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7 Transboundary Animal Diseases

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Executive Summary

Transboundary animal diseases (TADs) are highly contagious epidemics with the potential for very rapid spread, causing serious economic and sometimes public health consequences while threatening farmers' livelihoods. TADs often cause high morbidity and mortality in susceptible animal populations. Some TADs are also emerging infectious diseases, food-borne diseases and/or zoonoses: these are covered in other chapters. This chapter covers those high-impact, highly contagious animal diseases, such as foot-and-mouth disease (FMD), that do not infect humans but do affect food and nutrition security and trade that the International Livestock Research Institute (ILRI) has been working on since the 1990s. These are: African swine fever (ASF), mycoplasma disease (both contagious bovine pleuropneumonia (CBPP) and contagious caprine pleuropneumonia (CCPP), peste des petits ruminants (PPR) and Newcastle disease (ND). Other TADs, which were to a lesser degree the focus of ILRI research, are briefly mentioned (including FMD, classical swine fever (CSF) and rinderpest).

ILRI's contribution in the global context

ILRI has been involved in ASF research since 2003. Originally, the focus was on diagnostics and molecular epidemiology. A large project in western Kenya broadened this by introducing a multidisciplinary approach. With the start of the CGIAR Research Programme (CRP) on Livestock and Fish in 2012, a major research-to-development initiative started in Uganda. From 2008, ILRI has been a key player in conducting research on the mycoplasma diseases: first, CBPP, and, more recently, CCPP. This research agenda started in response to the African Union's listing of CBPP as the most economically important transboundary livestock disease on the African continent in the post-rinderpest era. ILRI has been significantly involved in PPR research since 2010, with the primary aim of developing appropriate and proven PPR vaccination strategies that can progressively control the disease in developing countries. Finally, ILRI has made small but strategic inputs to the understanding and control of rinderpest, FMD, CSF, ND and some other TADs.

Impacts of ILRI's research

Scientific impacts

Molecular epidemiology highlights include: the isolation and genetic characterization of CBPP and ASF and other pathogens; a better understanding of disease dynamics; and improved understanding of immunity in local African breeds and European breeds.

Technical research contributions to vaccine development for CBPP, CCPP, ASF and PPR have been developing a new challenge model for CCPP for vaccine development, improved diagnostic tests for CBPP and ASF, and construction of biological components using synthetic biology to identify vaccine candidates.

Field epidemiology research highlights include: a better understanding of disease dynamics by mathematical modelling of ASF, CBPP and rinderpest and also using social networks to understand ASF transmission; investigating reservoirs of ASF and rinderpest and the role of carriers in ASF; conducting large-scale studies on the prevalence and risk factors for ASF, showing the importance of this disease; contributing to a major gap analysis of FMD research, shaping the path of FMD control; and a large vaccine trial of an improved mycoplasma vaccine, which did not demonstrate superiority but did show the feasibility of CBPP control. ILRI and partners pioneered the first attempt to describe the entire disease burden of any naturally occurring animal population in the world by a landmark study in which a cohort of several hundred calves were followed for a year and assessed for more than 100 pathogens.

Socio-economic research highlights include: extending knowledge, attitude and practice related to TADs; understanding the economic factors in the adoption of the CBPP and the ND vaccine; the first *ex ante* assessment of the costs and benefits of ASF control through improving biosecurity; developing estimates for the economic benefits of rinderpest, PPR and CBPP control that influenced investment; challenging conventional wisdom that training and awareness were enough to motivate disease control by farmers and traders; and incorporating gender, as a measure of inequality, into the analysis of the distributional effects of most TADs (see Chapter 18, this volume).

Development impacts

Mycoplasma studies at ILRI have been undertaken since the mid-2000s, but the initial focus was on upstream research, which can be expected to bring about development impact several decades later. ASF research became more development oriented with the start of the CRP on Livestock and Fish, and end-user benefits are starting to be documented but not yet on a large scale. Already, ILRI evidence has helped national partners to better target ASF surveillance and response in Uganda, safeguarding smallholders' stock. A thermostable PPR vaccine developed by ILRI is under production in Mali and Kenya and will play a major role in global control efforts as the vaccine does not require a cold chain. ILRI made a small contribution to generating the evidence that motivated the global eradication of rinderpest, one of the greatest successes of global animal disease control.

Policy impacts

ILRI, the Food and Agriculture Organization of the United Nations (FAO) and the African Union-Interafrican Bureau for Animal Resources (AU-IBAR) have been collaborating since 2013 to develop an Africa-wide strategy for the prevention and control of ASF (FAO/AU-IBAR/ILRI, 2017). ILRI evidence has stimulated the local government in Uganda to invest in ASF control.

In 2015, FAO and the World Organization for Animal Health (OIE) launched an international initiative for the progressive control of PPR and its global eradication by 2030. ILRI hosted the second meeting of the Global PPR Research Alliance (GPRA), and ILRI scientists contributed to the development of the first pan-African strategy for the progressive control of PPR.

ILRI developed a policy analysis for the implementation of CBPP control strategies in pastoral regions of sub-Saharan Africa. ILRI has also contributed to a major gap analysis for the Global Foot-and-Mouth Disease Research Alliance (GFRA) and to the Global African Swine Fever Research Alliance (GASFRA) and along with FAO and the African Union helped develop a regional strategy for ASF control.

Capacity building

Several dozen graduate fellows have participated in this research. Farmers, butchers, government veterinarians and scientists in Uganda

have benefitted from training. One manual on ASF has been developed and is widely being used by the private sector in training farmers.

African Swine Fever

African swine fever (ASF) is a haemorrhagic viral disease in pigs resulting in mortality rates approaching 100% (Steinaa *et al.*, 2016). ASF is native to southern and eastern Africa, where it was historically maintained in a wildlife (sylvatic) cycle involving warthogs, the natural reservoir, and soft ticks. It first came to attention when susceptible exotic pig breeds were introduced in the early 1900s to eastern Africa. It spread within Africa and, in the 1950s, to Europe and subsequently to South America and the Caribbean (Costard *et al.*, 2009). In the 1990s, the disease was eradicated from Europe, except in Sardinia (Galindo and Alonso, 2017). However, in 2007, the disease expanded once more out of Africa into the Caucasus (Georgia). ASF was recently confirmed in China (Wang *et al.*, 2018) and in Vietnam and Cambodia.

Unlike many other viral pathogens, ASF is remarkably stable, surviving in pork, pig waste and the environment. No drugs or vaccines exist for treating or preventing ASF. Control relies on biosecurity and surveillance, diagnosis and slaughter, all difficult to apply given the persistence of the virus. Limited diagnostic capacities and poor knowledge about the epidemiology of the ASF virus have long hindered its control.

Research

ILRI research on ASF began in 2003 through collaboration with the European Union Reference Laboratory for ASF diagnostics at the Centre for Animal Health Research (CISA), National Institute for Agricultural and Food Research and Technology, Spain. This worked towards the development of improved diagnostic tests and also assessed viral prevalence and molecular diversity in East and Central Africa using assays developed at CISA, as reported by Bishop *et al.* (2015), Gallardo *et al.* (2009, 2011, 2013) and Okoth *et al.* (2013). The CISA provided staff expertise, intellectual input, diagnostic reagents and use of their Biosafety Level 3 laboratory for viral culture and *in vivo* infections of swine. In 2004, a collaboration with the Friedrich-Loeffler-Institut (FLI) in Germany started, aiming to develop an ASF vaccine, led by Richard Bishop.

The capacity for diagnosis was used between 2006 and 2008 to further train laboratory technicians and field epidemiologists in Kenya, Uganda, Tanzania, Rwanda and Burundi. Subsequently, diagnostic tests have been validated with national veterinary services in much of East Africa. ILRI and the other organizations made available both facilities and material from recent outbreaks of ASF in the eastern Africa region for this purpose. The work focused on extensive studies of ASF outbreaks and sylvatic (wild pig-based) cycles in Kenya and Uganda.

ILRI was also a partner in a Swedish-led consortium to assess the impact of ASF in Uganda, starting in 2010. This project conducted outbreak investigations and also investigated the role of bush pigs in transmission. It was followed by another Swedish-led initiative, which focused more on interventions.

From 2012, the Biosciences eastern and central Africa-ILRI Hub (BecA-ILRI Hub), in partnership with the Commonwealth Scientific and Industrial Research Organisation (CSIRO), conducted studies in the border region of Kenya and Uganda. This project represented the most comprehensive study of ASF disease yet attempted. Using the biosciences capacity for diagnosis and epidemiological surveillance at the BecA-ILRI Hub and epidemiological research incorporating participatory and quantitative approaches, state-of-the-art diagnostics, molecular biology, genetics and genomics, mathematical modelling and social network studies enabled the development of evidence-based recommendations for disease mitigation. There were important advances in immunology of ASF, and two potential vaccine candidates were produced by deleting a gene in two different ASF viruses – the Kenyan 1033 strain (genotype IX) and the Sardinia strain (genotype I).

