Rinderpest: the fall of a virus

Human history is shaped by many factors, viruses being one among them. The 10,000-yr-old rinderpest virus (RPV) has been affecting cattle and other cloven-hoofed animals since the beginning of domestication[1]. It has wrought havoc in the lives of poor peasants around the world, and has brought down mighty empires (Figure 1). Conquerors, colonizers and commerce seem to have helped the originally Asian virus spread to newer geographical areas over the years – the Huns and the Mongols are said to have spread the disease in Europe, the Italian colonizers in Africa[2], and trade is said to have brought the disease to India from China (interview with M. Rajasekhar, Project Directorate on Animal Disease Monitoring and Surveillance, Indian Council of Agricultural Research, Bangalore, on 16 July 2011). After more than two centuries of relentless effort by generations of veterinarians and the creation of numerous organizations with rinderpest eradication as their primary goal (such as the first ever institution devoted to veterinary sciences, set up in Lyon, France, 250 years ago; the World Organization for Animal Health (OIE) in 1924 (http://www.oie.int/for-the-media/rinderpest/), the Food and Agriculture Organization (FAO) in 1945, the Indian Veterinary Research Institute (IVRI), Mukteshwar, and Civil Veterinary Departments in India), the FAO declared on 28 June 2011 that RPV has been wiped-off the face of the earth, making it the second pathogen to be eradicated from the world, after smallpox.

The virus

Rinderpest is an RNA virus, belonging to the *Morbillivirus* subgroup of Paramyxoviridae[3], a group of viruses with a history of causing deadly diseases in animals ranging from lions to race horses[4] (Figure 2). Like all other morbilliviruses (including the measles virus that affects humans), RPV has the ability to cause immunosuppression, making the affected animals susceptible to other ailments too. Within about a week of infection by RPV, the animals would suffer from fever, constipation, congestion of mucus membranes, depression, lesions in the mouth and other symptoms, and up to 70% of the infected animals would die in 6–12 days, devastating the economies of the affected countries[3]. Animals that survived were immune to RPV for life[5], but M. S. Shaila (Indian Institute of Science, Bangalore), who has been involved in rinderpest research for the last three decades, says (in an interview with her dated 12 July 2011), 'Although mortality is very high, the morbidity is higher. The overall well-being of the animals is lowered, and the yield of the milk is low, even among the survivors.' This made the effect of the disease on the economies of the countries all the more intense. Starvation, diseases and death set in, nearly wiping out some indigenous communities, such as the Masai in Africa, who depended entirely on domesticated or wild grazing animals for their sustenance[5,6].

Eradication of RPV: efforts by India and the rest of the world

Rinderpest has been a persistent problem in India for centuries, infecting animals such as cattle, wild buffaloes, nilgai and even sheep, goats and swine[7]. The first steps that were taken to eradicate rinderpest in India were in the late 1800s, when the British government appointed the Hallen Commission to study the disease. J. H. B. Hallen made a report about the disease in India, including the region

Figure 1. Devastation caused by the rinderpest virus. Source: http://commons.wikimedia.org/wiki/File:Rinderpest_1896-CN.jpg.

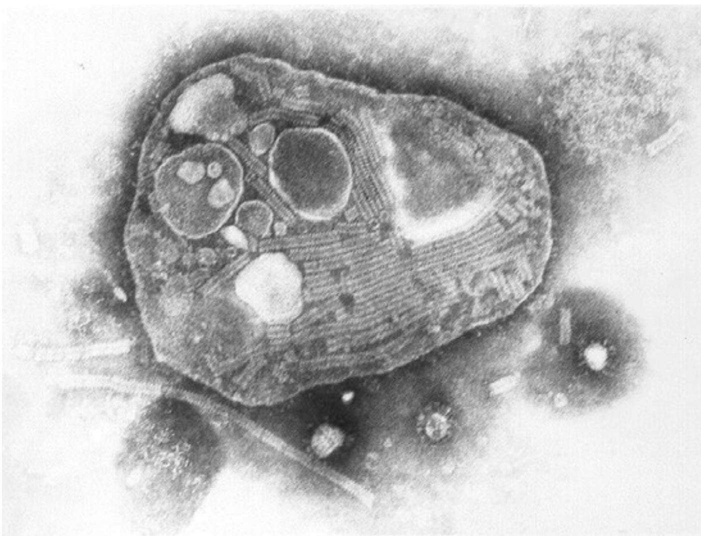

Figure 2. An electron photomicrograph of the rinderpest virus. Courtesy: M. S. Shaila.

