Vaccination spells the end for a devastating plague

At a time when highly pathogenic virus diseases such as avian influenza and AIDS are threatening to overwhelm us, **Tom Barrett** reports some good news: the virtual global eradication of rinderpest virus through a concerted vaccination campaign.

Rinderpest, or cattle plague, bears all the hallmarks of a disease capable of causing economic and social disaster. Wherever it has occurred, it has caused terrible destruction of cattle, adversely affected agriculture and rural livelihoods, bringing in its wake famine and starvation.

Rinderpest is a morbillivirus, its closest relative being human measles virus. Infections begin in the upper respiratory tract and, after a variable incubation period, spread from the local lymph nodes via the lymph and blood to other lymphatic tissues, before progressing to the mucosal surfaces, causing the formation of necrotic lesions and discharges from the nose and eyes. The gut mucosa is also affected, leading to severe and bloody diarrhoea and death as a result of dehydration. Virulent strains also affect the immune system and cause an increased susceptibility to other pathogens. During vaccination campaigns, farmers were made aware of rinderpest by advertising it as the disease of the three D's (discharge, diarrhoea and death).

Disease and warfare

Rinderpest has long been associated with wars and invasions where there is uncontrolled movement of people and their cattle. Invasion by the Huns into Europe in the late 4th century resulted in an outbreak of a highly contagious disease of cattle which was clearly identified for the first time as rinderpest by the Latin writer Severus Sanctus Endeleichus. Subsequent accounts describe pandemics that followed the Mongol invasions of Western Europe. Cattle plague was probably the first agrobiological weapon ever employed.

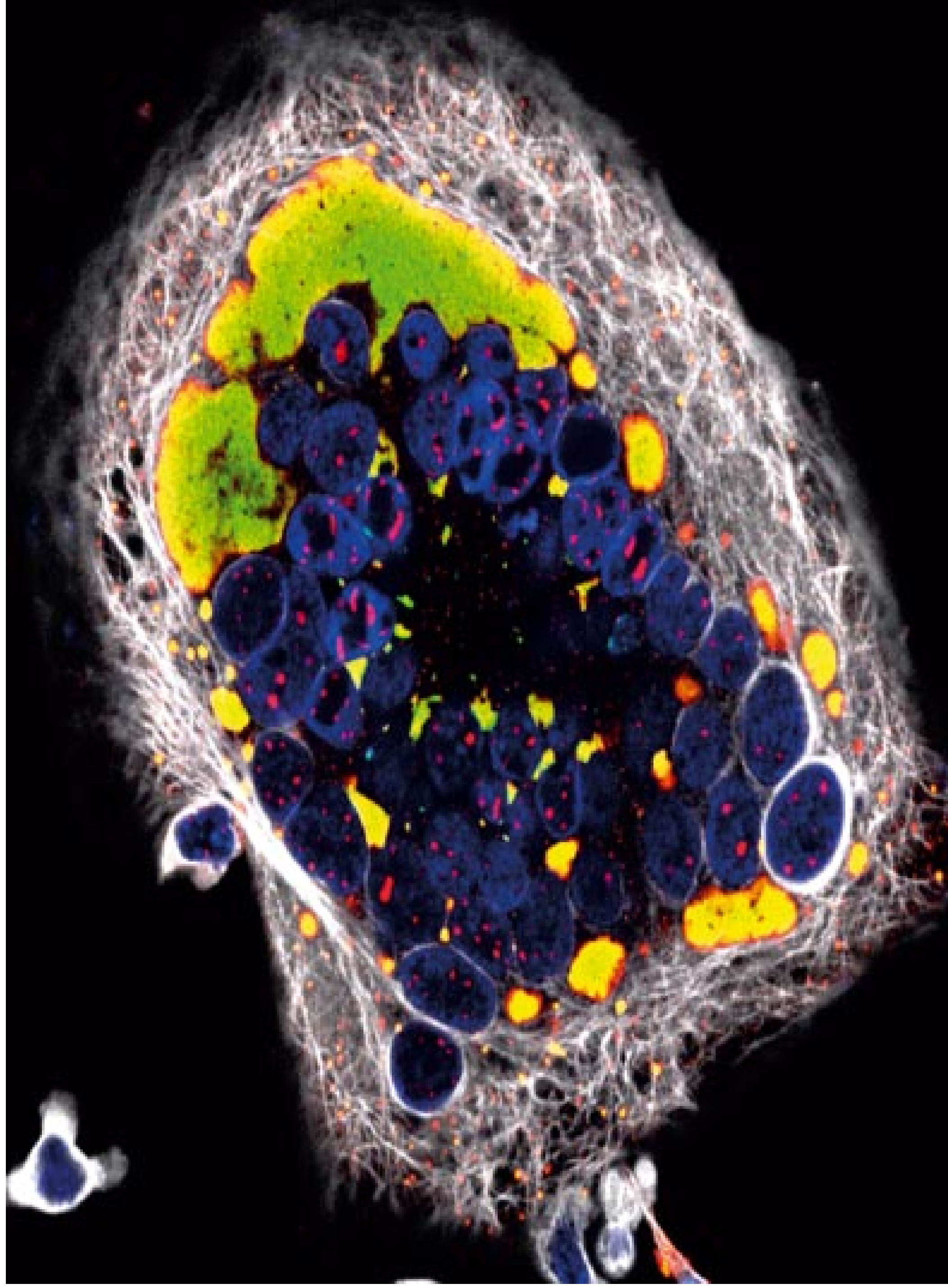
'*The secret weapons of the invaders were Grey Steppe oxen. Their value was a strong innate resistance manifested by slow spread of virus and by the absence of clinical signs. A troop of Grey Steppe cattle could shed rinderpest virus for months provoking epidemics that devastated buffalo and cattle populations of invaded countries. The sequelae were no transport, untilled fields, starving peasants, and overthrown governments*'.