In 2011, the CRP on Livestock and Fish identified the smallholder pig value chain in Uganda as a high-potential target to translate research into development interventions (Ouma *et al.*, 2015). ASF was identified by the farmers and pig value chain stakeholders as the major constraint to smallholder pig farming (Dione *et al.*, 2014). This background analysis generated information on the epidemiology of ASF and led to testing of 'best-bet' interventions to manage ASF and other pig diseases (Dione *et al.*, 2018a,b).

In collaboration with Chinese researchers, ILRI has been researching genomic characterization of domestic pigs and wild boars in Asia and the genetic resistance of domestic pigs and wild boars to ASF. With the spread of ASF into Asia, ILRI has been providing support to countries in the region.

Research impact: technologies

Diagnostics

Reliable diagnostics are key to the rapid containment and management of disease outbreaks. As such, ILRI contributed to validation of diagnostic tests developed by their international partner, CISA. However, samples taken from outbreak areas, surprisingly, did not test positive for ASF antibodies using the OIE protocols (Gallardo *et al.*, 2013; Okoth *et al.*, 2013). Analysis of blood and serum samples using a polymerase chain reaction (PCR) assay found positivity to ASF virus (ASFV) of 28% in two independent samplings in south-western Kenya and 0% PCR positivity in central Kenya, but no animals were seropositive in either study site using the OIE indirect ELISA, and none of the animals sampled exhibited clinical symptoms of ASF. Failure of the OIE protocol might be related to the characteristics of African pigs (Gallardo *et al.*, 2013), opening opportunities for further research on host-pathogen interactions.

ILRI scientists were part of a Swedish-led team that evaluated a rapid diagnostic approach using a portable, commercial real-time PCR (Zsak *et al.*, 2005). Trials suggested that it could be used effectively at the pen side or in a field laboratory with performance at a level comparable to sophisticated molecular laboratories (Leblanc *et al.*, 2013). This was subsequently confirmed in Uganda (Liu *et al.*, 2016).

Vaccines

In collaboration with FLI, ILRI studied the immune responses to African ASFV strains and generated additional knowledge of the Kenyan pig major histocompatibility complex (MHC)[1]. Using an experimental animal model with an isolated virulent virus from Kenya, it was found that immunity could be obtained by increasing doses of the virulent strain. This method is now being used for studying the immune response to such isolates. Immune responses were characterized by very low antibody titres but solid cellular immune responses (Steinaa *et al.*, 2016).

Another advance was sequencing MHC molecules from Kenyan pigs to identify which antigens can be used for a vaccine that induces cellular immunity. This revealed new sequences (Sørensen *et al.*, 2017); ILRI has received sequences from approximately 34 other Kenyan pigs, which are currently being evaluated. Of particular importance was the achievement of generating two vaccine candidates by deleting a gene, which should attenuate the virus. Recently, cutting-edge CRISPR/Cas (clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9) gene-editing technology and synthetic biology approaches for generating ASF vaccine candidates have been introduced to the ILRI ASF research programme. Using CRISPR/Cas9 is faster, cheaper, more accurate and more efficient than other existing genome-editing methods.

Research impact: molecular epidemiology

ILRI used molecular epidemiology to track viruses causing outbreaks, helping to understand the spatial and temporal relationships among them. Complete sequencing of the p54 gene from ASFV isolates revealed regional differences and the value of p54 gene sequencing as an additional, intermediate-resolution, molecular epidemiological tool for typing of ASFV (Gallardo *et al.*, 2009). Whole-genome phylogenetics, including a newly sequenced virulent isolate from Spain, identified two clusters. One contained South African isolates from ticks and warthog, suggesting derivation from a sylvatic (wildlife-to-pig) transmission cycle. The second contained isolates from West Africa and the Iberian Peninsula, suggesting a domestic (pig-to-pig) transmission cycle. This provides valuable insights into control, as disease maintained in a sylvatic cycle is harder to control than disease maintained in a domestic cycle. Comparative genomics revealed high diversity within a limited sample of the ASFV gene pool (de Villers *et al.*, 2010) but revealed that genetically similar ASFVs may be circulating between Kenya and Uganda (Gallardo *et al.*, 2011).

Scientists later enriched the publicly available ASFV genome bank with sequences from East Africa. Genome sequencing and annotation of a recent pig-derived p72 genotype IX and a

tick-derived genotype X isolate from Kenya were carried out using the Illumina platform and this was compared with a Kenya 1950 isolate. The three genomes constituted a cluster that was phylogenetically distinct from other ASFV genomes but 98–99% conserved within the group. There were multiple differences among East African genomes in the 360 and 110 multi-copy gene families (Bishop *et al.*, 2015). This information is not only important in tracking movement of the viruses but also helps with recognition of new viruses being introduced into East Africa, indicating a breach in transboundary disease control. A practical implication of the genetic similarity of the Kenyan and Ugandan viral isolates is that ASF control requires a regional approach to control. There was also a classification of the ASFV genome series of multi-gene families, with the goal of providing standard comparisons and naming schemes, thereby enhancing the capacity to search for novel vaccine targets in ASFV.

Research impact: field epidemiology and control

Transmission dynamics

Understanding transmission dynamics is needed before control is feasible. Recent findings that high levels of detection of ASFV DNA in pigs slaughtered in Kenya during a period with no reported outbreaks provided support for the hypothesis that subclinical, chronically infected or recovered pigs may be responsible for persistence of the virus in endemic areas (Thomas *et al.*, 2016). Other findings indicated that carrier pigs may play a role in ASFV maintenance and help explain the disease outbreaks that have occurred without any evidence of any of the known transmission sources (pigs clinically ill with ASF or adjacent populations of resistant African wild pigs) (Abworo *et al.*, 2017). These findings have significantly increased scientific knowledge of the epidemiology of ASF in the field in Africa, which has contributed to the design of effective surveillance and control strategies.

The role of the ancestral sylvatic cycle of ASFV was not well understood in the endemic areas of eastern Africa. Scientists therefore explored for the first time the coexistence of different ASFV genotypes in the soft ticks found in warthog burrows and adult wild warthogs in Kenya. The data from this and earlier studies suggest that there has been transfer of viruses of at least two different p72 genotypes from wild to domestic pigs in East Africa (Gallardo *et al.*, 2011).

Although warthogs are considered the main wild vertebrate host of the virus in the endemic African setting, they are not the only wild African pigs with a potential role in ASF epidemiology. The bush pig, *Potamochoerus larvatus*, is an elusive, nocturnal pig known to be susceptible to ASF, and might be a link between the sylvatic and domestic cycle. Studies from south-west Kenya showed similarity in viruses in bush pigs and domestic pigs (Okoth *et al.*, 2013), indicating possible transmission between the two species or the presence of an intermediary vector. Initial results following a bush pig with a radio collar revealed close interactions between the species (Ståhl *et al.*, 2014). Other studies have reported an apparent strong association of viral infections with pig breeds, suggesting that some breeds may be resistant to infection and offering opportunities for genetic resistance as a disease mitigation measure as well as encouraging the conservation of tolerant breeds (Mujibi *et al.*, 2018).

Participatory epidemiology studies in three districts of central Uganda found that farmers considered ASF and parasites to be the major health constraint to pig production. They also reported ASF as the primary cause of pig mortality, with epidemics occurring mainly during the dry season (Dione *et al.*, 2014). Other studies have revealed widespread under-reporting of ASF by farmers, traders and animal healthcare professionals and the motivations for this (Atherstone *et al.*, 2019).

Risk factors

Understanding risk factors can help target control efforts to where they will have most effect. ILRI scientists have explored risk factors for ASF in Uganda and Kenya (Dione *et al.*, 2015; Nantima *et al.*, 2015). Key drivers of outbreaks were panic sales of pigs and inadequate disposal of dead pigs. In an innovative study, ASF transmission paths and nodes were described using social network analysis (Lichoti *et al.*, 2016, 2017). This showed the importance of commerce in spreading ASFV between farms and across regions, implying that greater emphasis should be placed on post-farm nodes in the prevention and control of the disease (Dione *et al.*, 2016a).

Control

By combining knowledge and data from the various studies, it was possible to estimate disease transmission dynamics using geospatial mapping and mathematical modelling. This was used for *ex ante* assessment of the effectiveness of different ASF control strategies and to identify the optimum time for deployment of interventions in the field to minimize the losses following ASF outbreaks (Barongo *et al.*, 2015, 2016). This provided evidence to help national and international partners conduct targeted surveillance of pig diseases, including important zoonoses (Dione *et al.*, 2017). The evidence generated has informed the development of an ASF control strategy for Africa (FAO/AU-IBAR/ILRI, 2017).

