



paper

## CONTROL OF CONTAGIOUS BOVINE PLEUROPNEUMONIA

A policy for coordinated actions

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# CONTROL OF CONTAGIOUS BOVINE PLEUROPNEUMONIA

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A policy for coordinated actions

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# List of acronyms

<b>AMR</b>	antimicrobial resistance
<b>AU-IBAR</b>	African Union Interafrican Bureau for Animal Resources
<b>AU-PANVAC</b>	African Union Pan African Veterinary Vaccine Centre
<b>CAHW</b>	community animal health worker
<b>CBPP</b>	contagious bovine pleuropneumonia
<b>CFT</b>	complement fixation test
<b>ELISA</b>	enzyme-linked immunosorbent assay
<b>Ep</b>	macroscopic pathologic lesions
<b>GALVmed</b>	Global Alliance for Livestock Veterinary Medicines
<b>IAEA</b>	International Atomic Energy Agency
<b>MmmSC</b>	<i>Mycoplasma mycoides</i> subspecies <i>mycoides</i> small colony
<b>OIE</b>	World Organisation for Animal Health
<b>PCR</b>	polymerase chain reaction
<b>RECs</b>	Regional Economic Communities
<b>WHO</b>	World Health Organisation

# Purpose of the document

The purpose of this document is to act as a follow-up on the recommendations of the Fifth Meeting of the FAO-OIE-AU/IBAR-IAEA Consultative Group on CBPP (contagious bovine pleuropneumonia) and provide an evidence-based policy for the implementation of sound control of CBPP by all stakeholders at global, regional and country levels. The policy describes a road map to CBPP control that is cognizant of the situation on the ground. Although not prescriptive, the document includes examples of combinations of interventions and control measures that should offer the opportunity to improve impact. Guidance on monitoring and assessment of programme impact as a tool to validate and further improve strategies is provided.

The policy builds on historic lessons and the technical, epidemiological and social dimensions of the problem today. A summary of past programmes and successes is provided in Annex I. Evidence on the efficacy of control tools in today's socio-economic context is presented in Annex II. This includes information on the use of antibiotics designed to both mitigate the current risk of the development of antimicrobial resistance (AMR) issues and enhance CBPP control.

## **Main conclusions of the Fifth Meeting of the FAO-OIE-AU/IBAR-IAEA Consultative Group on CBPP**

The Fifth Meeting of the FAO-OIE-AU/IBAR-IAEA Consultative Group on CBPP concluded that a period of innovation in policy leading to new strategies would result in better CBPP control and set the stage for a time when CBPP can be eradicated (FAO-OIE-AU/IBAR-IAEA, 2016). The meeting found that:

- Policies and strategies need to be reassessed based on current socio-economic and animal health institutional realities and current knowledge regarding the technologies available for control;
- Public, private and community partnerships are essential to successful surveillance and control of CBPP;
- Vaccination remains the principle tool for control programmes and a vaccine with at least two years' duration of immunity is needed;
- Antibiotics are widely used and potentially an important tool when applied to affected and exposed animals in a controlled manner in combination with vaccination of populations at risk;
- Research on CBPP is a priority and should emphasize effective and quality vaccines, point of care diagnostics, strategies for responsible incorporation of antibiotics in control programmes, and epidemiologic and socio-economic analysis to support programme strategy; and
- Eradication is a challenging and distant objective best achieved through a phased programme of progressive control.

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# Executive summary

The policies in addressing the control and management of contagious bovine pleuropneumonia (CBPP) are in disarray at both the national and international levels. There has not been significant improvement in the efficacies of available vaccines or diagnostic assays for several decades while social conditions have evolved and populations have grown, making many traditional quarantine interventions logistically more problematic. Classic strategies of mass vaccination and strict movement control that once were perceived as successful in rolling back the disease have largely fallen by the wayside due to high costs, concerns of declining impact and growing public resistance. Officially, treatment with antibiotics is discouraged or prohibited, yet their use is widespread. CBPP is an enigmatic disease, and research results often lack reproducibility for reasons mainly related to the fundamental pathobiology of the agent. This complicates strategic dialogue and delays decision-making. The regulatory and policy environment is still geared towards expected free public-supported programmes, although the level of implementation is insufficient to be of real service to farmers. This situation led The Fifth FAO-OIE-AU/IBAR-IAEA\* Meeting of the Consultative Group on CBPP to conclude:

*“The failure to contain CBPP is largely the result of the lack of a coherent and achievable policy with realistic approaches for coordinated and progressive control.”*

(FAO-OIE-AU/IBAR-IAEA, 2016)

The lack of a coherent and achievable vision for CBPP has driven the disease’s resurgence over recent decades and an increase in the unregulated use of antibiotics.

Current vaccines are unable to achieve a sufficient reduction in the effective transmissibility of CBPP in the absence of movement control. Only combinations of control measures can accomplish improved disease and risk management. Of the alternative combinations currently available, treatment of cases with antibiotics combined with vaccination of animals at risk will have the greatest impact on transmission. The body of research on antibiotics indicates that antibiotic use in treatment assists in clinical recovery, can clear infection and reduces mortality. However, much more importantly in managing disease spread, antibiotics suppress transmission.

