# Distribution, delivery and improvement of the Infection and Treatment Method vaccine for East Coast fever

Report of a Workshop, Nairobi, Kenya,
19-20 August 2014

February 2015

# Contents

# Communiqué

On 19 and 20 August 2014, 45 participants from Kenya, Uganda, Tanzania, Malawi, Botswana, United Kingdom, Belgium and Ethiopia (Annex 2) participated in a workshop on the 'Distribution, delivery and improvement of the Infection and Treatment Method (ITM) vaccine for East Coast fever (ECF)'. The participants included representatives of Departments of Veterinary Services, regulatory authorities, international development organizations, research institutions, and private and public partners involved in the delivery of the vaccine. The workshop was held on the campus of the International Livestock Research Institute (ILRI), Nairobi, Kenya.

The workshop was organized against the background of an increasing demand for the ITM vaccine, the result of the numerous efforts over the past three decades to promote the sustainable manufacture, availability and safe and effective delivery of the vaccine. Nevertheless, significant challenges remain and the workshop was designed to bring together various partners, stakeholders and field implementers to share practical knowledge, information, and good practices concerning the development and delivery of the vaccine.

Workshop participants reviewed experiences in the production and delivery of the ITM vaccine in eastern and southern Africa. They further identified a preliminary list of research improvements related to the current product and the process to manufacture it.

After two days' deliberations, the workshop generated the following recommendations for action by all stakeholders as per their respective responsibilities.

***Considering*** the continued socio-economic impact of ECF in the affected countries,

***Empathising*** with livestock farmers, who continuously need to be made aware of and require access to the vaccine in order to improve adoption,

***Recognizing*** the wide array of partners and stakeholders involved in the ECF ITM domain,

***Realising*** the need for a coherent partnership framework encompassing both public and private sectors for effective and efficient management of the ECF ITM vaccine,

***Reflecting*** on the roles by various stakeholders and the need for better, more regular networking and information sharing on ECF ITM,

***Recognising*** the significant progress that has been made in the recent past on ECF ITM vaccine in terms of manufacturing, registration and distribution,

***Aware*** of the imminent launch of a new batch of the vaccine from Centre for Ticks and Tick-borne Diseases (CTTBD), Malawi,

***Understanding*** that the availability of a new generation vaccine is several years from reality,

***Accepting*** that significant improvements can be made to the current ECF ITM vaccine and the production technology,

***Acknowledging*** the need for further targeted research on ECF ITM and its production, marketing and adoption,

***Aware of*** the need for regulatory harmonisation through mutual recognition protocols for affected countries for use of the vaccine,

the workshop concluded that:

1. 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.
2. 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.
3. Improvement is desired in the way that liquid nitrogen is handled in the field at all stages of the delivery chain, in the thermostability of the diluent (preferably stable at room temperature) and in the current dose presentations, which are not optimal.
4. The allocation of vaccine to countries and distributors must reflect a fair market distribution governed by transparent and reliable processes.
5. Standard operating procedures for vaccine delivery need to be established, based on best practices derived from field experience.
6. Centralized and uniform training and certification of vaccinators is essential to ensure that the vaccine is delivered safely and effectively.
7. Filling the vaccine supply gap in the short term is a critical issue to address.
8. The registration process in the various countries is key to ensuring wide availability of the vaccine and requires appropriate actions now.
9. An emerging, demand-driven research agenda for the ITM vaccine must be developed and pursued.

Further to the conclusions above, participants identified several short-term actions needed to take this work forward:

1. 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 (CTTBD).
2. The roles of the Local Technical Representatives (LTR) as well as those of in-country distributors and importers need to be finalised (Global Alliance for Livestock Veterinary Medicines (GALVmed)/CTTBD). It would be useful to better document and explain the various roles and support provided by GALVmed, CTTBD, ILRI and others in the development and distribution of the vaccine (GALVmed).
3. Compile, validate, extend and share all the proposed delivery improvements (GALVmed/CTTBD)
4. Compile, validate, extend and share all the proposed process/product improvements/research agenda (GALVmed/ILRI/CTTBD)
5. Follow up a joint ECF communication process to catalyze and support continuing sharing and awareness and exchange of already existing materials and other information across countries – by newsletter, websites, etc. (GALVmed/ILRI).
6. Evaluate these actions after a set time to reevaluate priorities (GALVmed/ILRI/CTTBD).