In the absence of a vaccine, the most common recommendation for ASF control has been to implement biosecurity measures such as footbaths, fencing and quarantine. Such measures are usually promoted through training and public information campaigns. A randomized control trial was carried out to evaluate the effects of training farmers in biosecurity on the Kenya-Uganda border. The trial found that, although farmer knowledge improved after the trial, farmer practices did not (Nantima *et al.*, 2016). Another attempt in Bangladesh (with poultry) to promote biosecurity through training and public information also indicated that information was insufficient to change behaviour and that additional motivation was needed (Rimi *et al.*, 2016).

ILRI was a member of GASFRA. This organized four scientific conferences from 2013 to 2016 to conduct gap analyses of current knowledge and the available countermeasures to effectively control and mitigate the impact of a disease outbreak of ASF. Based on these analyses, a report was generated setting out the priority research needs (Seixas *et al.*, 2018).

ILRI, in partnership with FAO and the African Union, elaborated a strategy joined with an action plan to allow a progressive and coordinated control of ASF at the regional level. To achieve this objective, it prioritized the strengthening of capacities of technical services and the improvement of current production systems, creating optimal conditions for the modernization and development of the pig industry in a healthy context (FAO/AU-IBAR/ILRI, 2017).

Research impact: socio-economic studies

Scientists also explored the knowledge, attitudes, practices, capacities and incentives of pig value chain actors in relation to ASF and biosecurity (Chenais, 2016). This showed that respondents were well aware of the clinical signs of ASF, the routes for disease spread and the measures for disease control. However, awareness of the control measures did not guarantee their implementation. A majority of middlemen and butchers acknowledged having sold live pigs, carcasses or pork that they believed was infected with ASF. Factors that limit the adoption of biosecurity measures by farmers include cost and cultural factors such as the stigma related to the use of footbaths and the restriction of farm visits to neighbours or traders.

The results of an *ex ante* model projected that, although biosecurity measures would reduce ASF outbreaks, they would also lead to a 6.2% reduction in profit per year while giving a 7.8 % increase in profits accruing to butchers, traders, collectors and wholesalers (Ouma *et al.*, 2018). This could explain the low adoption of biosecurity practices by farmers and a need for other incentives for farmers (Nantima *et al.*, 2016).

Other studies assessed the gender dimensions of pig management and disease control. These found that, during disease outbreaks, especially of ASF, both men and women provided animal health care. Therefore, control information should explicitly target both men and women within the same household. This broader outreach would help spread knowledge of pig husbandry and ensure that action during outbreaks does not rely on a few individuals (Dione *et al.*, 2016b,c).

Mycoplasma Disease

Mycoplasmas are the smallest and simplest self-replicating bacteria. Several species of mycoplasma infect humans, causing pneumonia, urinary tract infections and sexually transmitted disease. Hundreds more species infect animals. CBPP is an infectious disease of cattle caused by the small-colony type of *Mycoplasma mycoides*; CCPP is a devastating disease of goats caused by *Mycoplasma capricolum*.

CBPP was introduced to Africa in the 1800s and is now one of the most important livestock

diseases in sub-Saharan Africa. It is now estimated to menace the livelihoods of nearly 25 million people in 19 African countries.

While eradication is the surest way to control CBPP, it is expensive and can only be tried during major outbreaks and on major trade routes. Eradication is generally infeasible in Africa because of animal movements and the limited resources of national veterinary services. The current control strategy relies on using a live vaccine. Unfortunately, this has limited efficacy, a short duration of immunity and causes severe side effects (including the loss of the animal's tail). The current diagnostic tests have limited sensitivity and are only useful at the herd level and are not practical at individual levels.

Research

An ILRI review of animal health and poverty issues identified CBPP and CCPP as major problems (Perry *et al.*, 2002), although CBPP research had not begun until the late 1990s. At this time, Ethiopia was experiencing major new outbreaks. ILRI initially supported a thesis on the cost of CBPP control in Ethiopia (Laval, 1999). Scientists subsequently estimated the presence and prevalence of CBPP in the Ethiopian highlands (Bonnet *et al.*, 2005), defined the basic epidemiological parameters of the disease in southern Sudan (Mariner *et al.*, 2006a) and promised a control model in East Africa (Mariner *et al.*, 2006b).

Careful analysis of the existing literature on CBPP suggested the key information and technologies needed to develop better control measures in an African environment (Jores *et al.*, 2013b). Research then focused on host-mycoplasma interactions, epidemiological models, improved diagnostics, elucidation of protective responses and identification of potential vaccine antigens.

Research impact: technologies

Diagnostics

In the absence of good vaccines, recurrent testing using improved diagnostic assays in combination with elimination of CBPP-positive animals or herds is a control option (Ssematimba *et al.*, 2015). ILRI research found that the inaccuracy of the official (OIE) prescribed assays (complement fixation test and competitive ELISA) make them suitable for use at the herd level only (Nkando *et al.*, 2012). This was confirmed by a comparison of four serological assays: one complement fixation assay developed in house and three OIE-recommended tests (Schubert *et al.*, 2011). None of the four tests detected all infected animals. ILRI scientists later contributed to the development of a novel, successfully validated, real-time PCR assay (Schnee *et al.*, 2011).

ILRI scientists next set out to develop an improved serological test, seeking to find novel mycoplasma antigens recognized by sera from infected cattle, thus having diagnostic potential to improve test sensitivity (Jores *et al.*, 2009; Naseem *et al.*, 2010). A systematic comparison of 17 selected *Mycoplasma mycoides* subsp. *mycoides* (*Mmm*) immunogens commenced, a standardized ELISA protocol was developed, and well-defined serum samples were used to compare individual proteins and protein combinations with respect to sensitivity and specificity (Heller *et al.*, 2016). The resulting assay, comprising the two best-performing immunogens, had an overall diagnostic accuracy comparable to the OIE-prescribed tests, and work to optimize the test further is under way.

The assay was further transferred to a lateral flow test format in collaboration with a commercial company, enabling rapid diagnosis (less than 30 min) of CBPP (Heller *et al.*, 2016). The test is currently undergoing final optimization and evaluation. A rapid and field-applicable recombinase polymerase amplification assay was also developed for a related pathogenic mycoplasma, *M. capricolum* subsp. *capripneumoniae* (*Mccp*) that could be further developed to make it commercial (Liljander *et al.*, 2015).

Vaccines

An early study suggested a minor role for $CD4^+$ T-lymphocytes, which are involved in helping and regulating immune responses, in protection in a primary infection (Jores *et al.*, 2008), despite some earlier publications suggesting such a link. This was confirmed in a later study in cattle depleted for $CD4^+$ T-lymphocytes (Sacchini *et al.*, 2011). Differences in disease severity are probably largely due to differences in cattle genotypes. Inflammatory cytokines, as expected, were found during infections in lung tissues (Sterner-Kock *et al.*,

2016) and in plasma (Sacchini *et al.*, 2012). Depletion of $CD4^+$ T-cells did not significantly influence cytokine levels, again suggesting their minor role in control of a primary infection.

Several approaches were followed to identify protective antigens. Although antibody titres in a primary infection did not seem to correlate with a positive outcome for the animal (Schieck *et al.*, 2014), it was hypothesized that antibodies protect in a secondary infection or after vaccination. ILRI scientists and colleagues contributed towards the characterization of the *in vitro* core surface proteome of cultured mycoplasma, thus identifying candidate *Mmm* antigens for the development of improved control measures (Krasteva *et al.*, 2014). Another study characterized proteins expressed *in vivo* by mycoplasma obtained from pleural effusion (Weldearegay *et al.*, 2015).

Evidence was obtained by an ILRI student that whole, inactive mycoplasma were protective (Mwirigi *et al.*, 2016a). Immunizations were carried out with the live vaccine and with two formulations of inactivated *Mmm*. Heat-inactivated mycoplasma were found to be as protective as the live vaccine. This confirmed that live mycoplasma are not required for induction of immunity and suggested that protection can be induced by purified molecules, which are much preferable as vaccines.

Virulence factors are molecules produced by pathogens that allow them to infect hosts and evade the immune system and are currently the focus of intense research. If vaccines could be developed against virulence factors they could be helpful in preventing disease or reducing severity. For *Mmm*, no virulence factors have been confirmed *in vivo*. However, for the closely related goat mycoplasma, *Mycoplasma mycoides* subsp. *capri* (*Mmc*), biology tools such as genome transplantation can be employed to gain insight into the function of genes. The whole genome of *Mmc* is transferred into yeast cells, where it can be modified using molecular tools available for yeast, and the modified genome is then transplanted back into mycoplasma cells and the resulting mutant can be characterized. This approach was used to generate a mutant mycoplasma lacking the polysaccharide coating (an outer layer composed of carbohydrates), and *in vivo* experiments demonstrated that the polysaccharide coating is indeed a virulence factor (Schieck *et al.*, 2016; Jores *et al.*, 2018). The polysaccharide molecules were purified, coupled to a protein and administered twice to cattle (Mwirigi *et al.*, 2016b). After challenge, the severity of disease in the immunized cattle was significantly reduced. It is interesting to know that carbohydrate can protect, and this is in agreement with the hypothesis that prevention of adhesion to lung cells is protective, but the polysaccharide coating would not be suitable for vaccine production, as it would be too expensive to produce.