which later became Pakistan, and one of his recommendations was to establish a veterinary institute in the country. According to Hallen's recommendation, the Imperial Bacteriological Laboratory was set up in Pune. The institution, which was the first of its kind in India, then moved to Mukteshwar and later came to be known as the Indian Veterinary Research Institute (interview with M. Rajasekhar). Around that time, E. Semmer in Russia, and Arnold Theiler and Herbert Watkins-Pitchford in South Africa had developed the serum simultaneous method for immunization of cattle – the blood of infected cattle would be injected into healthy ones to elicit an immune response, while at the same time serum containing antibodies against the virus would also be injected, to protect the animals from the live virus[8]. IVRI was shifted to Mukteshwar from Pune mainly because of the serum production activities that the institution undertook (interview with M. Rajasekhar). The initial effort to eradicate rinderpest from India also saw the establishment of the Mysore Serum Institute at Bangalore in 1926. The Institute of Animal Health and Veterinary Biologicals stands today on the land donated by the Maharajas of Mysore for setting up the Serum Institute (interview with M. Rajasekhar), (http://www.iahvb.co.in/). Though the serum simultaneous method had a few drawbacks (it did not always protect the animals from the disease and the immunized cattle had to be isolated for some days as they could infect other healthy ones), it was widely used till the 1930s both in India and Africa.

In the 1930s, the goat adapted rinderpest vaccine (GTV) was developed by J. T. Edwards at IVRI and this quickly replaced the serum simultaneous method as the most preferred method of vaccination of cattle. Rajasekhar says that in the hilly terrains of India and Nepal, people used to get goats injected with the virus and carried these 'animal vaccine reservoirs' on their shoulders from place to place to vaccinate cattle. Such enormous human effort in a way characterizes the drive towards rinderpest eradication around the world[5]. Vaccination in Africa, for instance, was extremely challenging. A description of the vaccination efforts in the continent says: 'Just reaching them (villages and the cattle) was hard. Land Rovers broke down, fuel and cash ran short. Vaccine was packaged with salt so it could be dissolved in saline, but salt, which was valuable, was stolen[9].'

Despite tremendous efforts by veterinarians and though GTV was much better than the methods that were used earlier, rinderpest could still not be eradicated. The vaccine had some drawbacks – it sometimes caused adverse reactions in the vaccinated animals, it could not be used to vaccinate crossbred animals, it was not heat stable, and there was no cold chain mechanism or any other way in which the vaccine could be kept viable. Further, the vaccination effort lacked structure and some scientists feel that rinderpest eradication became more of a management problem rather than a vaccination problem (interview with M. S. Shaila). Talking about the results of rinderpest vaccination in India in the 1950s, Rajasekhar says, 'The highest seroconversion was in Gujarat – about 30%; in Uttar Pradesh, Bihar, Andhra Pradesh and a few other states it was 5–10%; in Karnataka it was about 13%. This was very poor. We hadn't done anything'. The effectiveness of GTV and the realization that rinderpest was a major problem in India catalysed the launch of the first mass rinderpest vaccination campaign in India in 1954 – the National Rinderpest Eradication Programme (NREP)[10]. As part of NREP, 26 million vaccinations were carried out in 1958–59, and the disease which recorded more than 8000 outbreaks in 1956–57, with about 400,000 infected animals of which about 200,000 died[7], was brought down to about 300 outbreaks in less than 10 years[10].

The 1960s saw another major improvement that catalysed the eradication of rinderpest around the world. This was the development of the tissue-cultured vaccine by Walter Plowright in Kenya, which was 'probably the best vaccine ever made' (interview with M. Rajasekhar). Plowright was awarded the 1991 World Food Prize in recognition of this contribution. The Plowright vaccine allowed production to be scaled up manifold, and more importantly, it worked even for European breeds, a character that the previous vaccines did not possess. However, despite being so effective, this vaccine also had problems when it came to actual application in the field – it was heat susceptible and had to be maintained at low temperatures throughout and it had to be used quickly after reconstitution as it would become non-viable over time. These constraints became particularly problematic in tropical countries like Africa and India. Vaccinators were forced to try to make the best use of the situation by carrying the vaccine on ice or by vaccinating only in the early mornings when the temperatures are low (interview with M. Rajasekhar). As a result, though the disease was largely defeated, there were still instances of cattle being wiped out by the virus. One such incident was in South India: 'In the 1960s, there was a massive outbreak and nearly about 20,000 animals died in Bangalore alone. People were devastated. We couldn't even remove the animals off the roads', says Rajasekhar, who attributes his decision to work on rinderpest to the deep impression that such devastation left on him.