# Introduction

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, with the more productive European and improved zebu breeds being particularly susceptible. ECF occurs in 11 countries in eastern, southern and central Africa where the tick vector, *Rhipicephalus appendiculatus,* is found. The parasite infects bovine lymphocytes, causing a profound lymphoproliferation. 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 ITM procedure employs well-characterized live sporozoite forms of theilerial parasites which are administered to cattle simultaneously with a long-acting formulation of the antibiotic oxytetracycline. Without the antibiotic treatment, the sporozoite inoculation would be lethal, but the oxytetracycline suppresses the infection, by a largely unknown mechanism. The result is an asymptomatic or mild episode of ECF, which induces a life-long immunity to the disease.

ITM was initially developed and refined at the former East African Veterinary Research Organisation (EAVRO), 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 in to inoculate cattle. The most widely used version is known as the 'Muguga cocktail', a combination of three parasite stabilates. The combination of strains is believed to be necessary because of the heterogeneity in field populations of *T. parva*, although this is yet to be formally established. 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 (FAO). A decade later, this time at the request from regional stakeholders convened under the auspices of the African Union-Interafrican Bureau for Animal Resources (AU-IBAR), ILRI produced a second batch, which is now being used in eastern Africa. A third batch is currently in production at CTTBD in Malawi, facilitated by GALVmed and the Bill and Melinda Gates Foundation and using tick and parasite seed stabilates transferred from ILRI.

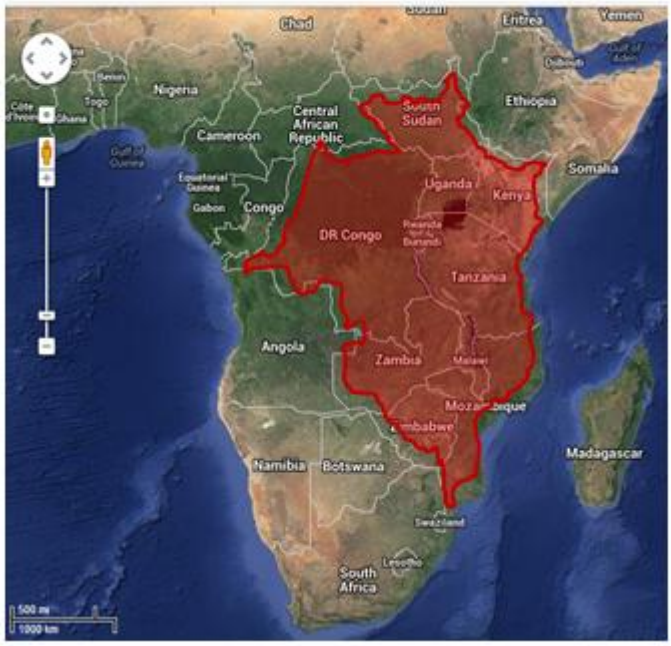
To date, over one million cattle have been immunized with the ILRI-produced vaccines. These have been delivered by commercial distributors, in particular VetAgro Limited who pioneered the commercial feasibility of the vaccine in pastoral areas in northern Tanzania. The vaccine has been registered in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

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.

Other strains have also been used in field vaccination of cattle. The Kenyan Agricultural Research Institute (KARI) undertook commercialization in Kenya of an alternative version based on the Marikebuni isolate of the parasite. The vaccine was sold under the trade name of ECFiM. In southern Africa, where the diversity of parasite strains is thought not to be as great as in eastern Africa, single local isolates have been used in the vaccine. In Zimbabwe, funds from Belgium and the Danish International Development Agency (Danida) allowed production and use of locally isolated parasite stocks throughout the country. In Zambia,

with support from Belgium, two stocks were identified that have formed the basis of that country's vaccination program.

**East Coast Fever endemic regions (red)**



# The August 2014 meeting[1]

The meeting in August 2014 was organized[2] by GALVmed and ILRI to bring together key parties involved in ITM. The objectives of the meeting were twofold: to provide an update on the production of the next batch of the ITM vaccine, and to address the challenges in the delivery of the vaccine. The specific aims of the meeting were to:

- provide information on future vaccine production
- share and document experiences in delivering the current ITM vaccine for East Coast fever
- identify and recommend best practices for the delivery and application of the vaccine
- guide the development of a research agenda to improve the vaccine, both the product itself and the process to manufacture it
- identify further research required to provide an evidence base on the impact of the vaccine

Participants (Annex 2) were drawn from a wide mix of organizations and represented distributors and vaccinators, Departments of Veterinary Services, regulatory agencies, researchers, vaccine manufacturers, and facilitators. It was perhaps the first such meeting of the full 'vaccine chain' for East Coast fever.

The meeting agenda is provided in Annex 1. The first day was essentially dedicated to the 'delivery' side of the vaccine while day 2 focused more on the continuing research agenda.

