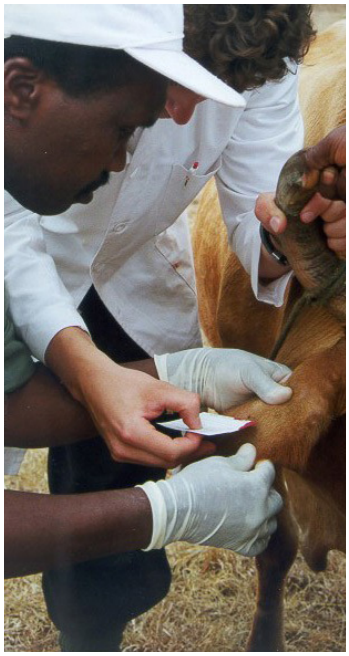

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Improving the Infection and Treatment Method vaccine for East Coast fever

Philip Toye and Peter Ballantyne

East Coast fever (ECF) is a devastating tick-borne disease of cattle caused by the protozoan parasite, *Theileria parva*. The disease causes high mortality (greater than 80%) in susceptible cattle populations. ECF occurs in 11 countries in eastern, southern and central Africa where the tick vector, *Rhipicephalus appendiculatus*, is found. ECF causes major economic losses throughout the region and affects both high-grade dairy cattle and young zebu cattle in smallholder and pastoralist systems and ranches.

The infection and treatment method (ITM) vaccine was developed at Muguga, Kenya, between 1967 and 1977. Since then, various versions of the vaccine have been developed, each differing in the strains of theilerial parasites used to inoculate cattle. The most widely used version is known as the 'Muguga cocktail', a combination of three parasite stabilates.

The International Livestock Research Institute (ILRI) produced the first commercial batch of the Muguga cocktail ITM vaccine in the mid-1990s, at the request of the Food and Agriculture Organization. A decade later, this time at the request of the African Union-Interafrican Bureau for Animal Resources, ILRI produced a second batch, which is now being used in eastern Africa. A third batch is being produced by the Centre for Ticks and Tick-Borne Diseases in Malawi, facilitated by GALVmed (the Global Alliance for Livestock Veterinary Medicines) and the Bill and Melinda Gates Foundation and using tick and parasite seed stabilates transferred from ILRI.

To date, over one million cattle have been immunized with the ILRI-produced vaccines. These have been delivered by commercial distributors, in particular VetAgro Limited who pioneered the commercial feasibility of the vaccine in northern Tanzania. The vaccine has been registered in Kenya, Malawi and Tanzania, and is approved for use in Uganda pending official registration.

Despite these successes, much needs to be done. Production of the live ECF vaccine is complicated, time-consuming and expensive. To produce one million doses of vaccine requires 130 cattle that have not previously been exposed to the disease, 500 rabbits and at least 600,000 ticks. The entire process of making, testing and releasing a batch takes up to 18 months. The product then requires a cold chain and careful handling throughout storage, distribution and delivery, before being administered by trained veterinary personnel.

To take stock of the current situation and identify improvements in the vaccine, including delivery, manufacturing processes and the product itself, ILRI and GALVmed recently convened a workshop on the 'distribution, delivery and improvement of the Infection and Treatment Method vaccine for East Coast fever (ECF)'.

Participants were drawn from Departments of Veterinary Services, regulatory authorities, international development organizations, manufacturers, research institutions, and private and public partners involved in the delivery of the vaccine. It was perhaps the first such meeting of the full 'vaccine chain' for East Coast fever.

Workshop participants came up with priority research activities in two areas: improving the production process and improving the end-product.

Research agenda for product and process improvements

In terms of a research agenda, participants identified and prioritized the most needed improvement in both the ITM product and its manufacturing process. Priority areas to work on to improve the product are:

1. Thermostability. The need for a cold chain is a major hindrance in the delivery of the vaccine. It operates at several stages:
    - The vaccine – making the vaccine stable at room temperature would have enormous benefits, although it is considered a long-term, high-risk undertaking at present.
    - The diluent – it was recognized that a simpler diluent would be cheaper and more stable at room temperature. Activities are already under way to develop such a diluent – a desired stability would be six months at room temperature.
    - Post-reconstitution stability – the sporozoites can be kept at 4°C for up to four hours without affecting vaccine performance. The need for increased time is less important if a smaller dose (5–10) package is available. Improve stabilizers to keep stabilate viable from 4 to 12 hours post thawing would be highly beneficial.
2. Removal of oxytetracycline (OTC). The need for OTC adds considerably to the cost of the vaccine. Extra labour is also required as the dose of tetracycline depends on the weight of the animal. In addition, the approval of different brands of OTC requires *in vivo* testing. It was suggested that research should be undertaken to explore ways of attenuating the parasite to make it self-limiting. One approach is by irradiation, as has been used in closely-related malaria organisms.
3. Different dose presentations. The current straw contains 40 doses, which is not suitable for smallholder areas where a presentation of 5 – 10 doses is desirable. The smaller dose straw would cost more on a per dose basis, although this would be offset by the reduction in wastage and the fact that the target animals are high value ones. Data on cost versus convenience is needed. Sensitization of farmers on the change in packaging is essential to avoid suspicion.
4. Buffalo challenge. Evidence is available indicating that the Muguga cocktail does not fully protect cattle that share pastures with buffalo; other reports indicate that the vaccine is effective against buffalo-derived challenge. Lack of protection limits the wider use of the vaccine and poses a reputational risk. It was requested that more epidemiological research be undertaken on the importance of buffalo (i.e. how many cattle are exposed to the buffalo-derived parasites) and how can the vaccine be changed to protect against the challenge of buffalo-derived parasites.

East Coast Fever endemic regions

5. Long term impact of mass immunization on epidemiology of the disease. Vaccination with ITM can induce a carrier state in immunized animals, which allows the parasites in the vaccine stabilate to be transmitted to other animals. The effect of this on the existing parasite population is not known.
6. One vaccine for all regions. A single vaccine stabilate that could be applied in all regions where ECF exists would provide efficiencies of scale in the manufacturing and distribution of the vaccine. However, due to the existence of strain variation among the *T. parva* parasites, there are concerns whether broad immunity in the field can be induced by a vaccine composed of a single stabilate.

In terms of the vaccine manufacturing process, improvements that require research inputs are:

1. Decreasing the number of animals used in the production process. The current procedure requires a large number of animals both to produce the vaccine and for the pre-release testing. One alternative to using animals in the production process is to use an *in vitro* culture of the parasite. This is considered very challenging from a technical perspective and not for immediate application. In terms of testing, the current protocol requires three rounds of testing for each vaccine batch, plus an initial infectivity trial. This should be re-examined to see if it can be reduced. It was noted that work is ongoing to establish an in vitro correlate of infectivity, which could be used to assess the potency of each batch and reduce the amount of in vivo testing required.
2. Decreasing time for production. Concern was expressed about the current time required to produce a batch of the vaccine (up to 18 months), particularly with the expected increase in demand of the vaccine. The most immediate way to reduce the time is to decrease the number of rounds required for dose determination. The use of staggered production cycles should also be considered.

A next generation vaccine

Research at ILRI and elsewhere has demonstrated that there are two major entry points for development of a subunit vaccine for the control of ECF. The first is through generation of antibodies that have the capacity to neutralize sporozoites, the infective life-cycle stage of *T. parva*. The second is through priming of cytotoxic T cells that kill schizont-infected lymphocytes, the pathogenic stage of *T. parva*. Candidate *T. parva* vaccine antigens have been identified and under laboratory conditions they induce immunity to ECF in 30-50% of vaccinated cattle.

In January 2014, an inception workshop was held at ILRI to bring together leading experts in ECF and infectious disease research from more than eight institutions to work together to obtain proof-of-concept for a subunit vaccine for ECF. Over the next 5-10 years, this ECF Consortium will harness new science and undertake various research activities to fill current knowledge gaps. Its primary objective is to demonstrate immunity to ECF in 70-80% of a defined type of cattle given a defined parasite challenge, with a second phase to provide broad-spectrum immunity. In the interim, the ITM vaccine is the only vaccine solution available for the control of ECF and various research activities are being undertaken to improve the manufacture and delivery of this live, parasite-based vaccine.

More: http://ilvac.net/diseases/ecf/

3. Increasing batch sizes. It was noted that increasing the number of sporozoites produced in each manufacturing run would help to meet the expected increase in demand. Potential ways to achieve this include looking at alternative tick strains to increase sporozoite yields, improving grinding methods to increase recovery of sporozoites from ticks and improving the freezing process to allow for better sporozoite viability rates on thawing.
4. Improving diluent containers. Suggestions to improve the diluent container included: changing from a glass container to a plastic one, using a unique cap colour for each batch, and ensuring that the size of the container is suitable for the amount of diluent required for each batch of straws (which is related to the number of doses per straw).