Additional studies tested other potential pathogenic molecules for their capacity to protect against disease. Two promising protein candidates (Mulongo *et al.*, 2013, 2015) were investigated. Neither protein induced protection: in contrast, immunization with LppQ-N exacerbated pathogenesis as a result of the formation of immune complexes (Mulongo *et al.*, 2015). Immunization with the other candidate did induce good antibodies in cattle, but these antibodies did not inhibit the enzymatic function of the enzyme, which may have been necessary for the prevention of its pathogenicity (Mulongo *et al.*, 2013). These studies emphasize that care has to be taken when selecting candidate vaccine antigens, and that it is important to avoid including antigens that do not protect or that counterprotect in a subunit vaccine (Jores *et al.*, 2013b).

A successful approach in a comprehensive project was aimed at identifying candidate vaccine molecules using reverse vaccinology. As the genome of *Mmm* was available, a bioinformatics study selected 66 proteins that were likely to be present on the mycoplasma membrane or were secreted and were therefore accessible to the immune system. ILRI contributed synthetic genes for 38 of these *Mmm* proteins and the remaining were designed, and recombinant proteins produced. The potential antigens were ranked on their ability to elicit antibody responses, as tested in sera from immune animals (Perez-Casal *et al.*, 2015). After prioritization, the recombinant proteins were then pooled into groups of five antigens and administered to cattle. After challenge, three of the formulations induced protection (Nkando *et al.*, 2016). This suggests that more than one protein is protective, and further research suggested that a cocktail of four proteins mixed with an adjuvant formed a good vaccine. The Kenya Veterinary Vaccines Production Institute (KEVEVAPI) is currently acquiring the

capacity to produce and quality control the vaccine. Studies have been planned to determine its efficacy in the field and to determine how long immunity lasts.

Although in laboratory studies the efficacy of the subunit vaccine was the same as the live vaccine, it will still have a number of vital advantages: a lower price, no need for a cold chain (important to reach remote areas with little infrastructure) and the absence of serious side effects. This last condition is important to convince herders to vaccinate their animals. Another advantage of the subunit vaccine is that it may allow the development of a test to discriminate vaccinated from infected animals, which will greatly facilitate disease control.

Therapeutics

A study, initiated by the University of Nairobi and finalized at the BecA-ILRI Hub identified plants used by local herders to treat lung infections in their animals and tested extracts from these plants for their capacity to block *in vitro* mycoplasma growth (Kama-Kama *et al.*, 2016). Several had activity, and further research identified at least one chemical compound with bacteriostatic activity for *Mmm* (Kama-Kama *et al.*, 2017).

Research impact: molecular epidemiology

ILRI contributed to the isolation of new mycoplasma strains, as well as obtaining genome sequencing of several strains, including *Mmm* (Fischer *et al.*, 2015), *Mccp* (Falquet *et al.*, 2014) and *Mycoplasma feriruminatoris* sp. nov. (Fischer *et al.*, 2013; Jores *et al.*, 2013a). Additional important work was done by Gourgues and Barr (2016).

ILRI scientists improved our knowledge of the phylogenetic relationships and demographic history of mycoplasma of the 'mycoides cluster', a group of related mycoplasma that infect ruminants (Fischer *et al.*, 2012). They used multi-locus sequence typing on seven housekeeping genes from over 120 strains. Interestingly, the origin of *Mmm*, the cause of CBPP, dates back approximately 10,000 years, coinciding with the domestication of livestock. It is believed that the tradition of keeping goats and cattle in close proximity must have allowed a goat mycoplasma (*Mmc*) to jump to cattle and differentiate into a pathogenic species.

Host-mycoplasma interactions

Because *Mmm* causes a severe infection in the lungs, one step in the disease process must be the interaction of mycoplasma with cells in the lungs. A study demonstrated strong attachment of cultured mycoplasma to *in vitro*-cultured bovine lung epithelial cells. While all cell types bound mycoplasma to some degree, very high binding was only observed with lung or bronchial epithelial cells from cattle (Aye *et al.*, 2015). However, when the epithelial cells were derived from fetal lungs, no such binding was observed. This would explain why newborn and very young calves do not develop lung disease, as they may lack a receptor for mycoplasma attachment. As expected if strong attachment is an essential step in the disease process, the mycoplasma also showed only strong specificity for bovine cells, and not for cells from other species including sheep and goat. Preventing this binding step may thus prevent disease. Monoclonal antibodies were created against *Mmm*, and a number that inhibited attachment were selected. In one further study on these monoclonal antibodies, a mycoplasma molecule was identified as being involved in the adhesion process (Aye *et al.*, 2018) and could be a target for vaccination. Further testing was not carried out, as, in the meantime, the reverse vaccinology approach had successfully identified protective antigens (described earlier).

Research impact: field epidemiology and control

Modelling control strategies

Treatment of affected cattle with antimicrobials has been officially discouraged on the basis that it may favour the creation of chronic carriers, which are believed to be responsible for disease spread. However, a simulation model developed by ILRI and collaborators based on field data from Ethiopia found that antibiotics were the most efficient strategy, suggesting that the use of antimicrobials by smallholder farmers should be reconsidered (Lesnoff *et al.*, 2004).

Jeffrey Mariner and colleagues also developed mathematical models assessing the impact

of alternative control measures on the transmission dynamics of CBPP, incorporating field parameters from pastoral systems. The results indicated that a control strategy based on the currently available vaccines alone would not be sufficient to eradicate CBPP unless the efficacy, safety and duration of immunity could be substantially improved. According to the models, the farmers would benefit from reduced disease prevalence and mortality through vaccination of healthy animals combined with antimicrobial treatment of clinical cases (Mariner *et al.*, 2006b). The models also suggested that, under the prevailing inter-herd contact patterns, CBPP can be maintained indefinitely, even in moderate-sized herds (Mariner *et al.*, 2006a,b). A recent model predicted that CBPP could be eliminated in approximately 2 years provided that 75% of the animals in an isolated herd are vaccinated annually (minimum vaccine protection required is 18 months) and recommended that recurrent testing be done using an improved diagnostic test and elimination of positive animals (Ssematimba *et al.*, 2015).

Epidemiological surveys

When CBPP increased in the Ethiopian highlands, ILRI and partners responded by researching the problem and solutions. At that time, there was little information reported in the literature on within-herd spread of CBPP during outbreaks. In collaboration with the Centre de Coopération Internationale en Recherche Agronomique pour le Développement (CIRAD) and the National Animal Health Research Centre, a research programme was set up in a CBPP-infected zone in the Ethiopian highlands (Boji district in West Wellega Zone) to estimate the epidemiological parameters of the disease and to assess the effects of different disease-management strategies naturally implemented by the local farmers.

A longitudinal study was carried out, which found that 34% of cattle became seropositive over a 16-month observation period and 39% of these became clinically ill, while 13% died (Lesnoff *et al.*, 2004). There was no evidence that CBPP control measures used locally by farmers (including treatment) had any benefit. A subsequent study found that herd prevalence increased with herd size and that clinical signs observed in the survey were not indicative of disease prevalence (Bonnet *et al.*, 2005). These studies brought to attention some of the complications in controlling CBPP.

Vaccine trial

The current CBPP control strategy in Africa is based on immunization with a live vaccine (mainly strain T1/44). The vaccine confers immunity only for 6 months to 1 year and has occasionally shown severe side effects at the inoculation site: 3.8% of animals showed side effects including loss of their tail (Kairu-Wanyoike *et al.*, 2014b). The vaccine needs a cold chain and must be applied within 1 h of reconstitution. These characteristics lead to low acceptance and willingness by the animal owners to present their animals for vaccination. In addition, the vaccine is not widely available as the veterinary services regulate its use.

ILRI and partners conducted a 3-year immunization trial using a modified vaccine formulation – the commercially available T1/44 vaccine – while concurrently evaluating vaccine delivery systems. The programme concluded that the modified vaccine did not result in improved protection when deployed under field conditions (Nkando *et al.*, 2012). While stating that properly delivered vaccination significantly reduced the impact of CBPP in affected areas, the study also highlighted the need for annual boosting for sustained protection.