[1] Background materials are available at: http://livestock-fish.wikispaces.com/itm_convening

[2] The principal organizers of the meeting were Patrick Traill (GALVmed) and Philip Toye (ILRI). Peter Ballantyne (ILRI) facilitated the meeting.

# Production and supply of the vaccine

George Chaka of CTTBD gave a presentation on the current status and plans for sustainable production of the ITM vaccine[3].

He explained the process to produce bulk *Theileria parva* stabilate as well as infected *Rhipicephalus appendiculatus* adult ticks. He emphasized that it is a long, drawn-out process of about 18 months which:

- Closely follows the natural life cycle of the parasite in both cattle and tick
- Uses fairly low level production technology
- Is labour-intensive
- Has not much changed in the last 30 years
- Does not employ much automation of the production processes

In terms of the production timetable, he explained that the aim is to release a first batch of between 270,000 and 300,000 doses in late 2014, with a second batch to be released in September 2015 (around 1.5 to 2 million doses).

Questions from the audience focused on product quality and packaging as well as its availability to distributors.

**Question: How much confidence do you have in batch 1?**
*Answer: We are quite confident that we will be able to release the vaccine. Together with the stakeholders and collaborative partners we will manage to distribute the vaccine. There is no reason to doubt this effort[4].*

**Question: How will it be packaged?**
*Answer: Currently the vaccine is packed in 40 doses per straw.*

**Question: Why not use other packaging material besides straws**
*Answer: Since the vaccine is kept in liquid nitrogen, straws are affordable and storing them is easier.*

**Question: why not have 'ready to use' formulations rather than dilutions?**
*Answer: We would like to hear from participants what they think works best in the field. This also has cost implications.*

**Question: Are there any plans to inform the world on what CTTBD has/is doing?**
*Answer: There is a significant communication campaign planned, with prior information available to distributors.*

**Question: To ensure consistency of supply should we have more than one manufacturer?**
*Answer: An African Union-led ECF task force meeting in January 2009 agreed that CTTBD takes over production of the vaccine.*

***Question: Who is to blame in case of any liability in the production part of the vaccine?***
*Answer: CTTBD is solely responsible for the production. ILRI has helped with testing.*

---

[3] View the PDF at http://livestock-fish.wikispaces.com/file/detail/itm_convening_chaka.pdf
[4] The vaccine was technically released in December 2014.

# Vaccine availability

Patrick Traill from GALVmed provided an update on the current status and plans for supply, registration and distribution of the vaccine.

He explained that the current batch of the vaccine is registered in Kenya, Tanzania and Malawi and used under special permission in Uganda. Investigations to potentially register the vaccine are taking place in South Sudan, DR Congo, Rwanda, Burundi and Mozambique.

As CTTBD indicated, new batches of the vaccine are in preparation. Limited stocks of the current vaccine are available with some distributors; ILRI has a small stock for research purposes. He presented some data on the size of the market; the table below shows vaccination uptake projections based on current cattle populations and past uptake of the vaccine.

| Country | Cattle Population | Vaccine Uptake '13 | 10% of susceptible | 50% of susceptible |
|---|---|---|---|---|
| **Kenya** | 12 000 000 | 70 000 | 145 000 | 720 000 |
| **Malawi** | 950 000 | 2 000 | 12 000 | 57 000 |
| **Tanzania** | 18 000 000 | 160 000 | 215 000 | 1 000 000 |
| **Uganda** | 12 500 000 | 19 000 | 750 000 | 750 000 |
| | **43 450 000** | **254 000** | **522 000** | **2 500 000** |

He explained the process by which the LTR are appointed in each country by CTTBD to allow for vaccine to be available within the country and as part of the registration process. The current LTR status is:

- Malawi: CTTBD
- Kenya: KEVEVAPI
- Uganda: ERAM
- Tanzania: Process ongoing[5].

In terms of **registration**:

- Full registration and submission of CTTBD's ECF ITM dossier is ongoing
- This occurs in conjunction with LTR appointment
- In the short term to ensure vaccine availability it will be necessary to apply for a temporary/special/emergency import permit within Kenya, Malawi, Tanzania, Uganda.

The LTR process generated some discussion. It was made clear that the product owner, in this case CTTBD, is the one who appoints the LTR. The LTR must have qualifications to run a pharmaceutical company. Being a LTR does not imply sole distributorship; it means the organization is the sole agent of the owner of the product. The LTR facilitates distribution and wide access to the vaccine. It also has a role in quality control.

[5] Outside the meeting, it was agreed that Ronheam International will be the LTR.

