory authorities

Always safely dispose of unused medicines and containers and application equipment (including needles into a sharps container) when vaccination has been completed.

In some cases, particularly with live vaccines, it will be necessary to kill off the micro-organism by the use of agents such as disinfectants before disposal. This will prevent possible contamination.

If in any doubt always seek advice from your veterinary surgeon or whoever supplied the product.

The Responsible Use of Medicines in Agriculture Alliance (RUMA) was established in November 1997 to promote the highest standards of food safety, animal health and animal welfare in British livestock farming.

A unique initiative involving organisations representing every stage of the food chain, RUMA aims to promote a co-ordinated and integrated approach to best practice in the use of animal medicines.

RUMA membership spans the food chain and includes organisations representing interests in agriculture, veterinary practice, the pharmaceutical industry, farm assurance, training, retailers, consumers and animal welfare interests.

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RUMA is made up of the following organisations:

Agricultural Industries Confederation (AIC)
Animal Health Distributors Association (AHDA)
Animal Medicines Training Regulatory Authority (AMTRA)
Assured Food Standards (AFS)
British Poultry Council (BPC)
British Retail Consortium (BRC)
British Veterinary Association (BVA)
Linking Environment and Farming (LEAF)
Meat and Livestock Commission (MLC)
National Beef Association (NBA)
National Consumer Council (NCC)
National Farmers Union (NFU)
National Office of Animal Health (NOAH)
National Pig Association (NPA)
National Proficiency Test Council (NPTC)
National Sheep Association (NSA)
The Royal Association of British Dairy Farmers (RABDF)
Royal Pharmaceutical Society of Great Britain (RPSGB)
Royal Society for the Prevention of Cruelty to Animals (RSPCA)

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