Innovation brief

RESEARCH PROGRAM ON Livestock

CGIAR

Photo KINNAPA/Abraham Akilimali

A GENETIC APPROACH TO TACKLING EAST COAST FEVER

KEY MESSAGES

East Coast fever (ECF) kills over one million cattle a year in sub-Saharan Africa and it can destroy the livelihoods of smallholder farmers.

Although there is a live vaccine, which provides lifelong immunity after a single inoculation, it is expensive to produce, store and deploy. Therefore, scientists are searching for additional methods of control.

Scientists at the International Livestock Research Institute (ILRI) have identified some indigenous cattle that have shown high levels of tolerance to ECF, which could lead to a new approach to tackling the disease through selective breeding.

Selective breeding for disease tolerance and gene editing has the potential to provide a huge boost to the cattle industry in sub-Saharan Africa by reducing ECF-related deaths.

SUMMARY

Livestock are vitally important to the welfare and survival of hundreds of millions of households in Africa because they provide milk, meat, draught power and are a source of income. However, East Coast fever (ECF), a tick-borne parasitic disease that kills one animal every 30 seconds, poses a major threat to the livelihoods and welfare of pastoralists and dairy farmers. A live vaccine has provided immunity for some 1.5 million cattle, but its production is expensive and time-consuming. Scientists at ILRI are currently researching other methods of controlling the disease. One involves a genetic approach which takes advantage of the phenomenon of tolerance to ECF, found in indigenous cattle in regions where the disease is endemic.

Photo Liam Morrison/Roslin Institute

Boran bull 3167, the progenitor of a line of cattle shown to be tolerant to disease caused by Theileria parva.

Banner photo: A Masaai herder with his cattle at the Orkitikiti dam in the Kiteto district of Tanzania.

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INTRODUCTION

ECF and the closely related Corridor disease are both caused by the protozoan parasite *Theileria parva* and are transmitted to cattle by the brown ear tick, *Rhipicephalus appendiculatus*. The natural host for *T. parva* is the African buffalo, in which it causes few clinical symptoms. However, when the parasite affects domestic cattle in herds that have not previously been exposed to the disease, over 80% die within three to four weeks of infection. ECF's mode of transmission is cattle–tick–cattle, whereas Corridor disease is transmitted to cattle by ticks which have fed on buffalo.

With both diseases, the infective sporozoite stage of the parasite is introduced into the cattle when ticks are feeding. Sporozoites enter the host lymphocytes, a type of white blood cell, where they proliferate rapidly in animals which are not tolerant to the disease. Those which succumb become listless and anorexic, and the infection rapidly spreads to the lungs, liver and kidneys. Although closely related, the two diseases are clinically distinguishable, with Corridor disease exhibiting a significantly lower parasite load.

In the late 1960s, it was reported that in areas where ECF was endemic, indigenous cattle were less susceptible to the disease than recently introduced European cattle (*Bos taurus*) and indigenous cattle from non-endemic areas. The inherited nature of this tolerance became apparent in studies where calves born to resistant mothers and susceptible bulls were shown to have an intermediate susceptibility to ECF. Until recently, the mechanism by which tolerance was passed between generations was not understood. However, field trials in northern Kenya that were initially designed to test the efficacy of a vaccine shed new light on the phenomenon of tolerance to *T. parva* infection. In this context, tolerance is the ability of an animal to show only mild clinical symptoms, or none at all, following infection with a dose of the pathogen which causes a severe clinical reaction, and frequently death, in non-tolerant cattle.

EXPLORING TOLERANCE

In 2013, 24 healthy young Boran cattle (*Bos indicus*) were transported from ILRI's Kapiti Research Station, where they had never been exposed to the parasite which causes ECF and Corridor disease, to Ol Pejeta Conservancy in northern Kenya, where the diseases are endemic. The cattle grazed in an area where there were buffalo but no cattle. Twelve of the cattle were vaccinated using the Muguga cocktail live vaccine, primarily developed to provide protection against ECF, and 12 were left unvaccinated. Within a short period of time ticks had attached themselves to all the cattle. Clinical observations were made at regular intervals.

Three of the unvaccinated animals survived, as did three of the vaccinated animals. The three unvaccinated animals which survived, as well as one of the surviving vaccinated animals, were the first-generation offspring of an indigenous bull, known as 3167. These were the only four progeny of 3167 selected for the field trial, reflecting a 100% survival rate. Serendipitously, a field trial designed to test a vaccine had opened up the possibility of taking a completely different line of research. Over the next five years, ILRI scientists conducted a further four field trials at Ol Pejeta. Their purpose was to establish whether the first- and second-generation progeny of bull 3167 possessed a greater degree of tolerance to *T. parva* infection than unrelated cattle subjected to the same parasite burden, and to obtain genetic material from more animals for further analysis.