Rinderpest and veterinary medicine

Veterinary services were pre-occupied with rinderpest control for much of the 20th century. In the 1920s the Office Internationale des Épizooties (OIE), a body that acts as the World Organization for Animal Health, was established in response to the introduction of rinderpest into Australia and South America by trade in live animals. When the United Nations was established in 1945, one of the first specialized agencies to be set up was the Food and Agriculture Organization (FAO) with a mandate to consider ways that the activities of veterinary organizations could be properly co-ordinated internationally, with a particular view to mitigating the widespread ravages of animal plagues, especially rinderpest.

Control measures

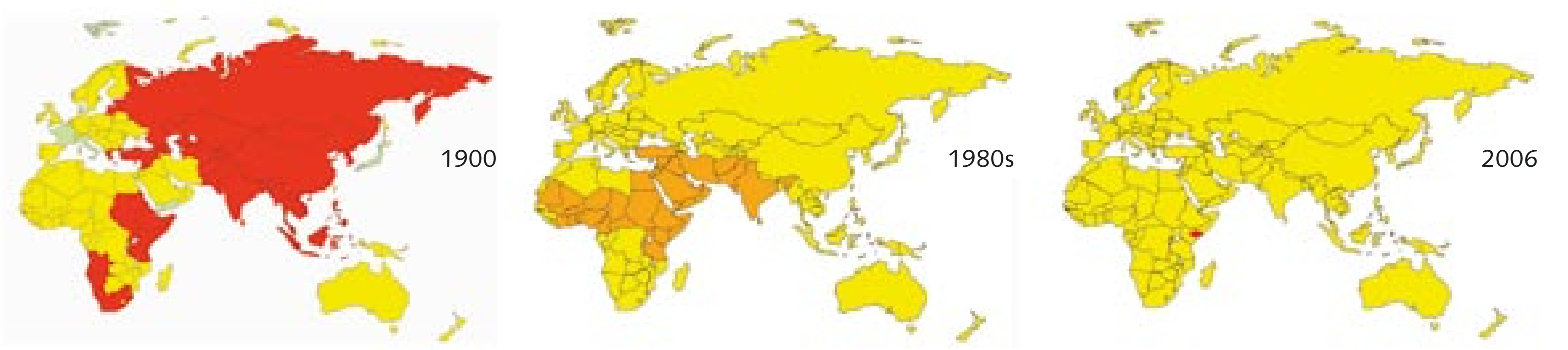
It was not until the pandemics in Europe in the early 18th century that the disease was first described scientifically and that effective control measures were introduced. In 1711 Pope Clement XI ordered his physician Dr Giovani Lancisi to investigate the cause and prescribe ways to control the plague that had killed so many cattle in the Papal herds. Lancisi understood the nature of infectious diseases without knowing their cause and he proposed slaughter of infected animals to reduce disease spread, burial of the carcasses in lime, movement controls on cattle and inspection of meat. He also introduced the idea of quarantine and his



