

CIFSRF final technical report : Novel livestock vaccines for viral diseases in Africa towards improved food security(CIFSRF Phase 2) - 107848

Research Organizations involved in the study:

Agricultural Research Council- Onderstepoort Veterinary Institute
Agricultural Research Council - Economics Analysis Unit
Human Sciences Research Council - Human and Social Development
Onderstepoort Biological Products
University of Alberta
National Centre for Foreign Animal Disease
Vaccine and Infectious Disease Organisation – International Vaccine Centre
Kenya Agricultural and Livestock Research Organization
Department of Veterinary Services - Kenya
Kenya Veterinary Vaccines Production Institute

Location of Study:

South Africa

Kenya

Canada

By: Lorne Babiuk, University of Alberta

David Wallace, ARC-OVI

Entire collaborative team

Period covered by the report: November 2014 – June 2018

This work was carried out with the aid of a grant from Canada's International Development Research Centre (IDRC), www.idrc.ca, and with financial support from the Government of Canada, provided through Global Affairs Canada (GAC), www.international.gc.ca



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1. EXECUTIVE SUMMARY:

The objective of this project was to contribute to food security in Africa by generating vaccines for prevention of some high-impact viral livestock diseases. We aimed at the refinement, testing and transition to production of several vaccines (most constructed during Phase 1 of CIFSRF funding), which are based on two different platform technologies.

The main advantage of the first technology based on a lumpy skin disease viral (LSDV) vector is the ability to construct combinations of vector and inserts, allowing adaptation to a variety of threats and markets. On this platform, two products were developed: 1) a LSDV-RVF (Rift Valley fever) -PPR (*peste des petits ruminants*) construct, which is adapted to most countries in sub-Saharan Africa for protection against lumpy skin disease (LSD), sheep pox (SPP), goat pox (GTP), RVF and PPR; and 2) a LSDV-RVF construct which is designed to prevent LSD, SPP, GTP and RVF, and which was developed specifically for South Africa and for other countries free from PPR. The use of this platform technology extends well beyond the current collaboration and more constructs are under consideration for other disease profiles.

The second platform technology is based on porcine adenovirus (PAdV) as a vector and examines multiple antigens, predicted using bioinformatics, for their potential to confer protective immunity against African swine fever (ASF).

The impact of the diseases we selected increased significantly during the lifetime of this project. Three of our target diseases (LSD, PPR and ASF) emerged in new areas in Asia and Europe. In the last decade the UN Food and Agriculture Organisation (FAO) and Office International des Epizooties (OIE) have taken the lead in developing a PPR eradication program. We expect that our LSDV-RVF-PPR vaccine will contribute to the program, if selected.

During the project term our team was focused on testing the vaccine constructs and transition to manufacturing. Refinement of the LSDV-RVF-PPR vaccine construct was finalized and the product demonstrated full protection with no clinical signs after challenges with sheep pox, goat pox, PPR and RVF in sheep and goats. The LSDV-RVF construct was also finished and achieved the required level of safety in cattle. More than 20 ASF genes were selected, synthesized and inserted in PAdV, and so far eight of them have been tested for protection against ASF challenge, albeit with negative results. The remaining ASF constructs will be tested after the project term ends.

Onderstepoort Biological Products, a South-African veterinary vaccine manufacturer and collaborator within this project, has taken the transition to manufacturing for both LSDV-RVF vaccines. Seed stocks and production stocks were established, small-batch stocks passed the pre-clinical tests for safety and potency, and thermal stability tests were initiated. An interesting development, which coincided with our work, was the lifting of the ban on development of PPR vaccines by the government of South Africa. As a result, OBP can now produce the LSDV-RVF-PPR vaccine.

A strong socio-economic research program, guiding the development of scaling-up strategies for vaccine roll out and use, was conducted in parallel to the vaccine development work. This research was focused on constraints of farmers, small-scale livestock farming trends and drivers, farmer knowledge, attitudes, perceptions and practices (KAPP) towards vaccines, use of vaccines, willingness-to-pay (WTP), and cost-benefit analysis (CBA) of vaccine development and use. Results of these activities were guiding the vaccine development work throughout the course of the project: studies conducted in five provinces in South Africa indicated that on average 97% of the livestock farmers interviewed expressed a desire for vaccines that protect against multiple diseases, 94 % highly preferred a vaccine that can be used in cattle, sheep and goats, but only 50% would choose a vaccine that needs refrigeration. On average, 73% of these farmers buy livestock vaccines, while 54 % strongly agree that vaccines are too expensive. Integration of gender into the project cut across all socio-economic studies, given the gender imbalances in African agriculture. Two policy dialogues were held (one as a stakeholder engagement session), as well as several presentations and training sessions for farmers and animal health practitioners.

Overall, we have utilised and refined a vaccine platform technology in which we constructed and/or evaluated two novel vaccines with excellent potential for prevention of five high-impact livestock diseases. We were regrettably not able to manage the planned field trials towards the product dossier, however, the potential for easy adoption of our vaccines by any current LSD vaccine manufacturer, plus the complete prevention of clinical signs in the vaccinated animals after challenge for all five diseases (LSD, GTP, SPP, RVF and PPR) has already attracted the attention of the biotech industry (e.g. OBP and KEVEVAPI) and animal health professional consortia (e.g. AgResults).

2. THE RESEARCH PROBLEM

Losses from infectious diseases are one of the most important causes of economic adversity to the livestock sector worldwide – an effect further magnified by deficient veterinary services and infrastructure, or by lack of effective treatment and prevention in certain countries. In addition, outbreaks impact animal producers by hampering local and international trade. On the African continent, 12 of the 16 most devastating animal diseases are prevalent today. Eight of them occur predominantly in Sub-Saharan Africa.

This project focused on six diseases, which are all listed by the OIE, and which are of importance to smallholder farmers in Africa: Rift Valley fever, *peste des petits ruminants*, lumpy skin disease, sheep pox, goat pox; and African swine fever. Our project aimed at development and production of vaccines for prevention and possible eradication of these threats.

The strategy of this project remained constant: using vectored vaccines as a platform technology, which can later be applied to other diseases of interest, including those which may emerge in the future. This technology was successfully applied to produce/evaluate two different vaccine products, and in addition, a pool of vaccine prototypes:

- LSDV-vectored vaccine for LSD, SPP, GTP, and RVF for use in countries free from PPR.
- LSDV-vectored vaccine for LSD, SPP, GTP, RVF, and PPR in countries endemic for these diseases.
- A pool of prototype porcine adenovirus-vectored vaccines for prevention of ASF.