In Africa, the 1950s and 1960s saw a great deal of effort in rinderpest eradication as part of what was known as the Joint Project 15 (JP15). Numerous vaccinations were carried out and the disease was almost entirely eliminated from the continent. Unfortunately, JP15 ended up being a standing example of what lack of surveillance can do to decades of hard work – the disease returned with a vengeance from a few foci of infection that still remained, which the project had failed to notice. It took three more decades and a lot more human effort to ultimately eradicate the disease from Africa[1].

The NREP in India also had only limited success, and as a result, 30 years after the first attempt to systematize rinderpest vaccination, the results were still far from satisfactory[1]. Rajasekhar says, 'We had been vaccinating for more than 55 years and the number of vaccinations we had done was more than the world bovine population. But the disease was still there because the vaccine quality was not monitored and vaccination was not monitored.' Responding to the need to eradicate the virus from the country, the Indian Government decided to give a 'final thrust' to the rinderpest eradication programme in the 1990s, by means of the National Project on Rinderpest Eradication (NPRE). This coincided with the formation of the South Asia Rinderpest Eradication Campaign (SAREC, on the lines of similar programmes for rinderpest eradication in other regions of the world like Africa)[7]. The European Union (EU) initially provided freeze dryers and cold-chain equipment for making vaccination easier and more effective, but subsequently the entire operational costs were borne by the Indian Government (interview with M. Rajasekhar). In all, the Indian government spent about Rs 3.41 billion on NPRE whereas the EU contributed about Rs 640 million. The total cost of rinderpest eradication from 1955 to 2000 is said to be about Rs 1668 billion[7].

The approach of NPRE to rinderpest eradication covered a whole gamut of activities ranging from mass immunization and large-scale production of the vaccine to seromonitoring, surveillance, communication and training. As part of the NPRE, the whole country was divided into four zones based on the rinderpest history of the various regions and the disease was systematically eradicated from these regions in a three-phase programme according to the OIE pathway (the OIE sequentially declared countries as being provisionally free of rinderpest, fully free of rinderpest disease and finally free of rinderpest infection)[7]. It was during the implementation of the NPRE that Rajasekhar began playing an important role in rinderpest eradication. He was responsible for the country's seromonitoring and serosurveillance, planning and training. 'We have trained more than 5000 scientists from 32 labs in ELISA techniques and that became the workforce. We developed a national sampling chain, which wasn't there earlier and we tested the samples at Bangalore. I had a list of 6.34 lakh villages on my computer and we would go back to each village and get the serum tested in bulls, cows and sheep and goats ... The whole country was charged. There was so much enthusiasm and fervour, like the freedom movement', he says. In 2006, the OIE testified that India had indeed achieved freedom from rinderpest, making it one of the first countries in Asia to reach this landmark[11] (http://www.fao.org/ag/againfo/programmes/documents/grep/GREP_situation.pdf). The 1990s also saw a major development in the global effort to eradicate rinderpest – the setting up of the Global Rinderpest Eradication Programme (GREP)[11], with the express goal of wiping RPV off the face of the earth by 2010. The GREP was intensified in 1998, with a mandate to understand the epidemiology of the disease in regions that were identified as reservoirs of the virus and then work on containment and eradication of the pathogen[12]. The last case of rinderpest was seen in 2001 in Kenya.

The rinderpest eradication programme in India is unique because the country had to overcome two challenges that other countries did not face. One was that because the cow is considered to be a sacred animal, large-scale slaughtering of cattle in order to contain the disease (which contributed to the eradication of the disease from Europe and Russia in the early 20th century[1]) was not possible. The other problem was that, sheep and goats were also infected with the rinderpest virus (interview with M. S. Shaila). This happened to be an exclusively South Indian phenomenon, and Shaila and her colleagues, who discovered this worrisome fact, had a hard time convincing others that this was indeed true. Shaila describes the experience: 'Earlier, people didn't even believe that the disease can occur in small ruminants, because the clinical manifestations were not so apparent and it was often subclinical. But they were carriers of the virus and they could spread it to cattle. So we developed more sensitive methods to prove that indeed the virus was in small ruminants. We also discovered the existence of another disease, a close relative of rinderpest, called peste de petits ruminants (PPR). We used molecular methods to differentially diagnose the two infections and we found that some of the outbreaks were due to PPR, which was new to the country, while some of the outbreaks were indeed rinderpest. Based on that information, the NPRE coordinator decided to vaccinate small ruminants also at least in South India.' This made the vaccination programme more difficult, but it also made the country extremely secure against the disease.

What next?

Rinderpest eradication might well be the most significant achievement in veterinary history, according to Peter Roeder, who was involved in the GREP from the start[5]. Yet, while eradication itself is important, the post-eradication phase for diseases is also equally crucial. The FAO and national governments are currently working towards making sure that the virus is destroyed in laboratories around the world (an initial survey carried out by the FAO has shown that the virus exists in laboratories in 20 countries around the world, under varying biosafety conditions[12]), excepting a few labs where the virus is kept safe for use in case of an emergency. Emergency vaccines for countries around the world are also being secured.