# Lessons from the delivery and uptake of the ITM vaccine

After the orienting presentations, participants formed groups to discuss lessons and good practices that could benefit distribution and uptake of the vaccine. In the first round, groups were formed to discuss critical factors and promising practices around different issues. A second 'synthesizing' round brought participants together according to their role in the vaccine chain. They were asked, from their perspectives, to prioritize activities to be undertaken. The outputs as recorded are presented below.

## The cold chain

| **Critical factors** | **Promising practices** |
|---|---|
| Liquid nitrogen<br>- Availability<br>- Cost of liquid nitrogen<br>- Supply reliability<br>- Cost of containers<br>- Transport restrictions of liquid nitrogen | - Share facilities for both Artificial Insemination and ITM<br>- Centralized sharing of vaccination equipment<br>- Leasing of vaccination equipment<br>- Establishment of credit facilities to finance acquisition of equipment<br>- Support for installation of liquid nitrogen plants<br>- Use of solar powered fridges (or kerosene)<br>- Mobilization of farmers for mass vaccination |
| Refrigeration<br>- Electricity supply<br>- Cost of 2-8°C refrigerator<br>- Both cold chain not user friendly (thawing process) | |

## Delivery and vaccination

| **Critical factors** | **Promising practices** |
|---|---|
| Packaging<br>- Too large, especially dairy<br>- Rising costs<br>- Presentation to animal | - Optimal size – 10 (price sensitive)<br>- Transport after reconstitution; approx. 4 hours max |
| Transportation<br>• Distributors to vaccinators<br>• Safe passage | • Use a crate -→ upright<br>• Container owned by vaccinator<br>• Three liters - 4 days |
| Liquid N2<br>- Availability<br>- Breakdown of plants<br>- Cost $ 250/l. (V)<br>- Plants to vaccinators<br>- Monitoring of liquid N2 level | - Distributor stock TZ (approx. 200 litres)<br>- Vaccinator stock<br>- Level of liquid N2 'ruler' |
| Anaphylaxis | - NOT a big problem; BUT who pays |
| Reactors | - NOT a big problem; BUT who pays |
| Training | - Standard operating procedures<br>- Refreshers<br>- Certification |
| Business training | - Finance / Equipment<br>- Specify minimal set of equipment |
| Monitoring | - This should be a requirement<br>- Ethical |

## Sensitization and awareness

| Critical factors | Promising practices |
|---|---|
| - cost of campaigns<br>- fear of farmers for practitioners<br>- ignorance<br>- identification of target groups<br>- deliberate misinformation<br>- lack of information on packaging of messages<br>- channels of communication<br>- availability of the vaccine<br>- lack of business approach | - collaboration of shareholders<br>- technical and commercial training<br>- use of experts<br>  o Opinion leaders<br>  o Reference farms<br>- E-ITM |

## Recording and monitoring

| Critical factors | Promising practices |
|---|---|
| - Vaccinating prerecording<br>- Vaccinators prerecording<br>- Reporting to authorities<br>- Post immunization monitor<br>- Injection site on animal<br>- Fraudulent vaccines<br>- Registered vaccinators<br>- Disease/impact<br>- Feedback to manufacturer | - Tags given to farmers<br>- Straws, tags with contacts<br>- Distribution number, location of farmer<br>- Vaccinator number, location of farmer<br>- Ear tag on same side as vaccination<br>- Ear tag quality<br>- Recording fraudulent vaccinations<br>- Community appointed vaccinator<br>- Record the frequency of dipping post vaccination, and the cost of dipping<br>- Distributor reports, numbers of vaccinators back to manufacturer. |

## Perspectives of distributors

- Availability/accessibility from manufacturers
- Accessibility in the country
- Packaging, 5,10,40 doses
- Cost of the vaccine
- Shortage of (OTC, Liquid nitrogen) accessories
- Awareness
- Registration
- Initial capital to vaccinators: support of cold chain
- Trained vaccinators
- Room temperature diluent

## Perspectives of DVS's

- Enhance collaboration between all stakeholders
  - lesson learnt
  - meetings
- Sensitization of all stakeholders/training and advocacy
- Target-vets livestock farmers, distributors

- Cost indication
- Fast tracking registration-legislation requirements
- M&E and documentation
- Confidence building/eliminate unethical issues
- Impact assessment
    - Document data and best practices
- Ensure availability of adequate quantities of the ECF vaccine (quality assured)
    - annual requirements/projections

## Perspectives of regulators

- harmonized, formalized system for distribution: confidence, especially with cross border trade
    - clear user instructions for both users and distributors
    - training of vaccinators
    - proper use of vaccine to achieve efficacy
- vaccinators could convince farmers of economic benefits of the vaccine
- documentation addressing the quality control of cold chain during distribution and recording/ reporting back through LTR and registration authorities.