Local production of veterinary vaccines significantly improves disease control, and prevention and eradication programs consider it the most effective tool (1). Our collaboration also supported the development of biotechnology manufacturing capacity in Africa – two vaccines are being earmarked for production in South Africa by Onderstepoort Biological Products (OBP) and testing in collaboration with the ARC-OVI. In addition, the LSDV-RVF-PPR vaccine will likely be tested in Kenya or another country endemic for the diseases, especially PPR. One of the outcomes of this project was the approval by the government of South Africa of an application which OBP filed, requesting permission to produce the PPR-containing vaccine within the country. This approval was a significant success, given the earlier firm policy to deny production of PPR vaccines. The results of this change will extend well beyond the limits of this collaboration and will have the potential to positively impact the strategy for eradication of PPR.

Simultaneously, the assessment of the potential social and economic impacts of the vaccines continued together with multiple stakeholder dialogues. These activities are aimed at forming a basis for a product launch strategy and building a business case for the vaccines.

Since the beginning of this project, we were aiming at diseases which are devastating livestock in Africa and South Asia. During the project term African swine fever migrated through southern Russia, Ukraine, and Belarus to Poland, Latvia, Estonia and Romania. Lumpy skin disease had multiple occurrences in southern Europe, while PPR breached the south-east border of the EU this summer (2018). These outbreaks necessitated emergency measures – quarantines and culling of the affected herds – which were met with growing dissent by farmers and political activists. Culling and quarantine have a history of success in helping eliminated certain infectious animal diseases from specific regions or countries, but recent protests demonstrate that sufficient funding and logistics may not be enough to enact these measures on a large scale today. Recently, research aimed at prevention of ASF and LSD received high priority for funding in the EU Horizon 2020 DEFEND program. Since 2013, FAO and OIE are actively working on a strategy for global control and eradication of PPR. The annual cost of PPR alone is estimated at 1.45 to 2.1 billion USD and the cost-benefit ratio of eradicating PPR is estimated between 18.5 and 60 (1, 2). The current plans for eradication involve live attenuated vaccines, justified mainly

by the ease of production in multiple countries affected by PPR. LSD vaccines are also produced in many countries in the same regions, and our LSDV-RVF-PPR vaccine could be easily manufactured using the existing LSD vaccine technology. Since our construct contains a single protective component of the PPR virus genome, it has much better potential than any live attenuated PPR vaccine for use as DIVA (Differentiating Infected from Vaccinated Animals), which will significantly improve the logistics of an eradication campaign.

In summary this project used vaccinology, sociology and economic analysis in an integrated approach to refine a vaccine platform technology based on LSDV, strains of which constitute a number of livestock vaccines currently manufactured in South Africa, Kenya and other countries in Africa and Asia. This novel platform, as utilised in the project, enables protection against up to 5 diseases (products can be adapted to include combinations of: LSD, SPP, GTP, RVF and PPR) in thermostable, state-of-the-art vaccine formulations, which can be manufactured using existing facilities and equipment, after adopting minor modifications of only some of the post-production processes.

3. PROGRESS TOWARDS MILESTONES

1.1 Inception workshop held, report developed and circulated - completed, planning workshop held jointly with CBPP vaccine development team, London, UK, January 2015.

1.2 Personnel identified and/or recruited, MOUs signed – completed

1.3 Development of key project implementation strategies including: i) impact pathway, ii) project M and E / results framework, iii) communication/scaling up strategy, and iv) gender and socio-economic studies framework – completed and strategies accepted

1.4 Equipment ordered - completed

1.5 PAdV-ASF prototype vaccines ranked by expression - completed

1.6 LSDV-RVF insertion vector plasmid/s designed and constructed – completed, output used to construct LSDV-RVF vaccine prototype

1.7 Permits and ethics approvals developed for: a) LSDV-RVF-PPR pre-existing immunity test, b) LSDV KO1 safety test, and c) LSDV-RVF-PPR field trial in sheep and goats – all permit documentation applications completed

1.8 Lists of documentation for registration of vaccines compiled – completed, with expertise from Onderstepoort Biological Products

1.9 One policy brief developed, one policy dialogue hosted – completed and published March 2015

1.10 Training for farmers and animal health practitioners started – Training launched as per schedule

2.1 LSDV-RVF construct generated and characterized – completed, characterised and construct submitted to manufacturer, OBP

2.2 ASF expression library (EL) generated – completed, after obtaining full sequence of a South African ASFV isolate

2.3 Permits and ethics approvals received for: a) LSDV-RVF protective efficacy trial, b) LSDV-RVF dossier trial in cattle, c) LSDV-RVF-PPR dossier trial in sheep and goats, d) protection trial PAdV-ASF, e) immunogenicity and protection ASF EL – completed, except LSDV-RVF-PPR trial in sheep and goats in Kenya

2.4 LSDV low-dose test complete – completed

2.5 Dossier collection started for: a) LSDV-RVF, b) LSDV-RVF-PPR – dossier compilation started

2.6 One publication submitted – completed

2.7 First communication with regulatory authorities complete. Report written on regulatory requirements and policies on GMM vaccines – completed, under guidance of OBP

2.8 Methods and study design completed for KAPP and WTP surveys at four Kenyan and four South African sites, sites selected and survey instruments developed, permits and approvals obtained in South Africa and Kenya – completed, in collaboration with members of the socio-economic team in Kenya

3.1 Annual workshop held – completed; joint workshop with the CBPP team in Saskatoon, October 2016

3.2 Protection trials complete for: a) LSDV-RVF, b) PAdV-ASF - completed

3.3 Permits and ethics approvals obtained for dossier trial, PAdV-ASF – completed for confined trials in South Africa, but not for field trial, since no protective construct was identified

3.4 Dossier collection started for ASF – not completed since no protective construct was identified

3.5 Training sessions complete in Kenya and South Africa – completed, with training sessions for farmers and animal health practitioners

3.6 First KAPP and WTP surveys completed at two sites in Kenya and two sites in South Africa, preliminary report – completed

3.7 One policy dialogue hosted – completed, Pretoria, September 2015

3.8 Progress reports on regulatory aspects delivered - completed

4.1 Post-trial analysis of ASF expression library complete – cancelled, Scientific Advisory Board (SAB) recommended, and the team accepted, that selection of antigens using bioinformatics had higher probability of success than expression library approach. Abandoned upon SAB advice

4.2 Trials completed towards dossier compilation: a) dossier trial LSDV-RVF in cattle, b) dossier trial LSDV-RVF-PPR, sheep and goats, c) field trial LSDV-RVF-PPR, sheep and goats; d) immunogenicity and protection ASF EL – a) completed; b) and c) - not completed because of delay of receiving GMO vaccine permit; d) completed, using alternative construct/s

