J. Comp. Path. 2010, Vol. 142, S120–S124

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Immune Protection in Animals: The Examples of Rinderpest and Foot-and-Mouth Disease

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Summary

Fading immune protection in farmed animals may present a problem, particularly in free-ranging animals in nomadic and transhumant pastoral systems, where animals are not readily available for large-scale blanket vaccination programmes. Two veterinary examples of fading immune protection are discussed: rinderpest and foot-and-mouth disease (FMD). Both are devastating viral diseases of cattle that have a huge impact on the farming economy. Both diseases can be controlled by vaccination, although the post-vaccination immunity afforded by the rinderpest vaccine is markedly different from that induced by FMD vaccines. These differences may in part explain the respective advancement of international eradication campaigns: while global eradication of rinderpest is imminent, FMD viruses are still actively circulating in many parts of the world.

Keywords: food-and-mouth disease; immune protection; rinderpest; vaccination

Rinderpest

Rinderpest Virus and Clinical Disease

Rinderpest is a viral disease of cattle that has a long history. The virus, a member of the *Morbillivirus* genus, mainly infects cattle (*Bos taurus* and *Bos indicus*). Morbidity is high, while the mortality rate is high with virulent strains, but variable with mild strains. A summary of the disease and the causative agent has been provided by the World Animal Health Organization (OIE) (http://www.oie.int/eng/maladies/fiches/a_A040.htm).

Clinical disease is easy to diagnose since infected animals classically present with the 'four Ds': discharge, diarrhoea and dehydration, leading to death. All domestic ruminant species can be infected including water buffalo and small ruminants. Wild ruminants, such as the African buffalo (*Syncerus caffer*) and all types of antelopes, as well as African warthogs (*Phacochoerus* spp.) are also susceptible to the virus, but do not act as a reservoir (Rossiter *et al*., 2006). In contrast, wildlife species are only infected sporadically and this most likely involves spread from cattle (Kock *et al*., 2006). The virus is thought to have emerged in central-east Asia and to have spread to Africa, where devastating outbreaks have been reported. Rinderpest was first identified in 1887 in eastern Africa and outbreaks spread through the entire sub-Saharan continent, arriving in western Africa in 1892 and in South Africa in 1896. The virus travelled to South America (Brazil) in 1921 and to Australia in 1923, although it never became established in these countries. North America has remained free of rinderpest.

Rinderpest Vaccines

Rinderpest viruses are of a single serotype (although three phylogenetic lineages have been described) and the attenuated strain used in vaccines confers life-long protection in cattle (Taylor *et al*., 2006). Some of the first-generation rinderpest vaccine strains were attenuated in goats. Egg- and rabbit-attenuated strains followed, which were replaced by tissue culture vaccines in the 1960s, when virus was grown on calf kidney cell cultures (Plowright and Ferris, 1962). In the mid-1980s, a heat-tolerant rinderpest virus strain was developed on Vero cells (Mariner *et al*., 1990). The thermostability of the vaccine strain (needed to

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0021-9975/$ - see front matter
doi:10.1016/j.jcpa.2009.11.003

reduce cold chain requirements) and the means of reconstitution of the vaccine and application to cattle in the field in warmer and remote areas proved essential for advancement of the eradication campaigns in Africa. Pilot studies in east and west Africa were conducted before the more widespread use of this product.

Herd Immunity and Rinderpest Control

The total control of rinderpest was proved to be possible when a high percentage of the total population of cattle were made permanently and solidly immune to infection through vaccination. This concept was further refined when modelling studies indicated that intermediate levels of rinderpest vaccination (60–80% of the susceptible population) could in fact prolong epidemics and account for persistence, whereas lower or higher coverage would result in shorter epidemics and drive infection to extinction at local or population levels (Fig. 1; Mariner *et al*., 2005). Post-infectious immunity (in surviving animals) as well as post-vaccination immunity proved to be life-long. Waning immunity at the level of individual animals is not therefore an issue with rinderpest vaccines. However, in the final stage of rinderpest eradication, it was essential to ascertain that the virus would not persist in parts of the Somali ecosystem, despite the problems associated with suboptimal vaccine coverage (Kock *et al*., 2006). Waning population immunity can occur through recruitment of naïve animals to the population after their maternal immunity has waned (maternally-derived antibody [MDA] disappears at around 10–11 months of age in cattle) and through gaps in coverage in previous vaccination campaigns. Moreover, calves with high titres of MDA do not respond to vaccination. Large scale vaccination campaigns have been implemented in cattle in various parts of the world and the target of maintaining strong herd immunity has been monitored serologically, using virus neutralisation assays (before 1985) and enzyme linked immunosorbent assays (ELISA; after 1985).