## Perspectives of researchers

- Diluent simplification
- Dose reduction/packaging
- Generate more evidence on impact of ECF-ITM(INFORMATION PACKAGING)
- cost of manufacturing (selling price to distributors)
- pricing model
- Additional quality control (vaccine contamination e.g. viruses, bacteria and fungi)
- Characterization of *T.parva* and comparison with immunizing parasite stocks

## Perspectives of facilitators

- Vaccinators
    - training, certification
    - business orientation
    - access to finance
- Cost of goods at the farmer level
    - straw size
    - liquid nitrogen
    - diluent
- Improving smart partnership
    - forums
    - common communication messages
    - listening to farmers
- Gaining buy-in from policy makers and leadership (sensitization and awareness)
- Assure sustainable supply chain

## Perspectives of manufacturers

- packaging: smaller pack sizes: 10 doses appropriate
- supportive government policies
  - clear policy on ECF ITM vaccination
  - facilitate awareness
  - demand creation
- consistent and sustainable supply of vaccine on the market
- availability of a vaccine, wide distribution network, enough vaccinators
- price reduction strategies or interventions
- process improvement
- production of large batches

## Key messages on vaccine delivery and uptake

Patrick Traill synthesized the main messages from this session as:

- Availability - we need vaccines
- Awareness - there needs to be a campaign to sensitize stakeholders
- Vaccinators have a key role – needs to be reinforced
- Having standard operating procedures essential within the country process
- Practical elements of the straw size - a critical issue in packaging of the vaccine
- The issue of smart partnerships, having a forum like this, on a regular basis is very critical

The image below is a word cloud generated (via http://www.wordle.net) from the text in this section. Larger terms represent increasing frequency of use of that term.

## Outlook for a next generation vaccine

Before engaging in the discussion on research priorities for the ITM vaccine, it was important to obtain an overview on the prospects for an alternative vaccine against ECF. Vish Nene gave a presentation looking to the 'next generation' ECF vaccine[6].

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. This Consortium is funded by the Bill and Melinda Gates Foundation, the Normal Borlaug Commemorative Research Initiative of the Feed the Future program of USAID-USDA-ARS and the Department for International Development of the United Kingdom[7].

The ECF Consortium will harness new science and undertake various research activities to fill current knowledge gaps. This involves testing of existing antigens to improve their efficacy, identifying new antigens, mapping bovine responses to infection and vaccination and a genomics approach to understand more about how the pathogen genome is evolving. The primary objective in this four-year research Consortium 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.

**Questions from participants**

Is this team dealing with process improvement? *Not directly, but the team is working on developing methods to determine infective sporozoite counts. Such methods will be transferred to CTTBD who will then use them to accelerate process improvements.*

A lot of resources are being used to develop the vaccines, have you ever considered looking for a vaccine for the vector? Would it be cheaper or faster? *ILRI is assessing a potential role of vector vaccines as a means of research on developing an ECF vaccine.*

Is there the possibility of removing Liquid Nitrogen from the process? *This does not seem likely in the short to medium term.*

Have you found cattle populations that are more resistant to ECF? *There is currently little evidence to support resistance/tolerance to ECF in the same manner as there is for cattle resistance to trypanosomosis.*

---

[6] See presentation at http://www.slideshare.net/ILRI/itm-convening-nene

[7] More information at http://ilvac.net/diseases/ecf/

# Research priorities for product and process improvement

## The process

At dinner during the evening of day 1, participants were asked to describe briefly the most needed improvement in either the ITM product or manufacturing process. A clustered list of the responses is attached at Annex 3.

In the morning of day 2, participants reviewed clusters of products and process improvement ideas that had been documented the previous evening. Groups were asked to work on these ideas, to prioritize them and to assess the likelihood of success and the time required for development. A summary of the discussion and main ideas is provided below, separated according to whether the improvement will change the product or the manufacturing process.

## Product improvements

**1. Thermostability**

The need for a cold chain was viewed as a major hindrance in the delivery of the vaccine. The cold chain operates at several stages:

- Vaccine – making the vaccine stable at room temperature is considered a long-term, high-risk undertaking at present. In areas where there is a reliable supply of liquid nitrogen, storage at -20°C or at 4°C may be less reliable due to irregular electricity supplies

- Diluent – it was recognized that a simpler diluent would be cheaper and more stable at room temperature. Activities are already under way at CTTBD to develop such a diluent. A desired stability would be six months at room temperature.