4.3 Permits and ethics approvals obtained for: a) field trial LSDV-RVF, cattle, b) field trial PAdV-ASF in pigs – not completed due to delays in preceding trials and construct purification; b) not completed since no protective construct was identified

4.4 Dossier documentation assembled for LSDV-RVF-PPR, sheep and goats – partially completed, as not all trial data was generated

4.5 Publication (KAPP and WTP survey results) – completed

5.1 Annual workshop held – jointly with the CBPP vaccine team, Nairobi, July 2017

5.2 PAdV construction with selected expression library genes 50% complete – completed, for antigens selected using bioinformatics

5.3 Dossier trial PAdV-ASF complete – not completed, since no protective construct was identified

5.4 Master seed stocks generated for all constructs which have undergone dossier trials – completed, for LSDV-RVF vaccine only

5.5 Training session of farmers and animal healthcare practitioners complete – completed

5.6 One policy dialogue on livestock vaccines, including new generation vaccines, hosted – completed, Pretoria, November 2017 (as a Stakeholder Engagement meeting)

6.1 Construction of PAdV with selected ASFV expression library clones complete – completed for antigens selected using bioinformatics

6.2 Permits and ethics approval obtained for protection trial of PAdV-expression library clones – completed

6.3 Master seed stocks prepared for all constructs – completed, for LSDV-RVF constructs, but not for PAdV-ASF since no protective construct was identified

6.4 Second KAPP and WTP surveys completed at two additional Kenyan and South African sites, preliminary report submitted – completed

6.5 One publication submitted (KAPP and WTP survey results) - completed

7.1 Project Final meeting/workshop/conference held to disseminate project results and recommend key strategies for future scaling up – involving project partners, stakeholders and policy makers – jointly with the CBPP project, Pretoria, June 2018

7.2 End of project evaluation and impact assessment documenting progress towards the key objectives and research for development outcomes, highlighting progress towards development of three next-generation vaccines – completed

7.3 At least 5 publishable manuscripts developed and/or submitted for peer-review journals. Present project strategies and results at a minimum of 2 scientific and/or 2 international development conferences - completed

7.4 Field trials completed: a) LSDV-RVF, cattle, b) PAdV-ASF pigs – not completed due to delayed characterisation of a) and no protective effect so far obtained in b)

7.5 Dossier trial completed PAdV-ASF EL clones – not completed since no protective construct was identified

7.6 Field trial data processed for LSDV-RVF, LSDV-RVF-PPR, PAdV-ASF vaccines.

- not completed; LSDV-RVF construct characterisation was delayed, LSDV-RVF-PPR GMO permit and contract signing was delayed, and PAdV-ASF protective construct was not identified

7.7 Vaccine roll-out strategy developed, tested and ready for use – not completed since not all previous steps were finalized

7.8 KAPP and WTP study report submitted. One policy brief (KAPP and WTP) - complete

- 1 KAPP and WTP study articles accepted for conference presentation at the Agricultural Economics Association of South Africa Conference (25-27 September, 2018, Cape town).

- 2 posters (CBA and KAPP) were presented at the 3rd Conference on Global Food Security, (3-6 December 2017, Cape town).

- 1 poster on national level Cost benefit Analysis presented at the 55th AEASA Conference (19-21 September 2017, Durban).

- 1 popular news articles published

- Communication Strategy,

- 5 Page summary for socio-economic studies integration in vaccine studies research completed

- 1 page project outcome story completed

4. SYNTHESIS OF RESEARCH ACTIVITIES AND RESULTS

Refinement of the Phase 1 vaccine constructs.

- LSDV-RVF-PPR

Testing and refinement of this construct continued from Phase 1 by generating three constructs containing different protein expression regulatory control signals (designated: S, N and F). Expression of the RVFV glycoproteins (which was not detectable in the Phase 1 construct) was shown for each of the three constructs and selection was carried out for removal of wildtype (parental) virus. Due to time constraints, the constructs were sent to Canada for further evaluation in sheep and goats. These constructs were tested at a dose of 10^3 plaque forming units (pfu) to evaluate protection from GTP, SPP and PPR. While all such trials performed previously within the project utilised a single disease challenge model, this trial used a dual challenge model with simultaneous capripox and PPR challenge. This challenge is harsh as both diseases can be lethal. The results revealed that there was only partial protection in both sheep and goats when using this model.

There were two possible explanations for this, 1) with these vaccine constructs the antibody responses were not effective, as neutralizing antibodies to PPRV were not detected following vaccination. This could also be caused by the presence of wildtype virus in the vaccine. 2) The dual challenge model was taxing on the animal's immune system and likely required a higher level of immunity against both diseases to obtain full protection. This could have implications for use of the vaccine in the field, possibly requiring a higher vaccine dose to protect against the possibility of simultaneous infection with two or more of the targeted pathogens, however, unlikely this is of occurring in reality. Thus, confirming the purity of the constructs became a critical matter, as presence of wildtype virus could adversely effect immune response levels. Evaluation of the purity and absence or presence of wildtype virus was managed using PCR and sequencing of the gene-deleted region, resulting in demonstration of presence of wildtype LSDV in the constructs (Appendix 1). Following this, the constructs were purified and evaluated for expression of all inserted antigens. Briefly, mRNA synthesis of the RVF virus glycoproteins and PPRV protein was confirmed using real-time RT-PCR and expression was verified using Western blot analysis and mass spectroscopy. Expression of the RVFV glycoproteins was also confirmed using immunofluorescence (Appendix 2). The purified vaccine constructs, which differ in the post-translational signaling and form of the inserted RVFV and PPRV antigens (native [N], secreted [S], and fusion [F]), were all subsequently demonstrated to be pure and expressing the recombinant protective antigens. All three were evaluated for protective efficacy against PPR challenge in sheep. Two of the vaccines (with the antigens in the native, N, as well as the secreted

form, S) elicited protection against PPR challenge, while the vaccine with the antigens in fusion form (F) elicited only partial protection. The generation of neutralizing antibodies to capripoxvirus was detected in all vaccinated sheep at levels indicative of protection. In addition, a number of the sheep elicited production of detectable levels of neutralizing antibodies to RVFV, in animals vaccinated with constructs expressing the native and secreted forms of the antigens. Overall, the vaccine construct with the antigens in the native (N) form performed the best and was thus selected as the vaccine construct of choice going forward.