Now that rinderpest has been overcome worldwide, one would wonder what future research on rinderpest virus would focus on. Shaila says that this would depend on what researchers can do to further their knowledge of virus biology. 'There is a lot to be learnt about how the virus interferes with the host immune mechanism; how the virus is so clever as to somehow interfere with the host mechanism that would eliminate it. One doesn't know much about the innate immune mechanisms against this group of viruses. Research in this area may help in understanding other pathogens that affect cattle,' she says.

Considering that smallpox is the only other disease that has been eradicated so far (in 1979), one might be curious to know which disease was more difficult to control. Shaila says, 'Intuitively I can say the rinderpest was much more complex. For smallpox, it was human vaccination; maybe when the children were small, they were all vaccinated, like for polio. But for rinderpest, that is not the case. That's why many foci of infection remained in eastern Africa and also in war torn regions like Somalia.' Rajasekhar too feels that rinderpest eradication was more complex, 'Vaccine pressure over decades eradicated smallpox. But the rinderpest virus is smart because it had an alternate host. Whenever there was vaccine pressure in cattle, it would take refuge in sheep and goats, and whenever there was an opportunity, it would come back to cattle. Smallpox eradication was done on a war footing – everybody would go and get vaccinated. But with animals it was difficult. The vaccine was not as robust as that for smallpox, and the number of vaccinations to be done was so much more ....'

The rinderpest eradication experience has also afforded a number of 'lessons' that can be applied to the eradication of other diseases. The FAO has declared that the next disease that it would look to eradicate globally is PPR. This disease is so closely related to RPV that it actually 'helped' the rinderpest eradication process. Rajasekhar says, 'In 1989, 30% of the sheep population in India was carrying antibodies for PPR. Since PPR buildup was there, and there was vaccine pressure on the other side, it was possible to eradicate rinderpest.' Roeder reiterates the same point: '... most vaccination programmes fell far short of achieving the magical 90%, or even 80%, immunity figure. In fact, the figure rarely even reached 65% .... Perhaps the answer lies in the discovery that PPR, prevalent in West Africa and much of Asia, infects cattle subclinically, inducing immunity against rinderpest in up to 50% of cattle'[13]. So how much of what we have learnt from the rinderpest eradication can we apply to the PPR eradication process? Many people feel that it is important to keep the mechanism and the 'management of vaccination' aspects that worked so well for rinderpest intact. The importance of a good vaccine, like the one used for rinderpest eradication is also stressed upon, and Rajasekhar says that PPR has a vaccine that is as efficient. But there are a few strategies that must be modified for PPR eradication. The fact that the PPR virus infects sheep and goats makes it a more complicated process to eradicate this disease. Rajasekhar describes the problem and a possible way out: 'You cannot replicate the rinderpest programme, because this is a different virus and a different host. The strategy we followed for rinderpest eradication was to vaccinate 80% of the population and sanitize the virus. We tried to develop herd immunity. But for PPR, you cannot develop herd immunity. The quantum of population jump is so much that you will always have a susceptible population. Further, the herdsmen do not keep their animals for more than two and a half years, even if the goats are vaccinated, because the meat becomes rough and it is not eatable. And there are other diseases that take away the immune population. I studied 10 years' data of PPR in India and it shows that eight districts in Andhra Pradesh contribute 85% of the outbreaks. If you can handle these, there is no virus available. So you go after the virus and not after vaccination; kill the virus, and it cannot spread.' In fact, in many places such as Ethiopia, mass vaccination was not resorted to even for rinderpest eradication. Roeder says, 'Targeted vaccination programmes were mounted from 1993, using innovative, community based delivery systems, and this cleared rinderpest from the 35 million Ethiopian cattle herd within three years, something that 30 years of institutionalized, mass vaccination programmes had failed to do'[13].

Eradication of PPR is probably even more important than rinderpest eradication, as the disease devastates the lives of the poorest of the poor – the nomadic herdsmen, whose livelihood depends entirely on these animals. But PPR is also more challenging than rinderpest because the porosity of the borders between countries when it comes to migration of sheep and goats is much higher than what it is for cattle. However, there is hope. According to Rajasekhar, if a national policy is in place for the eradication of the disease and if neighbouring countries join hands in the mission towards PPR eradication, much the same way as they did for rinderpest eradication, the next few years may see another virus wiped-off the face of the earth.

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ACKNOWLEDGEMENTS. I am grateful to Dr M. Rajasekhar and Prof. M. S. Shaila for allowing me to interview them and for generously providing me with useful information.

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