- Post-reconstitution stability – it is currently recognized that 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.

- Previous research indicated that the stabilate can be used for up to 12 hours post reconstitution (Musisi et al., 1991; communicated by B. Di Giulio)

**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 therefore 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 the 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. There are two ways to achieve this:

a) Filling with a diluted stabilate at the time of manufacture, together with the use of a smaller straw. This requires an estimate of the potency of the vaccine stabilate at the time of filling and the proportion of the batch that should be packaged in the smaller preparation. There will be increased storage costs due to the greater number of straws.
b) Post manufacture thawing of the routine, larger straws, diluting and re-packaging. There will be some loss of sporozoite viability during the process, but this method has the advantage of knowing the potency of the batch through the dose-determination assessment on the routine straws and the ability to make according to demand.

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 in some areas, whilst other reports have indicated that the vaccine is effective against buffalo-derived challenge. Lack of protection limits the wider use of the vaccine and poses a reputational risk for the vaccine. 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).

**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 as to whether broad immunity in the field can be induced by a vaccine composed of a single stabilate.

**7. Introduction of the vaccine into new areas.**
The issue of how to determine the safety and efficacy of the ITM vaccine prior to introduction into new countries or regions was also mentioned. There is currently no agreed procedure for this.

## Process improvements

**1. Decrease the number of animals used in the production process.**
The current procedure requires a large number of animals for the production of the vaccine and also for pre-release testing to ensure safety and to determine the potency (doses/straw) of the vaccine batch.

a. Vaccine production
   The alternative for using animals in the production process is the use of *in vitro* culture of the parasite. This is considered very challenging from a technical perspective and not for immediate application.

b. Potency testing.
   The current protocol for determining the dose of each batch requires three rounds of testing, plus an initial infectivity trial. This should be re-examined to see if it can be reduced. It was also noted that work is ongoing to establish an *in vitro* correlate of infectivity, which could be use to asses the potency of each batch and reduce the amount of *in vivo* testing required.

**2. Decrease 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 (as mentioned above). The use of staggered production cycles should also be considered.

**3. Increasing the batch size**

It was noted that increasing the number of sporozoites produced in each production would help to meet the expected increase in demand. Potential ways to achieve this include looking at alternative tick strains to increase sporozoite yields, to improve grinding methods to increase recovery of sporozoites from ticks and to improve the freezing process to allow for better sporozoite viability rates on thawing.

**4. Improve container for diluent**

The following improvements were suggested for the diluent container-

- Change from a glass container to a plastic one
- Use a unique cap colour for each batch
- Ensure that the size of container is suitable for the amount of diluent required for each batch of straws (which is related to the number of doses per straw).

# Key messages on product and process improvements

Phil Toye synthesized the main research priorities identified in this session as:

- Improve the thermostability of the diluent and possibly the vaccine
- Remove the need for the use of oxytetracycline
- Produce the vaccine at a suitable number of doses per straw
- Undertake further epidemiological research especially on the role of buffalo and the effects of the vaccine on current parasite populations
- Reducing the time and the number of stages required for production of each batch of the vaccine

# Synthesis and next steps

## Conclusions

Dirk Geysen compiled a first set of conclusions, as follows.

1. The ITM vaccine manufacturing process is complex; the processes can be improved (in the short term) resulting in more doses produced more quickly and at lower cost.
2. A next generation vaccine is on the way, but with at least a 10-year horizon.
3. Inadequate impact studies: more information is needed on what happens after vaccination.
4. Packaging of the doses; more adapted to different demands and customers.
5. The diluent is going to become more user- and distributor-friendly.
6. There is scope for research to reduce the need for OTC.
7. Liquid nitrogen: various options are needed to better manage and handle this in the field.
8. Allocation of doses to countries and distributors: there needs to be fair market distribution as well as transparent and reliable processes.
9. Standard operating procedures: These need to be built upon, based on existing best practices.
10. Vaccinators – certification and training is essential to enhance results on the ground.
11. Filling the vaccine gap in the short term is a critical issue to address
12. The registration process in the various countries is key to ensuring wide availability of the vaccine and requires appropriate actions now.
13. An emerging research agenda for the current ITM vaccine is apparent and should be taken up.

## Actions

Further to the conclusions above, participants identified a series of short term actions needed to take this work forward.