[Here, it should be noted that one of the tests recommended by OIE for diagnostics of PPR is based on RT-PCR targeting two PPRV genes. Our construct contains one of those genes (F), but not the second one, which means that when using this test on PPRV-infected animals, it will produce two amplicons, while those vaccinated with our construct will only produce one of them (for the fusion gene). This difference is a critical component of a DIVA (differentiate infected from vaccinated animals) test, which is important for disease control, and especially so for the upcoming PPR eradication program.]

Further, since protection against challenge with sheep pox and goat pox viruses is conferred by the LSDV vector, as was successfully demonstrated in Phase 1, the selected LSDV-RVF-PPR construct (N) was shown to protect against challenge with PPRV and RVFV in high biosafety confinement trials at NCFAD-Canada (Appendix 3). Challenge with PPRV resulted in no clinical signs and strongly reduced viral shedding in vaccinated animals. These findings correlated with strong virus neutralizing titers in the protected animals.

Challenge with RVFV also caused no clinical signs in the vaccinated animals. In sheep, vaccine efficacy, determined by the evaluation of viable virus detected using virus isolation from sera, revealed that control animals had detectable RVFV in sera in all 6 animals in the group. In contrast, all vaccinated sheep, with either 10^4 or 10^5 pfu of the LSDV-RVF-PPR N construct, did not have any detectable levels of viable RVFV. In goats, 5 out of 6 control animals had detectable RVFV in their sera, whereas vaccinated goats, also with either 10^4 or 10^5 pfu of the construct, had none. Therefore, the vaccine prevents viable RVFV circulation in sheep and goats (sterile immunity). These promising results indicate that the vaccine can undergo further trials towards production and licencing. Further, when tested using PCR, which reveals any traces of RVF viral genomic RNA, 2 out of 6 sheep vaccinated with 10^4 pfu and 2 out of 6 sheep vaccinated with 10^5 pfu did not have any detectable levels of RVFV genomic RNA in sera compared to 6 out of 6 unvaccinated controls. Although this level of protection was conferred to only 30% of the test animals, such a degree of sterilizing immunity is indicative of very high protective efficacy.

The production process development for this vaccine construct was restricted by the fact that South Africa is a PPR-free country. Subsequently, linked to project outputs, permission has been granted by the SA authorities to manufacture the vaccine, provided it is not tested in animals in

SA. Hence, small-scale process development of the LSDV-RVF-PPR vaccine is now earmarked for performance by OBP. It is envisaged that this will be achievable along similar lines to that of the LSD-RVF vaccine due to their sharing of a common vector strain (LSDV). Therefore, the stabilizer and formulations selected will first be evaluated and found suitable for the LSD-RVF vaccine. Following success, lyophilisation parameters will be determined and optimized.

- LSDV-RVF

During the project term we generated a stage-one construct (inactivation of the IL-10-like gene) and then in stage two inserted the RVFV glycoprotein genes into a field LSDV genome disrupting two other genes in two separate constructs (to produce two knockout-out [KO] LSDV-RVF vaccine constructs). The objective of these steps was to achieve attenuation which will minimize the injection site reactions in cattle, using a targeted approach, while ensuring improved immune responses were elicited. These steps were primarily informed by the results of the socio-economic surveys, which indicated that minimal injection site damage is an important factor for vaccine acceptance. In addition, we had available a similar construct, with insertion of the RVFV glycoproteins in the thymidine kinase gene of the OBP vaccine strain of LSDV, also with removal of the selectable marker genes – thus, marker-free (designated: LSDV-RVF MF). A decision was made to include this construct with the newly-developed ones and thus a contract was signed with OBP for additional development of this construct for vaccine formulation towards production. Of the two constructs generated first during the project, one was further purified (free from parental [wildtype] virus), and was confirmed to express the desired antigens (the LSDV-RVF MF construct was also previously shown to be pure and expression of the RVFV glycoproteins confirmed) (Appendix 4). These two constructs were transferred to the manufacturing partner (OBP, South Africa) by April 2017. OBP undertook process development for these vaccines and has produced master seed, seed stock and vaccine stocks (this is a requirement for registration purposes for dossier compilation – that the vaccine is used in trials in its final formulation). A safety and efficacy trial for the two LSDV-RVF vaccines has been performed and overall the LSDV-RVF MF vaccine performed well, and is now in readiness for requesting a permit towards next-stage field trials. A selection of the results of the safety and efficacy trial are shown in Appendix 4. Initially, the trial was to be performed in the institute's ABSL2 (for LSD) and ABSL3 (for RVF) facilities due to the higher safety and containment level requirement for RVF work. However, due to changing departmental (agriculture) requirements, the LSD trial had to be moved to the ABSL3 containment facility (TADs).

In brief, the two vaccines were evaluated in young cattle at different doses (doses are within practical levels for use in a commercial vaccine preparation):

- KO (high dose: 1×10^4 pfu; low dose: 1×10^3 pfu)

- MF (1.3×10^4 pfu, only)

Following vaccination, a number of animals in the KO Low and High dose groups (3 and 4, respectively) developed transient fever (above 40 degrees C), whereas none of the MF group cattle developed fever. In addition, mild lumps/nodules developed on two of the KO Low group cattle (out of a total of 10 vaccinated – five destined for LSD challenge and five for RVF challenge), and one developed more severe (generalised) nodules, whereas four animals in the KO High group developed severe (generalised) lumps – all five animals were euthanised and post-mortems were performed. In the MF group, only two animals showed mild, localised reactions which were within acceptable limits as indicated by LSD vaccine manufacturers (Appendix 4).

All cattle developed neutralising antibodies to LSDV following vaccination and against RVFV there were 40% in the KO Low group, 60% in the KO High group and 40% in the MF group (Appendix 4).

Post-challenge with LSDV, two cattle in the KO Low group had transient fever post-challenge, and two animals in the MF group (the remaining animals in the KO High group were not challenged). Two of the negative control group animals developed a transient fever (above 40 degrees C). However, there were no other post-challenge clinical signs in any of the animals, vaccinated or not.

Post-challenge with RVFV, in the KO Low group 3 of the 5 animals challenged developed a high fever (above 41 degrees C) and one animal died, and in the KO High and negative control groups all animals (5 in each) developed fevers lasting one day. In the MF group, two animals developed fever, also lasting a day. All negative control animals showed clinical signs such as inappetance and listlessness, which were absent in the vaccinated animals, one animal being severe, but recovering, and one animal died. In each of the vaccinated groups, 4 of the 5 animals challenged showed viraemia (measured using PCR) between days 3 and 6 post-challenge, and all 5 in the negative control group (Appendix 4). In the MF group, all 5 animals developed IgM antibodies and 4/5 developed IgG antibodies. In the KO Low group 3/5 animals developed IgM and IgG antibodies post-challenge, and all animals developed both IgM and IgG antibodies in the KO High group (Note: the IgM and IgG antibodies were measured against the RVFV N protein, which is only present in the whole, virulent RVFV – not the vaccines).