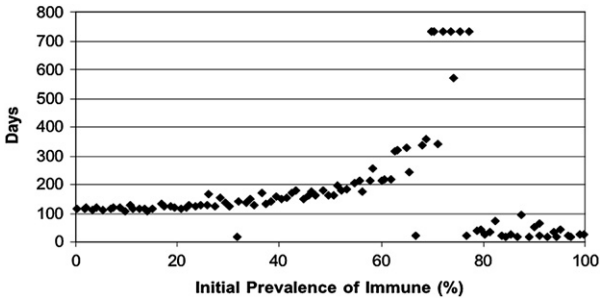

Fig. 1. Persistence of rinderpest in a given population as a function of the initial prevalence of protective immunity: the duration of an epizooty is longest when pre-outbreak immunity is between 60% and 80% (Mariner *et al*., 2005).

Rinderpest Eradication Campaigns

Large scale institutionalized vaccination campaigns aimed at eradicating rinderpest were implemented in southern India in the 1970 and 1980s, but these campaigns failed. The Indian government then proposed the establishment of a National Programme for Rinderpest Eradication, which proved successful by 1995. However, animals in Pakistan were still infected at that time and India maintained vaccination along its border until 2001, when Pakistan also achieved eradication. Similarly, multiple vaccination campaigns have proven necessary in Africa.

In 1962, 17 African countries reported active rinderpest infection and an international campaign called Joint Programme 15 (JP15) was started in 22 countries. This programme covered the entire intertropical region, over a period of 10 years and extended from west to east Africa, ending in the Horn of Africa. The first vaccine used was the goat-adapted vaccine, until this was replaced by Plowright's tissue culture-adapted virus vaccine. In 1976, the expected date of eradication, only two countries reported the disease.

However, the virus remained present in certain specific ecological niches such as in the Niger River delta in Mali and in some parts of southern Sudan and western Ethiopia. The achievements of JP15 were tragically undone when a new panzootic started in the Niger River (Sudd) and spread eastwards along the Sahel at the beginning of the 1980s and a second focal outbreak erupted in southern Sudan that spread rapidly westwards. One third of the cattle of the Fulani populations died; in Nigeria alone two million cattle fell sick and half a million perished. The epizootic spread south through Uganda by cattle looted by the victorious Tanzanian troops and ravaged the wildlife population of Tanzania.

With renewed vigour, the European Commission (EC) and other partners participated in the implementation of the Pan-African Rinderpest Campaign (PARC), which began in 1987 in 34 African countries and was coordinated by the Inter-African Bureau for Animal Resources of the African Union (AU-IBAR). In the mid-1990s, only limited foci of infection persisted in war-torn Sudan and Somalia. The Somali focus spilled over into Kenya and Tanzania, causing havoc in wildlife, but not in cattle. The virus was recovered from a gum erosion in one animal and proved to be an old African strain, virulent for wildlife, but non-fatal for cattle. At the end of the PARC project, rinderpest had not been totally eliminated and a new programme implemented by the AU-IBAR and mostly supported by the EC, the Pan-African Control of Epizootics (PACE), was put in place to continue the fight against the disease.

Imminent Global Eradication

An international initiative was launched in 1994, lead by the Food and Agriculture Organization (FAO) in close association with the World Organization for Animal Health (OIE) and regional organizations, particularly the AU-IBAR. This initiative aimed to eradicate the virus worldwide and was called the Global Rinderpest Eradication Programme (GREP), with the secretariat of the programme based at the headquarters of FAO in Rome (http://www.fao.org/ag/againfo/programmes/en/grep/home.html). The GREP concerned Africa as well as Asia and the Middle East, and proposed a common schedule to achieve rinderpest eradication by 2010 (Fig. 2). Appropriate efforts were undertaken to use thermostable vaccines (particularly in remote areas), to establish diagnostic laboratory networks with effective quality assurance controls, to monitor the post-vaccinal immunity and to develop subregional and regional approaches. Participatory approaches to disease detection were developed, particularly in remote and unsecure regions, whereby cattle holders were trained and could participate directly in vaccination and surveillance. This was of utmost importance since all cattle had to be vaccinated and then monitored, including in areas of conflict. This programme proved very successful (Diop and Bastiaensen, 2005; Normile, 2008) and FAO and the OIE should be in a position to declare the world free from rinderpest by 2010. This will be the first example of global eradication of an animal disease in human history.

Foot-and-Mouth Disease

Foot-and-Mouth Disease Viruses

The case of foot-and-mouth disease (FMD) is a very different story. FMD is one of the most contagious animal diseases and all wild and domestic cloven-hoofed animal species (artiodactyls) are susceptible to infection. FMD viruses belong to seven serotypes (A, O, C, Asia 1, Southern African Territories [SAT] 1, SAT 2 and SAT 3) and there are a plethora of antigenic variants within a given serotype (Table 1). Strains of different antigenic structure can co-circulate in a given region and there is very little, if any, cross protection between serotypes. This means that the vaccines against FMD must match the circulating wild-type strains in order to provide sufficient herd immunity in the area of the outbreaks; therefore, vaccines are generally multivalent. Furthermore, as the vaccines are killed, they typically must be given once or twice yearly in order to maintain effective herd immunity (Woolhouse *et al.*, 1996).