Research impact: socio-economics

Demand for vaccines

ILRI scientists and partners used structured questionnaires to assess farmer practices and perceptions of CBPP control, the willingness of farmers to pay, their preferences regarding vaccination and an estimation of the impact of CBPP (Kairu-Wanyoike *et al.*, 2013, 2014a,b, 2017). Pastoral populations consider CBPP a threat to their cattle, but awareness of prevention control methods varied. Many farmers were reluctant to vaccinate their cattle due in part to adverse reactions. The need for a better vaccine was reflected in the low willingness of farmers to pay for the current vaccine and vaccination. The willingness to pay was higher for a hypothetical preferred vaccine

and vaccine attributes such as the inclusion of a pH indicator (Kairu-Wanyoike *et al.*, 2014a).

Vaccine delivery systems

CBPP control measures and disease perceptions were further studied from a gendered socio-economic perspective in north-eastern Kenya (Muindi *et al.*, 2015). It was concluded that poor road infrastructure represented the main obstacle for vaccine delivery in the study area and that women, being better at recognizing the early clinical signs of CBPP, could play an important role in preventing disease spread by alerting the community and thus averting herd and trade losses by swift implementation of quarantine and ring vaccinations (Waithanji *et al.*, 2015). Furthermore, the studies concluded that there is a market for the implementation and adoption of an improved CBPP vaccine by both men and women if it is thermostable, more efficacious and safer than the current vaccine. Women also found affordability an important attribute for a new vaccine (Muindi *et al.*, 2015). These types of study are well known to overestimate demand and willingness to pay and should be regarded as promising but inconclusive in this context.

Policy analysis

ILRI contributed to a policy analysis for the implementation of CBPP control strategies in pastoral regions of sub-Saharan Africa (Onono *et al.*, 2017). This found that current vaccination was low and suggested the adoption of signed contractual agreements between the public and private sectors to support the vaccination of susceptible herds raised in endemic regions.

Peste des Petits Ruminants

PPR, or 'goat plague', is a highly contagious disease of wild and domestic sheep and goats (Taylor, 1984; Robinson *et al.*, 2011). The disease is caused by peste des petits ruminants virus, genus *Morbillivirus*, which is closely related to rinderpest virus. PPR is a devastating disease in naïve small ruminants. Outbreaks have occasionally been observed in camels and some species of wild Asian ungulates, but no clinical disease has been reported in African wildlife. The disease was recognized as a 'rinderpest-like' condition of goats in Nigeria in 1930 and was first characterized in Côte d'Ivoire in 1942. Until the 1980s, it was seen as a problem of West Africa: since then, it has spread rapidly to around 70 countries in Africa, the Middle East and Asia. The disease re-entered China in 2015 and spread to the borders with Korea and Vietnam. In 2016, Mongolia reported its first case in livestock and a subsequent mass mortality event in wildlife, especially the Saiga antelope. In 2018, the disease was reported in the European Union (Bulgaria). Kenya saw a series of epidemics in 2006–2008, killing almost 1.2 million small ruminants and causing a decline in milk production of 2.1 million litres (FAO, 2016). The mean annual global loss from PPR mortality has been estimated at US$1.5 billion, ranging from US$0.8 billion to US$2.7 billion (Mariner *et al.*, 2016).

Safe, effective and inexpensive live vaccines, based on the Nigeria 75/1 or Sungri strains, are available and widely used. The Nigeria 75/1 strain has been in use for decades without any adverse effects and has been shown to generate life-long immunity and to protect against all lineages of PPR. The availability of these vaccines combined with lessons learnt from the global eradication of rinderpest have inspired the international animal health community to target PPR for global eradication by 2030. ILRI aims to contribute to the global eradication effort while at the same time providing evidence to inform and guide it.

Research

ILRI has been involved in PPR research since 2010 with the aim of developing vaccination strategies for developing countries. ILRI hosted the second meeting of GPRA and its scientists contributed to the development of the first pan-African strategy for the progressive control of PPR (Elsawalhy *et al.*, 2010). Subsequently, ILRI scientists contributed to a business analysis for the global eradication of PPR (Jones *et al.*, 2016; Mariner *et al.*, 2016), and remain closely engaged with the FAO/OIE PPR Secretariat. ILRI scientists have been advocates for aggressive eradication of PPR through programmes that emphasize surveillance, epidemiological analysis and targeted vaccination.

Research impact: technologies

In southern Nigeria, ILCA developed and tested a package consisting of a tissue-culture rinderpest vaccine and a dipping programme to control mange. They reported that, as a result, kid survival had greatly increased, reproductive efficiency of does improved, and monthly mortality declined by 87% in goats and by 79% in sheep (Adeoye, 1985).

Research on PPR restarted in the 2000s (Balamurugan *et al.*, 2014). ILRI scientists demonstrated the feasibility of production of a thermostable vaccine for PPR, showing that effective PPR vaccines based on the attenuated Nigeria 75/1 strain could be thermostabilized using the protocol for the production of the thermostable rinderpest vaccine developed by Tufts University and the US Department of Agriculture (USDA) (Mariner *et al.*, 1990, 1991) and used in the Global Rinderpest Eradication Programme (GREP) (Mariner *et al.*, 2012). As the thermostable rinderpest manufacturing process is unencumbered by intellectual property constraints and could be used with the existing PPR vaccine produced in accordance with OIE norms, the vaccine was available for implementation in the field.

To identify the optimal process to achieve thermostability, two main approaches were compared, one based on the ThermoVax rinderpest vaccine developed by Tufts University and the USDA, which is free from intellectual property constraints, the other based on the patented Xerovac process. Thermostability was assessed in accelerated stability tests at a range of temperatures and using *in vitro* titration assays. The ThermoVax method used in rinderpest vaccine manufacture was found to provide the best long-term thermostability at 37°C. These batches consisted of existing PPR vaccine lyophilized in the same 72 h cycle that had been utilized in the production of thermostable rinderpest vaccine (Mariner *et al.*, 1991). Under OIE norms, changes to lyophilization procedures do not require revalidation of the immunogenicity of the vaccine. The ILRI team concluded that the efficiency of the lyophilization cycle, a key variable that impacts the efficacy of chemical stabilization, was the source of the enhanced stability, as this was the only variable changed in the batches found to have the highest levels of thermostability. Lyophilization is an activity that combines biological, chemical and physical sciences. Large-scale lyophilizers are purpose-built machines, and each has a different configuration of components that behaves uniquely. The lyophilization process has to be optimized for each machine. The result was a PPR vaccine that maintained the minimum required dose as a 25-dose presentation for over 5 months at 37°C and for over 10 days at 56°C. This level of thermostability is comparable to that achieved for the thermostable rinderpest vaccine used in the global eradication of rinderpest (Mariner *et al.*, 2017).

Current efforts focus on producing sufficient vaccine to enable pilot vaccination programmes. To this end, the Central Veterinary Laboratory in Mali and KEVEVAPI have started using the protocol with technical support from ILRI and Tufts University scientists. The performance of resulting batches will be assessed through the Pan African Veterinary Vaccine Centre (PANVAC) and its performance in the field and efficiency will be compared with conventional vaccine. Thus, this vaccine will be an important control tool for remote areas, providing essential support for global eradication efforts.

In addition, ILRI has supported the testing of novel DIVA (differentiation between infected and vaccinated animals) vaccines using African breeds, as ILRI is one of the few institutions where such tests can actually be done (Holzer *et al.*, 2016). DIVA vaccines differentiate between infected and vaccinated animals because the vaccines lack at least one antigenic protein that is present on the field virus. These vaccines are important for control because vaccination in poultry would have greater worldwide acceptance if naturally infected and vaccinated-only animals could be distinguished, and if culling were necessary then naturally infected animals could be targeted.

Research impact: field epidemiology and control

Vaccination strategies

ILRI has been active in advancing approaches using targeted vaccination as a more effective alternative to mass vaccination because it has higher effectiveness and lower cost. ILRI has also piloted more effective vaccination delivery systems based on public–private–community partnerships and quantity-based approaches to remuneration

for work done. One of the lessons of rinderpest eradication was that mass vaccination was not a successful approach for completing the eradication process. The success of eradication depended on the development of approaches that identified populations responsible for disease maintenance and then focused vaccination on those critical communities. This finding was applied to PPR as ILRI piloted vaccination activities in Karamoja, Uganda and Sudan. In Uganda, vaccination was implemented through community animal health workers with costs covered by the public sector. In Sudan, more conventional veterinary personnel were used, but the livestock owners covered the costs.

Global eradication

There are four components in the global eradication framework of PPR: (i) promoting an enabling environment and reinforcing veterinary capacities through public information, updating legal framework and preparing national and regional PPR plans; (ii) supporting diagnostic and surveillance systems, which includes assessment of the epidemiological situation and strengthening of regional epidemiology and laboratory networks; (iii) supporting PPR eradications and, if approximately 1.5 billion sheep and goats need to be vaccinated, controlling other small ruminant diseases in support of PPR eradication; and (iv) coordination at country, regional and global levels.