Thus, overall, the MF vaccine performed the best, resulting in acceptable post-vaccinal reactions, with animals from all vaccine groups developing antibodies to LSDV and averaging 50% to RVFV.

Following challenge with LSDV, reactions were extremely mild in all groups, including the negative control group, indicating that the challenge strain had lost some virulence, possibly due to the freeze-drying or cell passage process. However, this is not considered a problem, as the MF vaccine is based on the commercially available OBP vaccine, which is tried and tested.

Following challenge with RVFV, one animal died in the KO Low vaccine group and all animals in the negative control group showed clinical signs (two were severe, one of which died). Except for

transient fever, no other reactions were observed in the vaccinated animals. Most animals showed viraemia between 3 and 6 days post-challenge as detected using PCR.

- PAdV-ASF

From the onset of this project, the search for an ASF vaccine was viewed as a high-risk/high-gain activity. A number of strong and well-funded teams are working on a vaccine for ASF globally, with no known published breakthrough success so far. For this reason we chose a systematic but flexible approach, relying on frequent revisions and the advice of leading virologists and immunologists.

In the beginning of the project term, DNA from African isolates of ASFV was shipped to VIDO-InterVac, sequenced, and used to construct a DNA library. Sequence data was used for bioinformatics analysis and synthetic genes were ordered for the generation of a library for furthering the search for protective antigens.

Analysis of the available sequence of a Malawi strain of ASFV identified 74 open reading frames (ORFs), which showed homology ranging from 61.3% to 100% with corresponding ORFs in a Georgia strain of the virus. Bioinformatic analysis of these ORFs using computer-aided ligand docking tools identified 14 T-cell epitopes predicted to be interacting with porcine MHC Class I receptors. Similarly, using bioinformatic tools (EMBOSS, Vaxigen-2, Ellipro etc), B-cell epitopes were identified in a number of ORFs. Based on these results, we synthesized chimeric genes (codon-optimized) expressing a number of T-cell epitopes, and codon-optimized ORFs containing B-cell epitopes.

Virus-vectored constructs, first using porcine adenovirus (PAdV) as vector, and later, human adenovirus, were generated expressing the candidate vaccine ASFV antigens.

An import permit for the ASF Malawi genotype II virus for transportation from South Africa to NCFAD was obtained early in the project, so ASF challenge trials could be performed both in South Africa and Canada. The recombinants were selected for testing in animal trials to determine the induction of T-cell and B-cell responses against ASFV. The results of these trials were to become the basis in deciding the way forward for the ASF vaccine. After these PAdV-ASF constructs were tested and showed no protection, the project Scientific Advisory Board (SAB) recommended an update of the test outline, including several antigens per trial group. A positive outcome was the ASF animal model used for the challenge resulted in pigs developing clinical signs of ASF disease with animals requiring euthanasia starting on day 9 after infection. In addition, ASF DNA was detected in the blood of all infected pigs, indicating that the ASF virus replicated and caused the disease.

In parallel, recombinant DNA vaccines were synthesized based on ASFV ORFs containing the protein-coding regions of A224L, H240R, E111R, B125R, H233R, C84L, DP238L, H108R, KP177R

and I10L. To improve T-lymphocyte induction and recognition, the vaccine candidates were fused with ubiquitin, which was expected to enhance the introduction of the encoded protein into the MHC class I pathway. Four different DNA vaccines were produced, containing two or three fused antigens for evaluation of induced immune responses in mice sera and splenocytes.

A major constraint in the development of vaccines for ASF is the lack of information with regards to the correlates of protection. Although the viral p72 gene sequence is used to define various genotypes, this genotypic classification does not correlate with the ability of various attenuated ASF viruses to cross-protect immunized animals against heterologous challenge. To assist in identifying additional potential candidates we have embarked on sequencing selected ASFV strains, maintained within the virus repository at the ARC-OVI. We have identified two areas of focus: in the first instance we have selected representative isolates belonging to genotype II isolated from recent outbreaks in Tanzania, Malawi, Mozambique and Zambia. These viruses are epidemiologically linked to the Malawi strains being used to develop our vaccine. Analysis of the full genome sequences allowed us to predict the likelihood of cross-protection conferred by the vaccine to contemporary isolates, circulating in southern Africa. The second group of viruses was selected to represent a cross-section of the viruses found in Africa and was used to assess the genetic similarity between the viruses and antigens being used to develop the vaccine. The sequencing data was then used to create a pool of PAdV-ASF constructs, part of which were tested, but which conferred no protection. However, the tested constructs all elicited immune responses, and this data will be used in further research, based on the results of this project.

Field evaluations of the vaccines in Kenya and South Africa.

At the end of this project two vaccine constructs were tested in confined conditions and prepared for field trials. LSDV-RVF-PPR N vaccine demonstrated excellent protective efficacy in the target species – sheep and goats. The LSDV-RVF construct, which is targeted for use in cattle, sheep and goats in PPR-free countries enabled a rapid decrease in circulating RVF viral genome copies in blood and elicited production of high virus neutralizing antibody titers in sheep and goats.

The Phase 1 constructs had shortcomings – the lack of demonstrable RVFV gene expression and strong injection site reactions in cattle. However, the experience our team gained in using the LSDV vaccine vector platform technology enabled us to rapidly troubleshoot and re-construct the vectored vaccines in a manner which overcame the deficiencies of the first generation. Since potential manufacturers of the vaccines will have to make significant investments of effort, time and money, we applied maximum due diligence in characterizing the vaccine prototypes and

making sure that their product profiles match the requirements of stakeholders – stability, minimal vaccination site reactions and high levels of protection. Achieving these characteristics took time and thus we were unable to have the vaccines ready for field evaluations during the project term.

Our efforts were therefore focused on advancing these criteria as much as possible, thus precluding field trials.

As such, a project-specific agreement contract was signed with OBP and product development for manufacturing standards was started. A master seed stock was prepared for the LSDV-RVF construct and thermal stability assessment was initiated. Small-scale production process development of the vaccine was achieved and optimized. Vaccine yields comparable to the current commercial vaccine were obtained. A master seed stock of the vaccine construct was prepared and tested for potency, producing similar levels to the current commercial LSD vaccine. Tests for presence of mycoplasma were negative and thus the stock passed sterility control. The master seed complied with the required quality assurance tests (including moisture content for lyophilised products). The regulatory body in South Africa has however, updated requirements for testing of master seeds for new vaccine development.