1. A clear timetable for the vaccine availability to distributors is urgently needed. Information is also needed on any planned controlled release or field testing - for both batches (CTTBD).
2. LTR roles as well as those of in-country distributors and importers need to be finalised (GALVmed/CTTBD)
3. It would be useful to better document and explain the various roles and support provided by GALVmed, CTTBD, ILRI and others in the development and distribution of the vaccine (GALVmed).
4. Compile, validate, extend and share all the proposed delivery improvements (GALVmed/CTTBD)
5. Compile, validate, extend and share all the proposed process/product improvements/research agenda (GALVmed/ILRI/CTTBD)
6. Follow up a joint ECF communication process to catalyze and support continuing sharing and awareness and exchange of already existing materials and other information across countries – by newsletter, websites, etc. (GALVmed/ILRI).
7. Evaluate these actions after a set time to reevaluate priorities (GALVmed/ILRI/CTTBD)

# Annex 1: Agenda

| **Tuesday 19 August** | | **Topic** | **Presenter** |
|---|---|---|---|
| 08:30 | Registration | | |
| 09:00 | Session 1<br>Opening | Welcome, objectives; introductions | Jimmy Smith, ILRI<br>Peter Jeffries, GALVmed<br>Peter Ballantyne |
| 09:45 | Session 2<br>Production update | Current status and plans for sustainable vaccine production | CTTBD |
| 10:45 | Coffee | | |
| 11:15 | Session 3<br>Supply update | Current status and plans for vaccine supply, registration and distribution | GALVmed |
| 12:30 | Lunch | | |
| 14:00 | Session 4<br>Delivery challenges | Lessons learned, knowledge sharing, best practices in supplying, registering and delivering vaccines | Peter Ballantyne<br>Patrick Traill<br>Participants |
| 16:00 | Coffee | | |
| 16:30 | Session 4<br>Delivery challenges | Synthesis: Lessons, best practices | Patrick Traill |
| 17:00 | Session 5<br>Review | Reflections on the day / what tomorrow holds | Peter Ballantyne<br>Participants |
| 17:30 | Session 6<br>Reception then Dinner | Informal interactions<br>Dinner: focus group discussions on required improvements | |

| **Wednesday 20 August** | | **Topic** | **Presenter** |
|---|---|---|---|
| 08:30 | | Agenda for the day | Peter Ballantyne |
| 09:00 | Session 7<br>Looking to the future | Outlook for a new ECF vaccine:<br>▪ Anti-sporozoite<br>▪ Anti-schizont<br>▪ Anti-tick | Vish Nene |
| 09:45 | Session 8<br>Product improvements | Setting the Research for Development agenda: potential product improvements, feedback from focus groups | Phil Toye<br>Peter Ballantyne<br>Participants |
| 11:00 | Coffee | | |
| 11:30 | Session 8<br>Product improvements | Synthesis: Setting the Research for Development agenda: product improvements | Phil Toye |
| 12:15 | Session 9<br>Process improvements | Synthesis: Setting the Research for Development agenda: potential process improvements | CTTBD/GALVmed |
| 13:00 | Lunch | | |
| 14:00 | Tour of ILRI facilities | | |
| 14:45 | Session 10<br>ITM results and impact | Evaluating the impact of ITM<br><br>Discussion and synthesis of potential impact studies | James Rao<br><br>Participants |
| 16:00 | Coffee | | |
| 16:30 | Session 11<br>Next steps | Synthesis and wrap up<br>Close | Patrick Traill<br>Phil Toye |