▲ A giant syncytium formed when a B95a cell monolayer was infected with a version of the virus expressing GFP inserted into the polymerase gene. The nucleocapsid protein is stained red, the cellular tubulin filaments white and the nuclei blue. Where the virus nucleocapsids form, by co-location of the polymerase and nucleocapsid proteins, the cytoplasm stains yellow. *Tom Barrett*

▶ An animal infected with rinderpest showing a severe ocular discharge, a major clinical sign of infection. The virus antigen present in the discharge can be used for rinderpest detection using the pen-side test. *Tom Barrett*

▲ Stamps issued in Ethiopia and other African countries in the 1970s to advertise the campaign against rinderpest. *Tom Barrett*



▶ The eradication of rinderpest during the 20th century. *Tom Barrett*

policies were backed by strong legal enforcement with severe punishments for transgressors. By rigorous application of these sanitary measures the disease was eliminated from Europe by the late 1800s. These methods are still applied today to control and eliminate animal diseases such as avian influenza and foot and mouth disease. The economic and social devastation resulting from the cattle plague was the impetus to establish veterinary schools, the first being at Lyon, France, in 1762. The ability to effectively control rinderpest was considered to be a measure of the quality of a country's veterinary service.

Rinderpest in Africa

With its origins in Central Asia, the virus was probably first introduced into Egypt in the early 1800s, but it did not cause a pandemic in Africa until the late 1880s. This outbreak probably started when infected zebu cattle from Aden or Bombay were imported to Eritrea (then part of Abyssinia) by Italian troops fighting colonial wars in the region. For over a decade the plague swept over a whole continent of susceptible animals. At this time veterinary services were virtually non-existent in sub-Saharan Africa. 80–90 % of cattle, buffalo, eland, giraffe, wildebeest, kudu and various species of antelope succumbed. In Kenya, the Masai people suffered starvation and, together with a smallpox epidemic that followed the cattle plague, were severely reduced in numbers. Great tracts of land were depopulated, which facilitated the subsequent colonization of Kenya. One account states that *'never before in the memory of man, or by the voice of tradition, have the cattle died in such numbers; never before has the wild game suffered'.*

Control through vaccination

During the 1950s and 1960s individual countries in Africa, the Middle East and Asia carried out national rinderpest control programmes based on a policy of mass vaccination. Goat-adapted vaccine was favoured in India and Africa, while East Asian countries used either lapinized or egg-adapted vaccines. These vaccines, although efficacious, were not safe for use in all susceptible animals and so had limited use; nevertheless, Russia and China succeeded in eradicating the disease during this period. There was little co-ordination between neighbouring countries and vaccination in much of southern Asia, the Middle East and Africa in the 1960s and 1970s was not carried out effectively. Despite spectacular early successes, vaccination was not carried out rigorously enough to eliminate all endemic foci, resulting in a major resurgence of the disease in the early 1980s. This led to such great economic losses that a more concerted effort to eradicate the disease by mass vaccination was proposed in 1986 and funded by the European Union.

A safe and efficacious vaccine

A factor which contributed greatly to the decision to eradicate rinderpest was the development in the late 1950s of a highly efficacious vaccine, safe to use in all susceptible ruminants, by Dr Walter Plowright at the East African Veterinary Research Organization laboratories in Kenya. His approach was to take a virulent needle-passaged strain of the virus, chosen because it did not form mouth lesions and so had a reduced ability to transmit between cattle, and infect bovine kidney (BK) cells in suspension. These were then allowed to form monolayers and infected cells could be identified when they either rounded up or formed multinucleate syncytia. The virus required many passages to become attenuated for cattle: in fact, its virulence actually increased over the first 10 passages as manifest by an increased mortality rate (rising from 60 to 100 %) and shorter average survival time post-infection (falling from 9 to 3 days). It had also become readily transmissible by contact as it acquired the ability to form mouth lesions. By the 16th passage, however, the virulence had returned to a level equivalent to that of the parent virus. The ability to cause lesions, diarrhoea or death of the host also diminished after the 16th passage and from the 21st passage onwards only temperature reactions were observed. Finally, by 70th, 90th or 122nd BK cell passages, even these temperature reactions disappeared. This has turned out to be the most successful veterinary vaccine ever produced, saving millions of dollars annually and ridding farmers in the developing world of a devastating plague. In their introductory remarks in the published paper the authors modestly stated that they had, incidentally, furnished another attenuated strain suitable for the immunization of cattle (Plowright & Ferris, 1959)! If global eradication of rinderpest is achieved it will be the first animal viral disease for which this has been possible and only the second after smallpox. For this work, Dr Plowright was awarded the FAO's World Food Prize in 1999, the equivalent of a Nobel Prize in the area of food research. This breakthrough convinced veterinarians and scientists that rinderpest could be cost-effectively brought under control or even eradicated in many parts of the world.