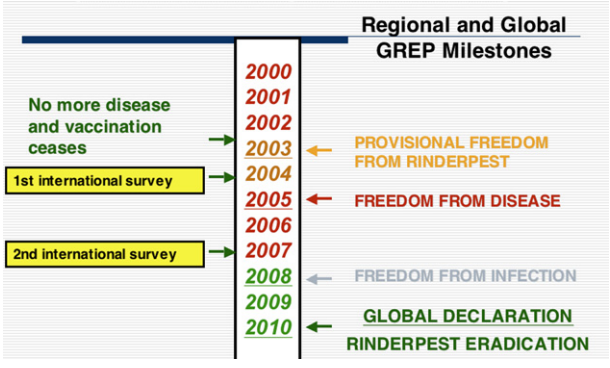

Fig. 2. The proposed OIE pathway to global rinderpest eradication.

Foot-and-Mouth Vaccines

There is a long list of criteria for the 'ideal FMD vaccine'. It should be safe and efficient, induce very fast and long-lasting clinical and virological protection, be easily administered and only require a minimum number of applications to achieve protection, allow the distinction between vaccinated and infected animals (through a 'differentiation of infected from vaccinated animals [DIVA] test'), allow storage at room temperature and be inexpensive.

Few of these criteria have been met by recently developed vaccines. Current FMD vaccines are inactivated vaccines developed from preparations of tissue culture-derived, purified virions in a formulation containing aluminium and saponin or oil adjuvants, forming a single or double oil emulsion. They are costly to produce, in particular the multivalent vaccines. These vaccines need to be stored at 4°C and the delivery of the vaccines can be difficult in developing countries where public veterinary services and public-private partnership are weak.

Table 1
Antigenic diversity and geographical distribution of the different foot-and-mouth disease virus serotypes

FMD type	*Extent of diversity*
O	The most prevalent serotype, with two main lineages: South America and 'Old Europe'; Middle East and Asia. There are several recognized vaccine strains (Manisa, BFS and Campos).
A	Second most prevalent serotype. High antigenic diversity. New antigenic variants emerge frequently.
C	Limited antigenic diversity and very restricted geographical distribution.
SAT 1–3	Highly genetically diverse. Limited endemic range with periodic excursions.
Asia 1	Middle East and Asia. Limited antigenic diversity.

Gaps in Immune Protection

At a population level, the loss of effective herd or flock immunity to FMD is the result of introducing naïve animals into the population. In enzootic areas, a natural cycle of infection/immunity can be observed, which may explain the observed inter-epidemic periods of over 2 years. In the field, post-vaccination duration of immunity (DOI) ranges from 4–6 months after the last vaccine injection in cattle, particularly with aqueous-based adjuvanted vaccines (Woolhouse *et al.*, 1996). As a consequence, there is a risk of 'immunity gaps' if national vaccination campaigns are not held with sufficient frequency (even twice a year may be insufficient) or have suboptimal coverage or do not include booster vaccination of young animals. Oil-based vaccines do provide prolonged immunity, but this does not extend beyond 12 months and this is the only vaccine formulation that can be used to protect swine.

At the level of the individual animal, MDA persists for 3–4 months if the dam has post-vaccination or post-infection immunity. MDA reduces the risk of infection and protects against myocarditis and sudden death, but once MDA titres decay the young animals become highly susceptible to FMD unless they are properly vaccinated (primary and booster injections). However, MDA interferes with vaccination, despite the fact that FMD vaccines are inactivated, and in the field, vaccination is often delayed until the young animals are at least 4 months old. In national FMD vaccination campaigns with compulsory timings (e.g. twice a year), many animals may be affected because of the immunity gap between loss of MDA protection and timing of first immunization. Many vaccination programmes do not incorporate a booster dose 1 month after first vaccination and, as a result, the animal receiving only this primary vaccination may have inadequate duration of protection.

Since young animals are often marketed and may not yet have received an effective primary course of immunoprophylaxis at the time of marketing, these animals may fuel epidemics through acquiring infection in the process of movement and marketing.

As a consequence, in areas enzootic for FMD, affected animals are generally 4–18 months of age.