Field evaluations of the vaccine constructs were to be conducted in South Africa (for LSD and RVF in cattle – the LSDV-RVF vaccine), while steps were taken to perform field evaluations in Kenya (for sheep and goat pox, PPR, and RVF in both sheep and goats – LSDV-RVF-PPR vaccine). To ensure the legal framework for such testing were in place, a contract was drafted between the ARC-OVI, the Kenya Agriculture and Livestock Research Organization (KALRO) and the Kenya Veterinary Vaccines Production Institute (KEVEVAPI). Although the senior management of each organization were very supportive of the contract and accepted the objectives and conditions, vetting via the respective legal offices and satisfying all institutional procedures turned out to be a highly protracted process. This contract could thus not be finalized during the project term, however, a number of significant advances were made. Through a separate sub-contract, the University of Alberta supported socio-economic studies of the targeted diseases in Kenya. The socio-economic teams in South Africa and Kenya worked in close synergy, with shared objectives and planning. Also, an existing facility for confined trials in Muguga, near Nairobi, was upgraded to fulfill all requirements for testing of a GMO vaccine. KALRO organized a stakeholder meeting where the team clarified all requirements to obtain a permit for testing the LSDV-RVF-PPR vaccine construct, followed by application for such a permit. This permit also met with significant delays by the issuing authorities and was not ready during the project term. Our initial plan was to establish production of the LSDV-RVF vaccine at OBP and of the LSDV-RVF-PPR vaccine at KEVEVAPI. Detailed evaluation of the transition to production with the main objective to ensure the fastest result required a modification of the plans. After OBP received permission to produce

PPR vaccines (but, without animal testing), the team consensus was that production by them will be faster, while the existing links and logistics with Kenya would be more efficient for animal trial testing of the vaccine. The delay in obtaining a trial permit in Kenya was discouraging, but many time-consuming processes are already complete there and thus the trials which will have to be performed beyond the term of this project will still benefit from the advances we made. Another option to ensure timely field trials, identified at the final project closure meeting in Pretoria, is to seek services of a Contract Research Organisation (CRO) to run the trials through them. The search for a suitable CRO should be managed by the developers and the contracted manufacturer, such as OBP.

Two main options were identified for procurement of animals for the field trial: 1) buying the animals and arranging for their care and management (which is expensive); and 2) “renting” the animals. This latter option involves a lower initial financial outlay, which is meant to cover food, management and a potential loss of profit due to the experiment (if market prices increase during the trial period; or hide damage due to adverse reaction site responses). This option is preferable, however it still requires a significant cost outlay, specifically for cattle. Currently, the project team and potential manufacturer (OBP) have prepared budgets and timelines for the proposed field trials and are seeking additional funding.

Dossier and master seed-stock/pilot-batch preparation of the vaccines.

Since manufacturers are normally the applicants for product registration of vaccines they have the final say in generation and selection of data which they will submit for product registration. As such, trials we conducted within the project were designed with such requirements in mind, for inclusion in the registration dossier. An outline of the registration requirements and the registration processes for new livestock vaccines is shown in Annex 2.

Briefly, the project provided data for: Laboratory safety in target animals, Dose determination, Operational health and safety, Laboratory efficacy in target animals, Quantification of antigen, Vaccine stability (ongoing), Summary of product characteristics, and Master seed stock characterization.

Future work will provide data for: Optimization of vaccine doses, Validation against commercial product, Withdrawal period, Safety in pregnant animals and overdose safety, Duration of immunity, and Field safety and efficacy.

Tests confirming the composition and structure of the constructs will also be included in the dossier, together with the manufacturer’s own tests for potency, sterility, and all other tests

mandated by regulatory requirements. Master seed stocks and vaccine stocks were produced for the LSDV-RVF vaccine.

OBP has already selected and optimized preferred cell lines, established SOPs, developed quality controls, and conducted stability testing. All the data obtained from these processes will also become part of the product dossier, together with the data from the trials which are planned beyond the term of this project.

Adoption strategies for vaccine uptake and use.

A detailed plan was prepared from the first year of the project linking socio-economic research studies in support of the vaccines launch. The first policy brief “Gender, small-scale livestock farming and food security: Policy implications in the South African context” was published in March 2015. It reflects on women, small-scale agriculture and food security in a global context, the role of livestock in rural households, the influence of livestock in empowerment of women, the role of small-scale livestock in the South African policy context, the role of livestock farming and gender in achieving food security and contains five policy recommendations.

A second policy dialogue was held in Pretoria (September 01, 2015), titled “New Generation Vaccines and Animal Health in Africa: Research, Policy and Delivery”, including the CBPP vaccine development team, scientists from Africa, Europe and Canada. This included policy makers from South Africa, vaccine manufacturers, prominent academics from South African and other African universities, and representatives from farming communities, which ensured a robust and critical discussion involving a range of perspectives.

A methodology and planning workshop for project members from Kenya and South Africa was organised from 15-18 February 2016. During the four-day workshop the South African and Kenyan socio-economic partners, together with the two lead South African scientists involved in the vaccine development work (Drs Wallace and Mather), delineated the different socio-economic studies, identified team leaders, and the deliverables for each study, together with the timeframes for delivery. In line with the scale-up strategy, the team prepared to engage in KAPP, WTP and cost-benefit analysis studies. Another follow up workshop for the socio-economic studies team was held in Nairobi from 5th-7th July 2016. During the workshops the teams presented and discussed results of the different socio-economic studies, assisted each other with design of the WTP study and prepared for the project annual meeting.

The KAPP study in South Africa focused on 5 provinces, and eight local municipalities and involved 593 households. A review of the national/regional regulatory, policy and legislative environment into which the 2-in-1 LSDV-RVF vaccine will enter was prepared. A brochure for communicating the results of the study to a non-scientific audience was prepared by a science communications company, Science Link, on behalf of the ARC. The brochure also serves to market the ARC and associated partners, and the on-going work on vaccine development. The socio-economic team followed up the KAPP study with focus group discussions in five provinces in South Africa between August and September 2017. The focus group discussions were held to gain in-depth perspectives from small-scale farmers on primary animal healthcare and narratives for gender dynamics in small scale livestock production. Some insightful results about the KAPPs of smallholder farmers in livestock primary healthcare showed moderate levels (65%) of vaccine use by smallholder households, and limited access to information on primary animal healthcare. The cost-benefit analysis study showed high benefit-cost ratios for RVF and LSD vaccinations, at both household and national levels.

Training sessions with farmers and animal healthcare practitioners were scheduled during the entire lifetime of the project and took place during all major outreach activities in which the ARC-OVI was involved. Our estimate is that ~ 288 people participated directly in such sessions, with the sphere of influence increasing daily due to the information materials (posters, pamphlets, cattle healthcare manual etc.) developed within the project now being available on the ARC Hub smartphone app.