ILRI facilitated scientists who had played leadership roles in the global eradication of rinderpest to assess key lessons from rinderpest eradication and help lay the foundation for the global eradication of PPR (Mariner *et al.*, 2012). Social innovations in animal health institutions were identified as key to capturing the benefits of technological developments such as the thermostable rinderpest vaccine. This activity fitted well with ILRI's mandate in representing the interests of developing countries and improving our understanding of animal health institutions to mitigate the impact of disease.

Newcastle Disease

Newcastle disease (ND) is a highly contagious disease of poultry and other birds caused by the Newcastle disease virus in the family *Paramyxoviridae*. It is considered the most important TAD in village poultry. Periodic outbreaks result in high mortality among free-ranging flocks and serve as a disincentive for poultry keepers to invest time or resources in their birds. Because of the difficulty of attaining biosecurity in backyard poultry, vaccination is the preferred control strategy. Live vaccines have been widely used since the 1950s and have made great progress in preventing and controlling ND. Live lentogenic B1 and LaSota vaccine strains of low virulence are commonly used worldwide for protection.

Research

Poultry disease was not a focus of research during ILRI's first decades, and for a number of reasons, stakeholders did not prioritize poultry health. Moreover, in Africa, poultry did not make important contributions to the diet, although that has changed due to imports and the establishment of intensive production. Poultry disease first rose to prominence at ILRI because of the highly pathogenic avian influenza (HPAI) pandemic (see Chapter 8, this volume). Subsequently, a project investigated ND vaccine impact in East Africa, and further work studied a range of poultry diseases in Ethiopia.

Research impact: technologies

Live vaccines can show low efficacy due to administration challenges or failure of birds to mount a sufficient immune response. ILRI research in Ethiopia investigated the potential for improving vaccination success in village chicken. ILRI conducted a study to compare the antibody response to ND in intensively reared and backyard chicken. The latter mounted a much weaker response. A follow-on experiment found that veterinary treatment (especially worming) before vaccination could dramatically improve the antibody response and hence the protection offered by the vaccine (Abera *et al.*, 2017).

Research impact: field epidemiology and control

In the early 2000s, desk research developed background papers on ND in Ethiopia (Dessie and

Jobre, 2004) and southern Africa (McDermott *et al.*, 2001). ND was also addressed along with HPAI in South-east Asia as discussed in Chapter 5 (this volume).

The first major research into poultry health in Ethiopia was launched in 2011. Its aim was to identify infectious diseases of Ethiopian village poultry and to improve their control. ND was identified by farmers as the highest priority disease. A longitudinal study subsequently found that ND was responsible for the death of 843 chickens of the cohort of 1358 birds (Jarso, 2015).

Because of the lack of previous research, ILRI was also able to identify some diseases for the first time. The poultry farm at the Ethiopian Institute of Agricultural Research (EIAR), Debre Zeit, represents an important centre for research, farmer training in poultry production and distribution of birds among smallholders. As such, it has vital links with farmers, especially intensive and semi-intensive producers. In 2012, respiratory disease was a major cause of morbidity and mortality. ILRI used a combination of serological and molecular methods for the detection of pathogens, reporting for the first time variant infectious bronchitis virus (793B genotype), avian metapneumovirus subtype B and *Mycoplasma synoviae* in poultry. This information was used for planning vaccination programmes (Hutton *et al.*, 2017).

Research impact: socio-economic studies

ILRI conducted an economic analysis in Nigeria and found that ND caused an estimated 25.5 million poultry deaths each year nationwide, costing 8.9 billion naira. Control comprising vaccination, sanitary measures and surveillance was estimated to cost 1.8 billion naira per year (Fadiga *et al.*, 2011). Within this study, a related *ex post* analysis examined efforts to stop HPAI in Nigeria. A stochastic epidemiological model was used to parameterize counterfactuals of disease evolution with and without interventions. The results indicated that a programme of HPAI control versus a baseline of endemic, high-mortality HPAI gave a benefit:cost ratio of 1.75 over a 5-year period.

Vaccine adoption

ND vaccines are widely used in intensive poultry production and are effective and inexpensive. While ND vaccines are readily available, uptake by poor farmers has been very limited. A project conducted a study in 2011 to investigate vaccine adoption in Kenya and Tanzania in order to understand the barriers and bridges to adoption (Lindahl *et al.*, 2019). In this study, two areas in Kenya and Tanzania were studied, where all villages were eligible for government control programmes, but some villages had received additional support to get vaccination from a project (Tanzania) or non-governmental organization (Kenya). Where vaccination support had been given, 59% of households overall had used vaccines against ND, which was significantly ($p < 0.001$) more than the 17% of households that had used the ND vaccine in areas with no additional support. However, many farmers stopped using vaccines, and even those who did use them often used them suboptimally and continued to experience losses from ND. Despite this, there were significantly fewer reported poultry deaths in villages with support. This showed the importance of additional support if vaccines are to be taken up by poor farmers, and also the gap between theoretical performance of disease control and disease control in practice. Even with considerable external support, almost no farmers vaccinated their poultry in accordance with recommendations and losses from ND continued.

The Ethiopian work later evaluated vaccine uptake. A contingent valuation method was conducted to elicit farmers' willingness to pay for village poultry vaccine services. Two hypothetical vaccine programmes were designed for ND and Gumboro disease. The results showed that farmers recognized the benefits of the vaccine programme and that many would be willing to pay for it (Terfa *et al.*, 2015).

Other Livestock Transboundary Diseases

Rinderpest

Rinderpest is an infectious viral disease that has killed hundreds of millions of cattle over hundreds of years, often causing famine. Rinderpest was formally declared to have been eradicated in 2011, becoming only the second disease (after smallpox) to have been eradicated. This is widely

regarded as the greatest veterinary achievement of our time. It was the result of decades of effort by a wide range of research institutes, donors, intergovernmental organizations, national governments, non-governmental organizations and cattle-keepers. FAO had a key leadership role.

ILRI made a small but strategic contribution. First, economists developed and disseminated some of the first estimates of the very large benefits that could be obtained from control (Tambi *et al.*, 1999). ILRI economists also contributed to *post hoc* assessments of the socio-economic direct and indirect benefits of rinderpest eradication (Roeder and Rich, 2009). Rich *et al.* (2014) examined the *ex post* impact of rinderpest eradication in Chad and India. An important innovation of this study was methodological, in terms of identifying impact from the producer level to national and international levels. Farm impacts were examined through the use of a herd demographic model and macroeconomic impacts with a computable general equilibrium (CGE) model. Baseline benefit:cost ratios associated with eradication in Chad were 4.0 over 1963–2002 (ranging from −5.8 to 47.2). In India, the final stage of eradication yielded a benefit:cost ratio of over 64.

ILRI scientists also developed a mathematical model for disease dynamics (Mariner *et al.*, 2005). Estimates from simulations suggested populations of around 200,000 head of cattle were needed to sustain transmission. This meant that communities smaller than 200,000 head did not need to be prioritized in the final stages of eradication as the disease would naturally fade out in these populations. Furthermore, this supported the view that, if the disease was controlled in cattle, it would fade out in wildlife populations as the fragmented populations remaining in Africa are not large enough to sustain infection even if biologically competent to do so. More importantly, modelling was shown to be an effective communication tool to engage decision makers, illustrating concepts such as fade out of disease from small populations and how suboptimal vaccination could contribute to virus persistence (Roeder *et al.*, 2013).

Small contributions were made to field epidemiology. By the 1990s, Somalia was one of the few remaining reservoirs for rinderpest, but control there was hampered by political instability. ILRI contributed to developing a risk map based on social and network risk factors (Ortiz-Pelaez *et al.*, 2010), a method originally developed for mapping FMD in the UK. This identified areas in the central and southern regions of Somalia where veterinary authorities could concentrate surveillance activities.

Participatory surveillance evolved during the global eradication of rinderpest when the tools used for participatory rural appraisal were adapted to searching for rinderpest outbreaks. The approach proved its utility by identifying occult foci of disease and providing appropriate intelligence to guide the eradication strategy (Mariner and Roeder, 2003). ILRI conducted an evaluation of participatory surveillance to provide guidance for appropriate use (Hannah *et al.*, 2012). This found that participatory surveillance was a useful epidemiological tool, most appropriate for small-scale farmers and applied in complement to conventional surveillance.