Selection of Vaccines

One contentious issue with waning FMD immunity is its potential influence on selection of antigenic variants. The narrow spectrum of cross protection with A and SAT serotypes and high viral evolution rate regularly produce antigenic variants that evade 'vaccine pressure'. It is clear from enzootic regions in west Asia that such variants emerge every 3–5 years. This may, however, relate to waning natural immunity rather than waning or partial vaccine immunity, since in regions with high vaccination coverage, such as those in several countries of South America, the emergence of antigenic variants is much less of a problem. However, close attention should be paid to the early detection of new variants.

FAO supports surveillance for antigenic threats, which includes sampling in high risk locations, shipment of samples to FAO/OIE laboratories and communication of new threats to Chief Veterinary Officers and to decision makers. Serological surveillance is performed by virus neutralisation and/or ELISA and antigenic matching using these tests provides a way to predict the suitability of vaccines to counter new virus variants; the latter matching tests require a highly competent international reference laboratory.

Regional Virus Pools

At the global level, FMD surveillance has allowed identification of seven major virus pools with

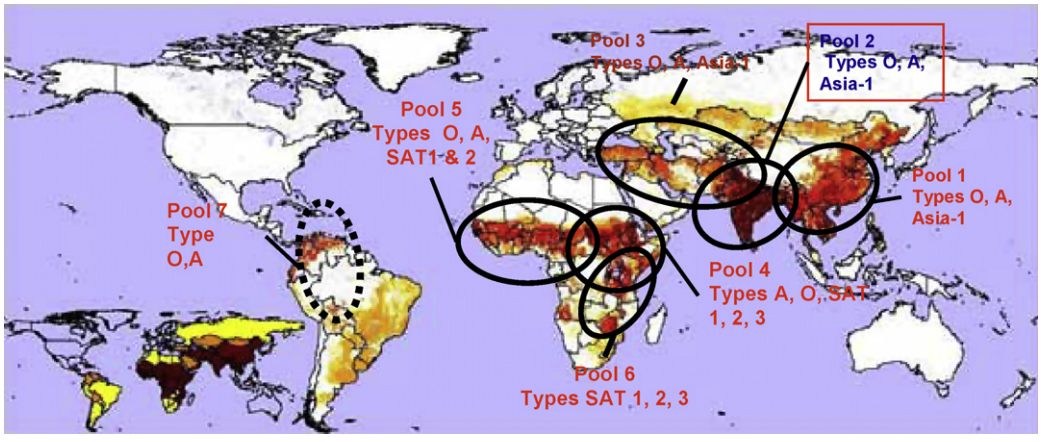

Fig. 3. Seven major regional pools of FMD viruses have been identified where circulation and evolution occur (FAO, 2008).

continual viral circulation and evolution. Epidemic 'jumps' arise between pools and to FMD-free regions (Fig. 3). These data are now used as a basis for action against the regional virus types, with adapted multivalent vaccines produced at that level (Rweyemamu *et al.*, 2008). Regional strategic maps have been produced as part of a global initiative that has been recently launched by FAO and OIE to progressively control FMD in the world (http://www.fao.org/news/story/en/item/29028/icode/). This initiative takes into account the impact on public good of this disease, which affects international and domestic trade and livestock productivity, as well as livelihoods of small farmers in developing countries. A specific Progressive Control Pathway (PCP) has been proposed that is not a 'top down' approach. In contrast, each infected country is encouraged to develop national risk reduction strategies that are supportive of the regional effort, under international coordination. This programme has a long-term aim (10–20 years), targeting the control of the virus, not its eradication. While several regional virus ecosystems such as South American and certain parts of Asia are expected to become free of the disease with vaccination by 2020, the aim of the programme is more modest in Africa.

Conclusions

Thanks to the efficacy of the rinderpest tissue culture vaccine, the implementation of regional and national campaigns in Asia and, more importantly, in Africa through the PARC and PACE coordinated by the AU-IBAR, as well as the launching and development of the GREP, rinderpest has been progressively controlled. Through the successful combined global and local efforts, the worldwide eradication of rinderpest is expected to be announced by FAO and OIE in 2010. In contrast, FMD is unlikely to be eradicated in the short term. FMD vaccination can provide a high cost:benefit ratio in certain husbandry sectors, but at the national level the high investment needed to control disease at the population level is less clear cut. Because of the high transmission rate of FMD viruses, disease control in enzootic areas is usually only achievable through vaccination, together with control of high risk animal marketing procedures. A world-wide regional approach to FMD control, based on regional road maps to implement risk-based control measures, has recently been launched by FAO and OIE. The presence of different strains and the lack of cross protection between them, the immunity gap between maternal and vaccine-induced immunity and the relatively short duration of protection add to the complexity of FMD control. However, FMD vaccination is only part of the disease prevention; control programmes and control of movements and other sanitary measures and, in emergency situations, culling (under certain conditions) may also be required.

Conflict of Interest

The author was an invited speaker at the Merial European Comparative Vaccinology Symposium and received travel expenses and an honorarium for this presentation.

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