On October 26th 2016, Drs Arshad Mather and David Wallace were awarded the ARC CEO and President's Award for excellence in service to the ARC and SA as a whole (and beyond) for their role in initiating and overall lead in the CIFSRF livestock viral vaccines project.

This is the highest award that can be awarded by the ARC to an employee/team.

A stakeholder engagement workshop titled "Livestock Vaccine Value chains in South Africa: Linking producers to the markets and end-users" was held at the HSRC on November 8, 2017. The event was attended by policy makers, farmers, private veterinary companies, researchers, and veterinary practitioners who work with smallholder farmers. Key recommendations emanating from the workshop was that multi-stakeholder collaborations should be strengthened and farmers must be more involved in all stages of the vaccine value chain to facilitate delivery of solutions that address their real needs. Another policy brief has been compiled from this workshop.

5. SYNTHESIS OF RESULTS TOWARDS AFS THEMES

Increasing agricultural productivity (Availability)

The development of novel vaccines for six infectious diseases of livestock, all with significant economic impacts, will have direct positive effects on food productivity by reducing losses due to the diseases in cattle, sheep, goats and pigs. The risk of losses due to both mortality or loss of animal production quality and volume will be reduced. In the socio-economic studies gender was integrated in all the studies and training activities, demonstrating the importance of inclusive research and development in livestock farming. Using the developed vaccines in disease control programs will have the potential to decrease the environmental impact of pharmaceutical treatments and other chemical methods (for example - insecticides used against vector insects) often used indirectly for disease control.

Improving access to resources, and/or markets and income (Accessibility)

The developed products will have potential impacts on income generation improvement by reducing losses due to infectious disease mortality, to loss of quality and volume of production and to import restrictions, all resulting from reducing the prevalence of infectious livestock diseases. Manufacturing vaccines based on farmer preferences will increase farmer adoption of vaccines, and improve animal health care leading to better access to markets and improved incomes for smallholder livestock farmers.

Improving nutrition (Utilization)

The project has a potential to improve nutrition by reduction of losses in animal production, thus increasing the availability of locally-derived animal food products. . Increased livestock productivity will result in improved milk and meat consumption at household level, leading to better nutrition, particularly for young children. During focus group discussions in South Africa the role of empowered women farmers in ensuring safe and nutritious food for the household was mentioned.

Informing policy

One of the outcomes of this project was the approval by the government of South Africa of an application which OBP filed, requesting permission to produce the LSDV-RVF-PPR vaccine in the country. This approval was a significant success, given the earlier firm policy to disallow production of any PPR-linked vaccines due to the PPR-free status of the country and sub-region. The results of this change will extend well beyond the limits of this collaboration and will have the potential to positively impact the strategy for global eradication of PPR. Two policy briefs were compiled by the socio-economics team in South Africa during the duration of the project.

6. PROJECT OUTPUTS

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Generation of Recombinant Capripoxvirus Vectors for Vaccines and Gene Knockout Function Studies, Hani Boshra , Jingxin Cao , Shawn Babiuk; *Methods in Molecular Biology*, Volume 1349: Vaccine Technologies for Veterinary Viral Diseases, pp 151-161; Springer Science+Business Media, New York, 2016, (Book Chapter)

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Smallholder livestock farmers’ Knowledge, Attitudes, Practices and Perceptions towards vaccinations: The case of five provinces in South Africa, HSRC (Report)

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Vaccines for livestock development: Farmer knowledge, attitudes and practices. 2017. Habiyaemye A, Maziya M, Mdlulwa Z, Masemola M and Chaminuka P. Poster presented at the 3rd Conference on Global Food Security, 3-6 December 2017, Cape Town.

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Using discrete choice experiment to estimate farmer preferences and marginal willingness to pay for livestock vaccines. 2018. Masemola, M., Ogundeji, A.A., & Chaminuka, P. Oral paper presented at the Agricultural Economics Association of South Africa (AEASA) 56th Conference, 25-27 September 2018, Cape Town, South Africa.

7. PROBLEMS AND CHALLENGES

The main challenge was and remains the unpredictability of living organisms (micro-organisms), which resulted in delays in obtaining pure cultures of the vectored-vaccines and in isolating pure viral genomic material for the ASFV sequencing. These risks were mitigated by sharing the workload between more team personnel and by modifications made to the research protocols for improved efficiency.

Another issue was (is) the complex interface between research and manufacturing, where,

often delays occurred regardless of the good will of the involved parties. Since these delays largely originated from the different natures of the business decision processes, we addressed them by adapting our plans to the needs of the manufacturers, who will be the leaders in the adoption and ultimate success of the vaccines.

A key challenge and lesson learnt from this phase was that the time required to ensure agreements are vetted and signed differs between different partners/countries and thus these took much longer than previously anticipated to effect. We could not overcome this obstacle entirely, and only achieved a level of readiness for testing of the LSDV-RVF-PPR vaccine outside of South Africa, without being able to perform the actual trials. This should be taken into consideration for future projects/phases and if possible, more lead time provided, and greater efforts exerted from the start.

Finally, we would recommend implementing a discussion/planning session (in a separate, dedicated meeting) for a commercialization road map early in the project lifetime. By way of example, the lack of clarity between the IP holders in this regard concerning the LSDV-RVF-PPR vaccine resulted in delays in providing key information regarding the vaccine's fitness for potential inclusion in the PPR eradication campaign to interested development agencies (e.g. AgResults).

8. OVERALL ASSESSMENT AND RECOMMENDATIONS

Overall the experience of working on this project was very positive. The relationship between research teams and the funding agency was excellent and the support for our R&D effort was enthusiastic. The project scope was similar to that of the world's most advanced international collaborations.

The project term is one area where extra flexibility could have resulted in stronger positive impacts. Longer no-cost extensions, agreed upon by research teams and justified before the funding agency, may have provided additional opportunities to optimize the project efficiency and increase impacts.

For example, the key scientists who worked on the development of the ASF vaccine will not cease the search for a new vaccine and new funding applications are already in progress. Full characterization of the identified immune responses is ongoing, and the results will be used to adjust the vaccination regimes in the follow-up experiments. There are more candidate antigens available, which are already included in PAdV-ASF constructs and will be used in protective efficacy trials. A longer no-cost extension would have permitted more trials and the potential successes could then have been assigned exclusively to the current project.