Foot-and-mouth disease

Foot-and-mouth disease (FMD) is often considered the most economically important global animal disease (see Chapter 5, this volume). Notable achievements in FMD research were: (i) an impact for specific regions; and (ii) participation in GFRA. In 2010, GFRA performed a gap analysis to identify areas where FMD research could have the greatest impact and to guide and coordinate future research efforts. The 2014 gap analysis was updated to include work published in 2015 and was the subject of a special issue of *Transboundary and Emerging Diseases*. Most of the research syntheses involved ILRI scientists (Vosloo and Knight-Jones, 2016). An earlier case study of the Philippines showed benefits of ILRI work. In 1999, the National Foot and Mouth Disease Task Force of the Philippines requested ILRI's support for a national FMD control and eradication program. An ILRI team complied with the request and, in 2002, published the results of its epidemiological and economic assessment of the potential benefits of eradicating FMD from the Philippines. The results clearly indicated significant potential economic benefits, particularly for Filipino swine producers, who were threatened by a virus subtype highly specific to pigs that was causing high piglet mortality, widespread pig abortions, and infertility. The joint ILRI-Filipino

evidence clearly showed the proposed eradication program to be a worthwhile investment of public funds. This public-private partnership for control and eradication continued until 2011, when the Philippines was declared free of foot and mouth. This official disease-free status opened up markets for pork products from the Philippines and motivated the country's producers to upgrade their piggeries.

Classical swine fever

Classical swine fever (CSF) is a highly contagious, potentially fatal viral disease of swine. It is endemic in much of Africa and Asia. In India, pigs are most important in the north-eastern states, and ILRI started to work with the sector in the early 2000s. ILRI conducted epidemiological and economic studies on CSF in the Indian states of Assam, Nagaland and Mizoram in 2011. These found that pig farmers incurred huge losses, over 2 billion Indian rupees each year, from mortality, treatment and replacement costs. ILRI suggested interventions such as vaccine-based control to the government and private sector. As a result, the Government of India initiated a national swine fever control programme targeting north-east India. Moreover, policy changed to better facilitate the licensing of vaccine production by public and private institutes. A subsequent ILRI project trained community animal health workers and started vaccination against pigs. No cases of disease were reported after vaccination. The State Government of Nagaland then mainstreamed the approach (Bett *et al.*, 2014). Although at an early stage, there is some evidence for ILRI research leading to positive outcomes (Padmakumar *et al.*, 2017).

Porcine reproductive and respiratory syndrome

Porcine reproductive and respiratory syndrome (PRRS) is an important disease in pig production and is endemic in Vietnam. ILRI conducted the first nationwide studies of PRRS in Vietnam, identifying spatial and temporal patterns that are useful in planning control (Fig. 7.1) (Lee *et al.*, 2019).

Lumpy skin disease

Lumpy skin disease (LSD) is an economically important TAD of cattle caused by the lumpy skin disease virus in the genus *Capripoxvirus*. Although it is present in most African countries, the disease is mild and inapparent, so difficult to detect. Failure to report subclinical cases of LSD due to lack of good diagnostic tools is a major limitation in LSD control. ILRI included LSD in several field epidemiology surveys showing its importance in Ethiopia and Tanzania. An economic analysis of the hides and skins value chain in Somaliland found that LSD was a significant impediment to the export trade (Wanyoike *et al.*, 2018).

A major limitation to LSD control is the difficulty of detecting it. Despite the availability of molecular diagnostic methods that are appropriate for LSD diagnosis, there is no single rapid, sensitive and inexpensive method. The BecA-ILRI Hub tested a loop-mediated isothermal amplification (LAMP) assay (Lamprey and Reid, 2004) for LSD diagnosis; this is a gene amplification procedure that can amplify a few copies of DNA to a large amount in less than 1 h using simple equipment. The tests suggested that LAMP would be an accurate and useful diagnostic tool (Mwanandota *et al.*, 2018).

Infectious bursal disease

Infectious bursal disease is an acute, highly contagious, viral disease of young chickens. The disease causes small-scale poultry farmers huge economic losses, both from the many birds that die outright and from lost productivity among surviving birds. With collaborators, ILRI conducted the first molecular characterization of the infectious bursal disease in Kenya. The Directorate of Veterinary Services plans to use the findings to develop improved vaccination, surveillance and control strategies for infectious bursal disease, such as procedures for virus diagnosis (ILRI, 2018).

Transboundary Animal Diseases in Systems

Transboundary animal diseases (TADs) do not occur in isolation but as part of complex

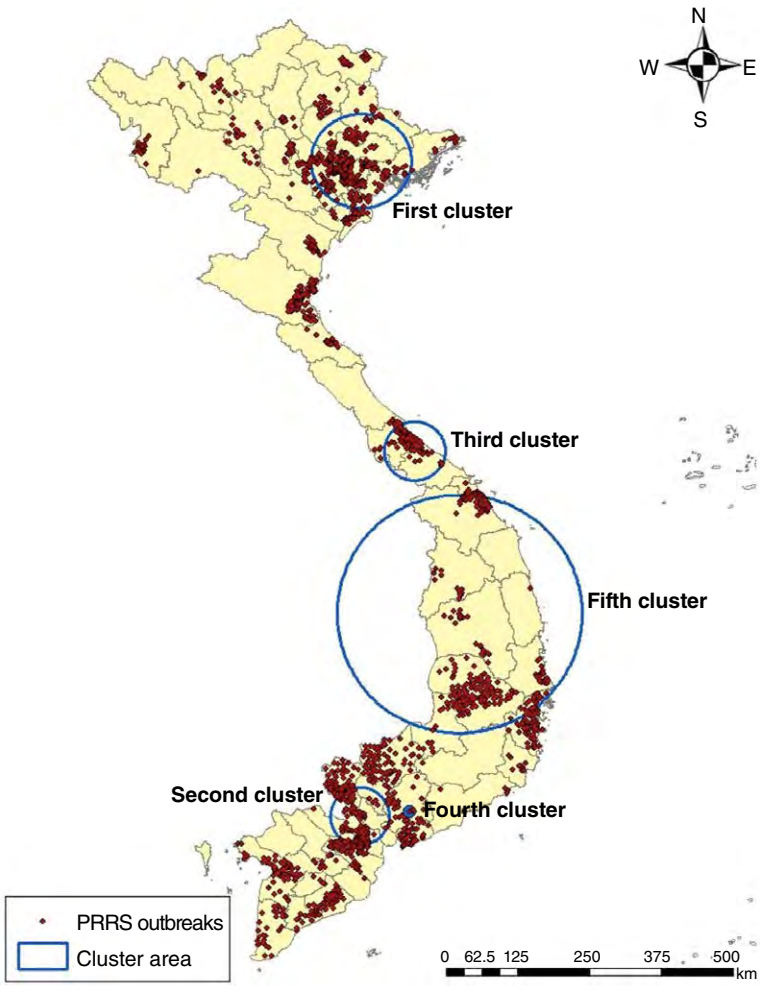

Fig. 7.1. Space-time cluster analysis of PRRS outbreaks from 2008 to 2016 in Vietnam. (from Lee *et al*., 2019).

ecosystems. Nearly all disease research focuses on a single disease or few closely related diseases, but in reality organisms are normally infected with a number of more or less pathogenic organisms at any one time. ILRI recruited a large cohort of calves in western Kenya to investigate a wide range of diseases (over 100) and to follow up each calf with monthly clinical examinations and laboratory testing for 51 weeks over a period of 3 years (Fig. 7.2) (Bronsvoort *et al.*, 2013). This enormous undertaking was the most ambitious veterinary epidemiological study to date carried out in a developing country. It was scientifically significant as the first attempt to describe the entire disease burden of any naturally occurring animal population in the world. This study generated a wide range of scientific findings, published in high-impact journals. These included several 'firsts' in terms of pathogens, parameters and disease associations that had not been reported previously. Research tools were developed and validated. Although many of the findings have implications for disease control, their development impacts have not yet been evaluated.