Monitoring the effectiveness of vaccination

The vast number of serum samples that had to be analysed to monitor the effectiveness of vaccination posed huge logistical problems. A simple, high-throughput competitive ELISA system, suitable for sera from all species, was developed at the World Reference Laboratory in Pirbright. A network of laboratories, co-ordinated by the FAO laboratory at the International Atomic Energy Agency (IAEA) in Vienna, was set up in each of the countries involved to ensure that local staff received effective training and that standards were maintained by an external quality assurance system. A rapid 'pen-side' test was also developed for diagnosis by local veterinarians during an outbreak. This speeded up reporting and obviated the need to await laboratory confirmation of disease. The test was used effectively to eliminate the last foci of infection from Pakistan.

The global rinderpest eradication campaign

In 1986 regional eradication campaigns were begun in the endemic regions: sub-Saharan Africa, South Asia and West Asia. In areas of unrest, community based animal health workers were used for vaccination and seromonitoring. In 1992, based on the success of the regional campaigns, the FAO agreed that global eradication of rinderpest was justified and feasible. The Global Rinderpest Eradication Programme (GREP) was launched formally in 1994 as the prime target of the then newly established priority programme, EMPRES (Emergency Prevention System for Transboundary Animal and Plant Pests and Diseases). This was to be a globally co-ordinated programme linking the existing regional and national efforts and with a time-bound target to achieve global eradication by the year 2010. The great efforts put into this project have ensured that the whole of the Asian continent (West, Central, South and East Asia) is now free of rinderpest, Pakistan being the final country in 2003. Most of the African continent has also been declared rinderpest-free with only one potential focus of infection remaining in the Horn of Africa. The last time rinderpest virus was positively identified in this ecosystem was in 2001 in wildlife and 2003 in cattle.

With the introduction of RT-PCR for diagnosis, sequencing showed that there were three lineages of the virus circulating in the world at that time, one in Asia and two, African lineages 1 and 2, in Africa. The virus which remains in Somalia is lineage 2 which causes only a mild to sub-clinical infection in cattle, but severe disease in certain wildlife species, especially buffalo. It is proving difficult to generate firm surveillance data on whether or not lineage 2 virus still circulates in this ecosystem.

Wherever rinderpest has occurred, it has caused terrible destruction of cattle, adversely affected agriculture and rural livelihoods, bringing in its wake famine and starvation.

The endgame

In the eradication campaign, mass vaccination has ceased and we are in a period of active surveillance to designate countries in Africa as rinderpest-free. The last time disease was unequivocally detected in Kenya was in 2001 when in buffalo in the Meru National Park were found to have been infected. Wildlife in Kenya therefore acts as sentinels for the spread of disease from Somalia and so they are being intensively monitored for signs of rinderpest. It was feared that even if rinderpest were eliminated from the domestic cattle populations, wild ruminants might act as a reservoir of infection, but evidence shows that when the disease is eliminated from cattle it disappears from surrounding wildlife. Nevertheless, during outbreaks, infected wildlife can spread the disease over large distances and play an important part in its epidemiology.

Rinderpest eradication can clearly be achieved in the near future if lessons are learnt from the past and the necessary commitment and funding are sustained until there is scientifically sound evidence for its complete elimination. One factor that may inhibit achievement of the goal by the target date of 2010 is a situation of political unrest such as that in Somalia, the last endemic focus of the disease.

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Further reading

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