LITERATURE

1. **Global control and eradication of *peste des petits ruminants***, OIE and FAO 2015
2. **The Economic Impact of Eradicating Peste des Petits Ruminants: A Benefit-Cost Analysis**, Bryony A. Jones, Karl M. Rich, Jeffrey C. Mariner, John Anderson, Martyn Jeggo, Sam Thevasagayam, Yi Cai, Andrew R. Peters, Peter Roeder, PLOS One, February 22, 2016

Annexes

Annex 1: AFS Themes

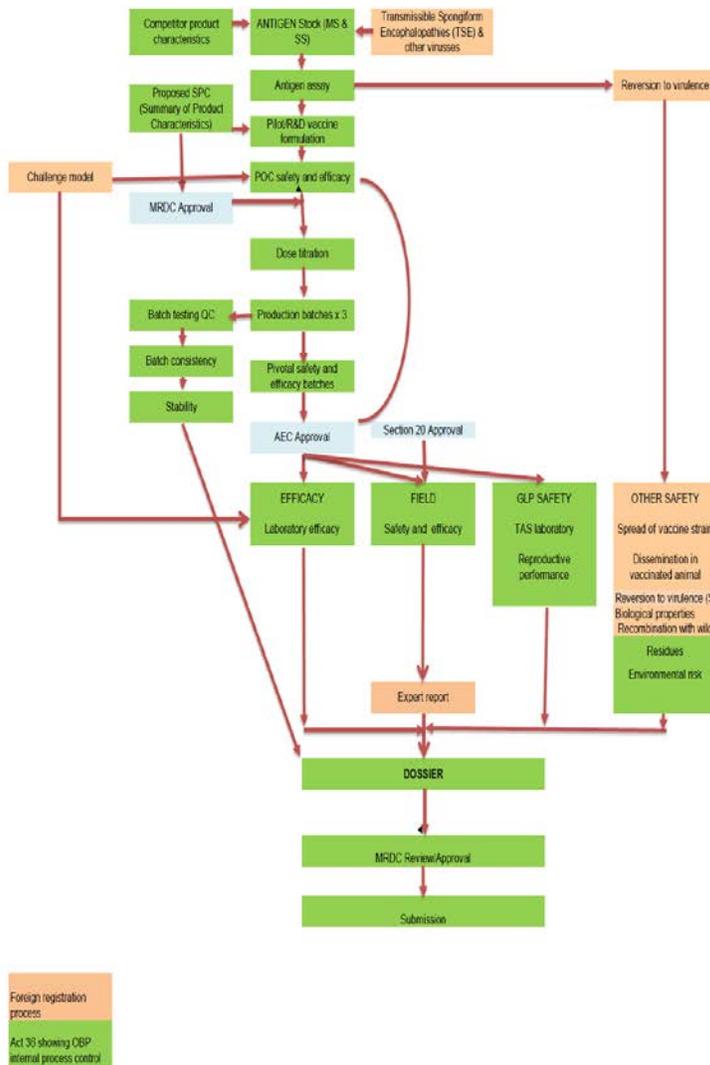
Increasing agricultural productivity

The main direct impact of our vaccines will be in this theme, predominantly by reducing loss of animals and loss of animal productivity and quality. It is important to note that when OIE examined the downstream effects of PPR, the consensus was that loss almost doubles due to downstream effects. We believe that prevention of epizootics will have stabilizing effect on animal product price volatility. Another downstream effect may be the increased security for women for whom sheep and goats are often sources of economic sustainability.

Informing policy

Vaccines, delivered using genetically engineered viruses, have one of the highest impact potentials of all state-of-the-art disease control methods. Development and successful application of such vaccines have an important role to play towards their wider adoption and towards using the full potential of modern science. In our project, scientific advisors to national government (Dr. Apiyo, Pharmacy and Poisons Board, Kenya; Prof. Mutui, National Biosafety Authority, Kenya) have been engaged in the policy dialogues and stakeholder meetings and have been informed about the principles of the new products, their safety and efficacy and their potential economic impacts. Officials (like Dr. Ochodo from Department of Veterinary Services, Kenya) have shown interest in the potential for vaccination campaigns and the opportunity to demonstrate government support for the farmers. In particular, a concept note for use of an e-Voucher system was developed linked to the CBPP project aiming at optimization of public funds expenditure towards vaccination campaigns. Such a system will provide better control of spending, but is also attractive to the government, because of the direct involvement of end-users with the support received from government programs. Thus, the concept may be applicable beyond the purpose for which it was developed, because the receiving of direct government support by the farmers may translate into political support for the authorities.

Annex 2: South Africa vaccine registration outline



Dossier Structure (data requirement)

Part A <u>General Information</u>	Part B <u>Production and Quality Control</u>	Part C <u>TAS</u>	Part D <u>Environmental and Occupational Health and Safety</u>	Part E <u>TAE</u>	Part F <u>Withdrawal Periods/Residue studies</u>
1, TOC	1, MS & WS	1, Single dose	1, OHS	1, Minimum protective dose	21 days
2, Purpose	2, Formulation	2, Repeated dose	2, Safety instructions	2, Immunogenicity (challenge)	
3, Justification	3, Starting material testing	3, Overdose	3, PPE	3, Passive/maternal Ab effect	
4, Summary (SPC?)	4, Manufacturing Procedure	4, Shed/Spread (live)	4, First Aid instructions (MSDS?)	4, Onset of immunity	
5, Foreign Reg status	5, Containers and Packaging	5, Reversion (Live)	5, Information for medical practitioners	5, Duration of protection	
6, GMP certification	6, Finished Products (QC)	6, Immunological effect	6, Environmental risk	6, Timing/response to booster	
7, Package Insert	7, Stability/Shelf life	7, Reproductive effect			
8, GMO/Animal Health	8, Analysis & Validation	8, Compatibility			
		9, Environmental effect			
		9, Safety in non TA			

Annex 3: Project outputs

The first pages of the following publications are in the report (omitted in this file to reduce file size):

Policy brief: Gender, small scale livestock farming and food security: Policy implications in the South African Context

Policy brief: Small-scale livestock farming and primary animal healthcare in South Africa: Challenges and policy implications

New livestock vaccines – a boost for emerging farmers in Africa

Conversation on policies: healthy livestock acts as a security against hunger

Generation of Recombinant Capripoxvirus Vectors for vaccines and Gene Knockout Function Studies

The socio-economics of livestock keeping in two South-African communities

Review: Capripox Diseases: Current Status and Opportunities for Control

Measuring the impact of livestock diseases

Evaluating the impact of 2010 Rift Valley fever outbreaks on sheep numbers in three provinces in South Africa

The importance of using vaccines

Small holder livestock farmers KAPP towards vaccinations: The case of five provinces in South Africa.