Some of the more novel and important outputs and findings were as follows:

- The cohort experienced a high mortality rate of 16%, with at least 13% of this due to

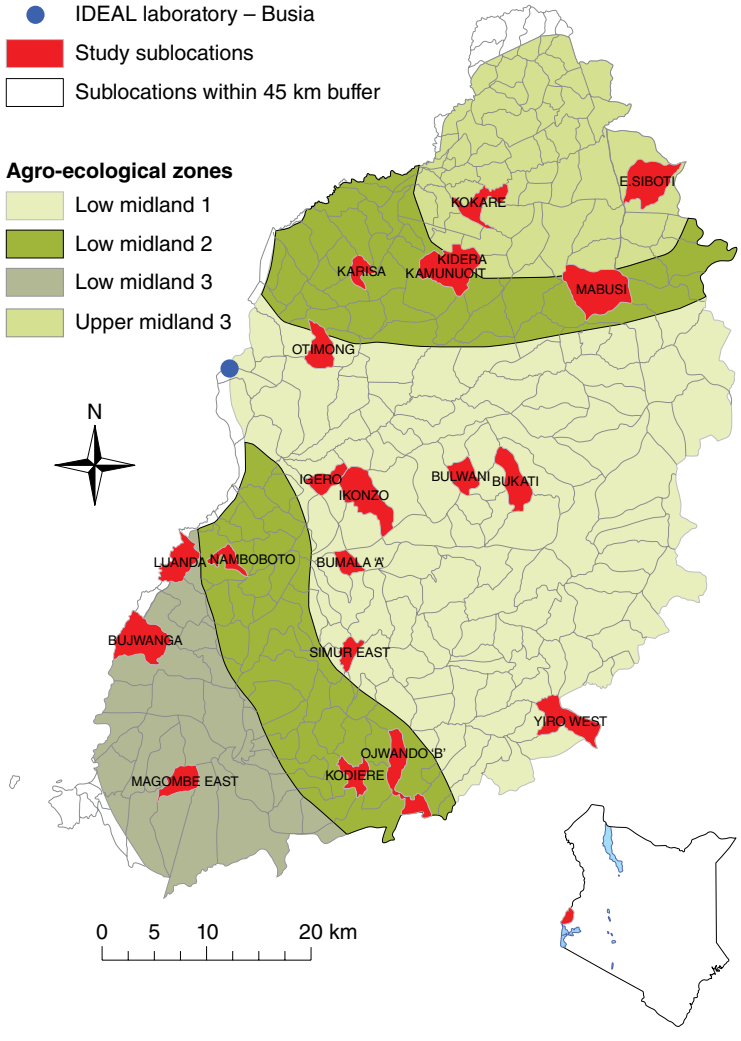

Fig. 7.2. Study area in western Kenya. (From de Clare Bronsvoort *et al.*, 2013.)

infectious diseases. Over 50 pathogens were detected in this population, with exposure to a further six viruses and bacteria. East Coast fever (ECF) was the main cause of death, accounting for 40% of all deaths, haemonchosis 12% and heartwater disease 7% (Thumbi *et al.*, 2013).

- Following a cohort of animals allowed investigation of coinfections. The study found that these were common and that the risk of ECF death was itself significantly increased by a high helminth burden and by coinfection with trypanosomiasis. Farmers that provided crop residues to their animals as a feed supplement had significantly lower deaths from helminths. This study gave empirical evidence on simple actions that could greatly reduce calf mortality (Thumbi *et al.*, 2014).
- Heterologous reactivity is the influence of past or current infection on the outcome of infection with another: this may be positive or negative. Because calves were followed over time, researchers were able to obtain the first quantitative estimates of the effects of heterologous reactivity for any parasitic disease. The study provided three strands of evidence for heterologous protection against

ECF in a population of indigenous African cattle. A natural challenge analysis found that infection with less pathogenic *Theileria* spp. reduced mortality from ECF; the case–control study quantified the level of protection (43% reduction in mortality); and the mathematical model of heterologous protection successfully predicted key features of the epidemiology of ECF. This suggested that heterologous protection may determine the burden and distribution of many parasitic diseases in host populations, including humans (Woolhouse *et al.*, 2015).

- Many more farmers reported carrying out disease control measures such as tick control and worming than were actually observed. This suggests that farmers are answering what they think they should be doing or maybe have done, but a significant proportion actually then appeared to not carry out these measures over the course of our observations. This highlighted the need for caution in interpreting responses, especially from cross-sectional data (Bronsvoort *et al.*, 2013).
- Investigation of antibodies to four tick-borne haemoparasites found that 90% of dams were seropositive for at least one of the parasites, while 93% of calves had received colostrum. Surprisingly, there was no discernible difference in mortality or growth rate between calves that had taken colostrum and those that had not. These results are also important for interpretation of serosurveys of young calves following natural infection or vaccination (Toye *et al.*, 2013a).
- Bluetongue virus (BTV) and epizootic haemorrhagic disease virus (EHDV) are members of the genus *Orbivirus*, transmitted by biting midges. BTV spread from Africa to Europe, resulting in high economic losses. The study found that BTV and EHDV are highly prevalent, with cattle being infected from an early age. This was the first report of EHDV from East Africa (Toye *et al.*, 2013b).
- Calf respiratory disease is a major problem globally but is little researched in Africa. The study found that three viruses often implicated (infectious bovine rhinotracheitis virus, bovine parainfluenza virus type 3 and bovine viral diarrhoea virus) all have an estimated seroprevalence of around 20% (Callaby *et al.*, 2016).
- This study was the first to accurately describe the haematological parameters for any African breed of cattle. Unlike European cattle breeds that experience a fall in red blood cells following birth, the West African cattle showed a rise. This is useful in understanding what is normal, but also suggests a possible mechanism for disease resistance (van Wyk *et al.*, 2013). Data from the study were also used to develop and validate a girth band to predict live weight of East African Shorthorn Zebu (Lesosky *et al.*, 2012). This is useful for research but also appropriate for dosing of animals.

Conclusion and Future Directions

Because TADs can spread rapidly and cause catastrophic losses, they are of extreme concern to the intensive livestock sector in high-income countries. In these industries, many TADs have been eradicated, and hence they are vulnerable to reintroduction from developing countries. Because TADs were seen as having been well studied, they were not initially prioritized by ILRI. This has gradually changed as evidence has emerged that TADs can have deep impacts in poor countries.

A more pragmatic reason is that, because of their potential impact on high-income countries, there is often funding available for TAD control. This introduces a certain tension between the priorities of rich and poor countries, as non-epidemic animal diseases are almost certainly of greater burden than the epidemic TADs. However, TAD research offers a bridge between low- and middle-income countries and high-income countries research by providing a subject of common interest but differing relative advantage. Novel approaches, pioneered by ILRI and collaborators, to investigating multiple diseases in cohorts of animals can help us better understand the relative importance of endemic and epidemic disease and how they interact.

External drivers, including demographic growth, climate change, biodiversity loss, urbanization, globalization and dietary change, have potentially profound effects on TAD dynamics, which ILRI can influence, mitigate and take leverage of to fulfil its mission.

Laboratory-based work has produced some notable achievements including generating fundamental knowledge on genetics and phylogenetics, new and improved diagnostics, and promising vaccine candidates. Much of this research is upstream and, by its nature, development benefits will take several decades to be visible. However, there is well-documented frustration with the technologies available for TAD management and control, and much potential for improvement.

Some of the identified priorities, which inform future research, include: cheap, simple, robust field diagnostics; thermostable vaccines that do not require a cold chain; DIVA vaccines that allow vaccinated and infected animals to be distinguished; vaccines that are inexpensive and provide life-long immunity; vaccines that are free of side effects; multivalent vaccines so that one shot will immunize against many diseases; ways of telling whether a vaccine is authentic and functional; and vaccines that are more effective and do not 'break down' as the result of challenges in administration and because animals are immunocompromised. As this chapter has summarized, ILRI is working actively in all these areas with some success and the promise of more to come.

Developing innovative and impactful TAD control requires a good understanding of how both diseases and people behave. ILRI TAD research has had success in developing mathematical models and understanding transmission dynamics, i.e. how diseases move among hosts, vectors and the environment. This information has been central to important control successes in the past and will be in the future. However, good models require good data on disease parameters, and these are often not available or can only be gathered at costs that investors are unwilling to pay.

Students and graduate fellows have always been involved in ILRI health research, and this has been important for capacity development as well as establishing and expanding networks. To a lesser extent, training has been extended to decision makers, implementers and value chain actors. This is likely to be more important in the future.

As the research agenda has developed, ILRI and its investors have increasingly focused on impact today as well as tomorrow. Field studies have shown that, while vaccines are theoretically the best measure for disease control, poor farmers have very little propensity to buy them and the public sector has very little capacity to deliver them at scale, at least on a continuous as opposed to a campaign basis. This has opened new directions to explore.

The eradication of rinderpest raises hopes that progressive control may be the one best solution for those TADs that can be eradicated, notably PPR. At the same time, there has been more attention on influencing farmers' behaviour as a form of control. Research on several TADs makes it clear that 'training and information' are inadequate and that other incentives, whether social, financial or changes in choice architecture (nudges), are needed.

Finally, there is a shift from scientific papers to field products. This means relying on markets as well as public services, and public-private partnerships are an active area of research and engagement. Future research will continue to develop and improve diagnostics and vaccines with increasing focus on applications. This will be accompanied by efforts to create novel approaches to TAD control that use market and social forces. Understanding these needs a value chain and consumer focus, as well as an appreciation of equity issues.

Note

[1] The TickRisk project, led by Maxime Madder and Eva De Clerq and based largely in Benin, and the WecatiC project, led by Hassane Adakal, have provided the above data, mostly collected during 2012–2013.

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