Other topics for research included identifying ticks which can yield greater number of sporozoites, and validating the use of other antibiotic formulations

Agenda for vaccine delivery and uptake

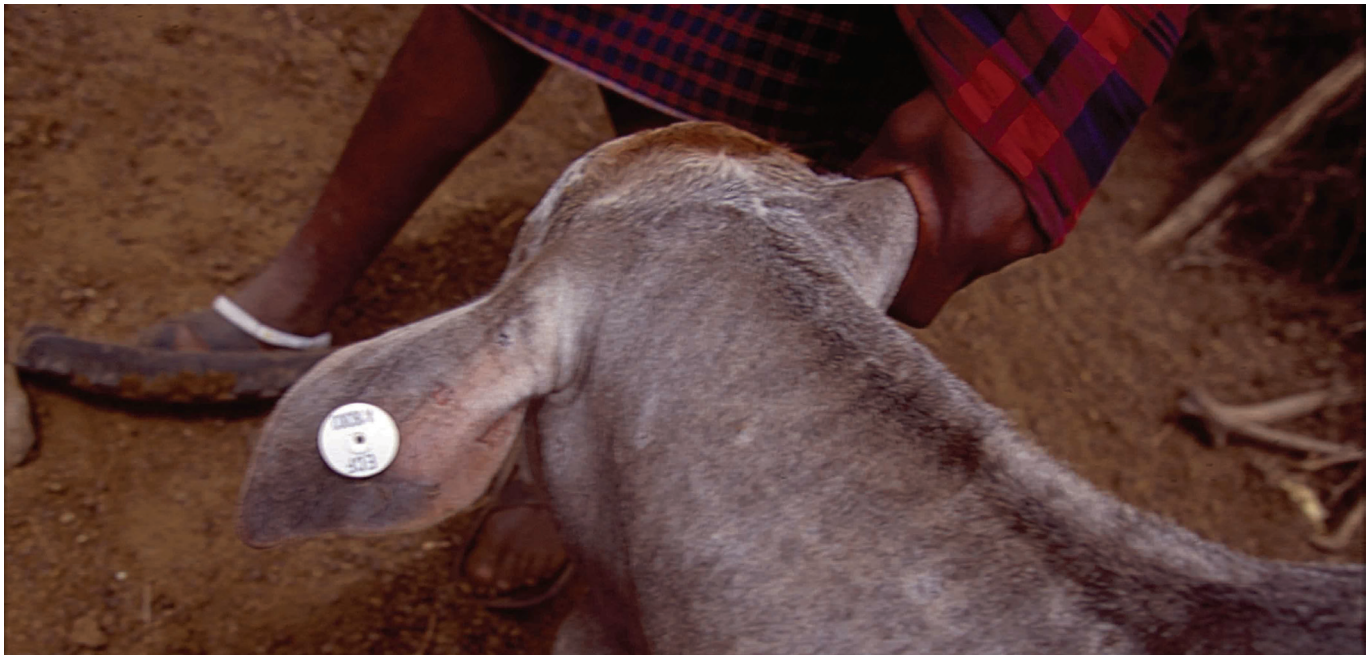
- Availability – there needs to be a reliable vaccine supply chain able to produce enough vaccine to meet demands
- Awareness - there needs to be a campaign to sensitize stakeholders
- Vaccinators have key roles at the front line – these need to be reinforced through training and certification
- Having standard operating procedures is essential to ensure good quality vaccine delivery and uptake
- Practical elements of the straw size are a critical issue in packaging of the vaccine
- Smart partnerships, where different actors can meet on a regular basis is very critical to fostering good communications and trust.

Priority actions

Workshop participants concluded that:

1. An emerging, demand-driven research agenda for the ITM vaccine must be tackled.
2. Although the ITM vaccine manufacturing process is complex, the production process can be improved (in the short term) resulting in quicker and cheaper manufacturing processes.
3. A next generation vaccine is under active research but has about a 10 year horizon, emphasizing the need to continue to improve the ITM vaccine and production technology, and to acquire further knowledge on the socio-economic impact of the vaccine and its effect on the epidemiology of the disease.
4. Filling the vaccine supply gap in the short term is a critical issue to address.
5. A clear timetable for the vaccine availability to distributors is urgently needed. Information is also needed on any planned controlled release or field-testing of future batches.
6. The registration process in the various countries is key to ensuring wide availability of the vaccine and requires appropriate actions now.

7. The allocation of vaccine to countries and distributors must reflect a fair market distribution governed by transparent and reliable processes.
8. Improvement is desired in the way that liquid nitrogen is handled in the field at all stages of the delivery chain, in the thermo-stability of the diluent (preferably stable at room temperature) and in the current dose presentations, which are not optimal.
9. Standard operating procedures for vaccine delivery need to be established, based on best practices derived from field experience.
10. Centralized and uniform training and certification of vaccinators is essential to ensure that the vaccine is delivered safely and effectively.
11. The roles of the Local Technical Representatives (LTR) as well as those of in-country distributors and importers need to be finalised.
12. A joint ECF communication process is needed to catalyze and support sharing and awareness and exchange of already existing materials and other information across countries.



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