# Annex 2: Participants

| Name | Organization | Country | E-mail address |
|---|---|---|---|
| Paul Bogere | Eram | Uganda | spbogere1@gmail.com |
| Ponsiano Kibirige | Scopevet | Uganda | ponsianokibirige@yahoo.com |
| Charles Sendere Rutebarika | DVS | Uganda | crutebarika@yahoo.com |
| David Karlvon Lubega | AFRISA | Uganda | drkanmich@gmail.com |
| Kenneth Mugabi | NLRI | Uganda | kmugabi@gmail.com |
| Gordon Sematiko | NDA | Uganda | gsematiko@nda.or.ug ; gsematiko@gmail.com |
| Antony Musoke | CTTBD | Uganda | tomusoke@gmail.com |
| Lieve Lynen | VetAgro | Tanzania | llynen@habari.co.tz |
| Beppe di Giulio | VetAgro | Tanzania | bdigiulio@habari.co.tz |
| Henry Mbwille | Ronheam | Tanzania | ronheam@gmail.com |
| Alice Mbwille | Ronheam | Tanzania | ronheam@gmail.com |
| Emmanuel Mutakhyawa | TFDA | Tanzania | rutamuta75@yahoo.com |
| Martin Ruheta | DVS | Tanzania | mruheta@yahoo.com |
| Arina Odek | Kevevapi | Kenya | arina@kevevapi@org |
| Eric Mitema | UON | Kenya | esmitema@uonbi.ac.ke |
| Bernard Chimera | DVS | Malawi | bernard.chimera@yahoo.com |
| Christie Peacock | Sidai | Kenya | christie.peacock@sidai.com |
| Daniel Mpilei | VetAid | Kenya | gkturasha@gmail.com |
| David Bett | KDFF | Kenya | dbett@kdff.co.ke |
| Rawlynce Bett | BMC | Kenya | rawlynce@gmail.com |
| Joseph Karanja | Tegea | Kenya | joekaranja@outlook.com |
| Nkhwachi Gondwe | CTTBD | Malawi | ncgondwe@cttbd.org ; ncgondwe@yahoo.com |
| George Chaka | CTTBD | Malawi | mihji_chaka2@yahoo.co.uk |
| Leonard Zondetsa | CTTBD | Malawi | zondetsaleonard@gmail.com |
| Namukolo Muyamwa | CTTBD | Malawi | nmuyamwa@yahoo.com |
| David Atuhaire | CTTBD | Malawi | kalenzid@gmail.com |
| Patrick Traill | GALVmed | UK | patrick.traill@galvmed.org |
| Victor Mbao | GALVmed | Malawi | victor.mbao@galvmed.org |
| Danny Goovaerts | GALVmed | Belgium | danny.goovaerts@galvmed.org |
| Heshborne Tindih | GALVmed | Kenya | Heshborne.Tindih@galvmed.org |
| Hameed Nuru | GALVmed | Botswana | hameed.nuru@galvmed.org |
| Samuel Adediran | GALVmed | Kenya | samuel.adediran@galvmed.org |
| Peter Jeffries | GALVmed | UK | peter.jeffries@galvmed.org |
| Jeremy Salt | GALVmed | UK | jeremy.salt@galvmed.org |
| Abdallah Twahir | GALVmed | Kenya | abdallah.twahir@galvmed.org |

| | | | |
|---|---|---|---|
| Gilly Cowan | GALVmed | UK | Gilly.Cowan@galvmed.org |
| Phil Toye | ILRI | Kenya | p.toye@cgiar.org |
| Suzanne Bertrand | ILRI | Kenya | s.bertrand@cgiar.org |
| Henry Kiara | ILRI | Kenya | H. Kiara@cgiar.org |
| Jimmy Smith | ILRI | Kenya | j.smith@cgiar.org |
| Peter Ballantyne | ILRI | Ethiopia | P.Ballantyne@cgiar.org |
| James Rao | ILRI | Kenya | j.rao@cgiar.org |
| Vish Nene | ILRI | Kenya | v.nene@cgiar.org |
| Cathryn Wanjohi | DVS | Kenya | c.wanjohi@yahoo.com |
| Waweru Kabaka | DVS | Kenya | wkabaka@gmail.com |
| Nathan Songok | DVS | Kenya | |
| Stephen Mwaura | ILRI | Kenya | s.mwaura@cgiar.org |
| Thomas Njoroge | ILRI | Kenya | t.njoroge@cgiar.org |
| Tony Brenton-Rule | ILRI | Kenya | tony.br@cgiar.org |
| Dirk Geysen | Institute of Tropical Medicine | Belgium | dgeysen@itg.be |

# Annex 3. List of proposed improvements*

*Participants at the dinner were asked to propose the most desirable improvements in the ITM vaccine or manufacturing process. The list is provided below, with some clustering of similar proposals.

1. Improving the cold chain. There were several aspects to this:
    - Removing the need for liquid nitrogen to store the vaccine
    - Developing a simpler diluent which can be kept at room temperature
    - Improving the post-reconstitution viability to allow for a longer duration between administration and delivery – especially important in smallholder areas with straws of 40 doses or more.
    - Providing better storage equipment for transport of the vaccine
2. Removing the need for oxytetracycline
3. Removing the need for live animals during the production process
4. Developing ticks which can yield greater number of sporozoites
5. Eradicate the vector
6. Produce one vaccine which can be used in all countries
7. Provide the vaccine in a smaller dose packaging
8. Decrease the cost of the vaccine
9. Develop a sub unit vaccine
10. Develop an ECF vaccine which can be administered as an aerosol
11. Validate the use of other antibiotic formulations

Additional suggestions for following field-research activities were suggested received from Dr. di Giulio:

- Age of first immunity
- Diluent thawing-freezing-thawing. After thawing, is it better to keep at refrigeration temperature.
- Checking for diluent pH
- Immunity duration in the field
- Immunization during when other diseases are present, such as: FMD, LSD etc.