The field trials involved 28 first-generation offspring of bull 3167; 47 second-generation offspring; and 46 unrelated cattle. The survival rate for the first generation was 67.9%, for the second generation 51.1%, and for unrelated cattle just 8.7%. The susceptible progeny of bull 3167 showed a level of disease midway between the surviving progeny and susceptible unrelated animals, in that the time to death was longer for susceptible progeny than for the unrelated animals. Clinical data showed that tolerance exhibited by the progeny of bull 3167 was associated with significantly fewer, and a delayed appearance of, infected lymphocytes, as well as a delayed and less severe fever.

Field observations were followed by *in vitro* studies which found that infected cells from surviving animals proliferated more slowly than those of animals susceptible to the disease, with the difference being observed as early as six days after the initiation of the cultures. There appear to be at least two possible mechanisms for tolerance:

1. The first of these could be at work within infected cells. The parasite operates by tricking lymphocytes into dividing, leading to the uncontrolled proliferation of infected cells, and sometimes the very rapid death of the affected animal. It is possible that in cattle tolerant to ECF and Corridor disease something disrupts the way in which the parasite tricks cells to proliferate.

2. The second possibility is that there is some form of innate immune response in tolerant animals, with a population of uninfected cells growing beside the infected cells and either suppressing their growth or killing them.

Further research should confirm which of these mechanisms is helping to thwart the progression of the disease within the host animals.

CRACKING THE GENETIC CODE FOR TOLERANCE

The conclusive evidence that there was a genetic basis for tolerance to *T. parva* infection in the offspring of 3167 was provided by the field trials at Ol Pejeta in 2015, which also happened to be the year when the Centre for Tropical Livestock Genetics and Health (CTLGH) was set up as a partnership between the Roslin Institute at the University of Edinburgh, Scotland's Rural College and ILRI. CTLGH brought scientists working on the Ol Pejeta trials in contact with some of the world's leading animal geneticists. They generated genotype data for 121 cattle, including 28 first-generation descendants of bull 3167, 47 second-generation descendants and 46 unrelated animals. After merging the datasets and using the survival data from the field trials, the scientists were able to identify a region on chromosome 15 associated with tolerance to infection by *T. parva*.

The actual gene, or group of genes, which confers tolerance might well be elsewhere on the chromosome, with this region simply having a regulatory influence. Identifying the gene, or group of genes, is now the subject of a new research programme. Among other things, it will be important to establish whether carrying the gene is associated with any negative factors. To give just one example, this is what happens with the blood disorder sickle cell anaemia in humans. The gene which confers resistance to malaria is also a cause of anaemia. A negative association with the genes conferring tolerance to *T. parva* might explain why they are not universally found in indigenous cattle in sub-Saharan Africa where ECF and Corridor disease are endemic.

In 2021, scientists at ILRI and their colleagues at CTLGH developed an assay based on a single mutation on chromosome 15 which can now be used to identify cattle carrying the genomic region associated with tolerance. This genetic marker has been tested in analysis of a field study conducted some 12 years ago in another production system on the Kenya–Uganda border around the town of Busia. This retrospective study confirmed the association of the genomic region on chromosome 15 with tolerance to the cattle-derived ECF.

Photo ILRI/David White

Hard ticks in ILRI's Tick Laboratory.

Photo ILRI/Jake Meyers

Cattle at ILRI's research station in Kapiti, Kenya.

IMPLICATIONS AND RECOMMENDATIONS: BREEDING FOR BETTER HEALTH

Scientists are now in a position to use the genetic marker to identify animals which could hand down resistance to ECF to future generations. The marker could be used in tandem with other genetic markers – such as those associated with high milk yields – to create an improved breed of cattle which could bring great benefits to pastoralists and farmers in areas where ECF is endemic.

The eventual identification of the gene, or group of genes, which confer tolerance to ECF could have a revolutionary impact. CTLGH was established to improve animal health by using techniques such as gene editing. In the case of disease tolerance, this would involve splicing the gene responsible for tolerance into an embryo of a bull which could later be used as breeding stock. All its progeny would then exhibit elevated tolerance to ECF, with major implications for the cattle industry in sub-Saharan Africa.

Farmers with ECF-tolerant cattle could reduce their use of tick-killing acaricides, although they might still deploy these for other diseases, and they would not need to vaccinate their animals. At present, farmers are reluctant to use more productive European breeds, such as Friesians and Ayrshires, in areas which are plagued by the ticks carrying *T. parva*. Instead, they continue to use indigenous cattle, or crossbreeds at best. Having access to European breed sires that have benefited from gene editing for disease tolerance could lead to significant increases in productivity and incomes for tens of thousands of livestock farmers.

Research on tolerance to ECF is also opening other new avenues for control of the disease. If and when scientists work out the precise mechanism by which tolerance works, they will be in a better position to develop a subunit vaccine – which would be a cheaper and safer alternative to the live vaccine currently in use – and it could also help in the development of new therapies for the treatment of the disease.

Photo ILRI/Dave

The African buffalo is the natural host of Theileria parva, the parasite that causes East Coast fever in cattle. In buffalo it shows very few clinical symptoms, whereas in cattle infection can be lethal.

Photo ILRI/Geoffrey Njenga

Boran cattle quench their thirst at a watering point in Isiolo County, Kenya.

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