In most countries, CBPP vaccine and vaccination are strictly controlled and implemented by government veterinary services. For vaccination to be a meaningful contributor to control, alone or in combination with treatment, *access to vaccine and vaccination must be enhanced*. Further, guidance is overdue on appropriate vaccination and treatment regimens that maximize the impact of vaccination and treatment and minimize the risk of emergence of antimicrobial resistance (AMR). Rationalization of CBPP control policies considering cur-

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\* Food and Agriculture Organisation of the United Nation (FAO)  
World Organisation for Animal Health (OIE)  
African Union Interafrican Bureau for Animal Resources (AU-IBAR)  
International Atomic Energy Agency (IAEA)

rent information and social forces is essential to reaching the goal of reducing inappropriate antibiotic use.

Given the scarcity of resources to fund public control programmes against CBPP, national efforts must be structured to mobilize all potential sources of investment and emphasize cost-effective delivery mechanisms. Livestock owners are willing to invest in antibiotics and vaccines for CBPP control. To optimize control, new accredited public-private-community partnerships with *liberalized* access to regulated vaccine supplies should be rolled out and the effect of this access should be validated. Programmes should be coordinated, accredited and closely monitored by the public sector.

Moving forward, a three-point time-bound approach is suggested:

- A period of scaling out of integrated control measures designed to optimize the contribution of vaccination, treatment and institutional arrangements for delivery and monitoring of CBPP control. Throughout this period, CBPP control will expand in an evidenced-based manner that incorporates action research.
- An aggressive control phase under government coordination and regulation that seeks to suppress prevalence in endemic areas to the point of elimination of the disease.
- At 10 years in the future, progress will be reviewed to consider the feasibility of eradication. The epidemiological status of the disease, impact of existing control programmes and availability of new tools will be significant factors in the analysis.

The map to the future requires significant technical and institutional change supported by applied action research to sort the successes from the failures. The re-establishment of control requires fresh thinking backed by concerted international leadership to reach fruition. This requires the leadership of FAO and OIE in dialogue with key stakeholders in the fight against AMR. The AU-IBAR together with the Regional Economic Communities are key stakeholders that will share in the ownership and implementation of the programme in conjunction with national authorities and livestock owners. As the full potential of new integrated approaches has yet to be measured, it is premature to set an eradication date. However, it is proposed that a 10-year period of treatment and vaccination innovation as well as aggressive risk management and animal movement control will provide sufficient information to make evidence-based decisions on eradication.

# CBPP policy objectives

The overall goal of the policy is to enhance the contribution that cattle make to the national economy, food and nutritional security, and the livelihoods of producers and other value chain actors through improved and coordinated control of CBPP.

The specific objectives that will contribute to this goal are:

- Enhanced technical efficacy of CBPP control packages in terms of protecting livelihoods, reducing the risk of the emergence of AMR, and minimizing the risk of CBPP transmission within cattle populations;
- Increased livestock-owner access to validated CBPP control interventions;
- Improved capture of market forces to help drive participation in control programmes by livestock owners and animal health service delivery value chain actors; and
- Renewed investment in the development of improved diagnostics, treatments and vaccines.



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## Definition and impact of CBPP

CBPP is an infection caused by *Mycoplasma mycoides* subspecies *mycoides* small colony type (MmmSC). Individual infections may be sub-clinical or result in peracute to chronic disease. CBPP is an insidious disease that lingers in herds, causing significant morbidity and mortality. The principal clinical manifestation is respiratory insufficiency due to pneumonia, hydrothorax and fibrin deposition on pleural surfaces. The disease has an incubation period on the order of three to eight weeks, and recovery occurs through a process of abscess-like sequestra formation in the lungs. Sequestra, a nidus of viable MmmSC, may remain infected for up to six months. Repeated attempts to demonstrate that animals with sequestra can transmit disease have failed (Windsor and Masiga, 1977). Serological tests mainly detect active infection or vaccination within a period of weeks, which means that an infection instigates a short-lived antibody response. Naturally recovered animals are said to be immune for life. The disease is currently endemic throughout sub-Saharan Africa except for several countries in southern Africa.

In areas where CBPP is endemic, prevalence of infection can reach as high as 10 percent, but is usually less than 5 percent. Considerable local variation in prevalence and impact is evident in the field. Some affected areas rank the disease as a high priority (e.g. South Sudan, northern Tanzania), whereas other areas indicate that the problem is only sporadic (e.g. Somalia areas). This is believed to be due to factors such as cattle density, herding patterns and environmental conditions. In endemic areas with high prevalence, chronic infection is common, with affected animals showing poor body condition and productivity over several months. The disease is a barrier to trade in live animals, and countries such as Botswana and Namibia have invested heavily to maintain their OIE disease-free status as part of the standard needed to export meat to Europe. On the other hand, CBPP is not transmitted in meat, suggesting that the value of a commodity-based approach to managing risk may be more appropriate.

Farmers invest considerable resources in the purchase of antibiotics for the control of CBPP, and in some countries areas affected by even just sporadic CBPP may experience restrictions on free movement or increased transaction costs, such as informal fees for movement permits within national markets. The indirect costs of control and reduction in the value of livestock because of the presence of CBPP are not well documented but are believed to be significant.



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# Principles of disease control and elimination

To clarify the discussion, it is useful to summarize the principle disease control options and their method of action. Reduction of clinical disease is of benefit to individual producers and not without merit. However, in disease control and eradication, the goal is to prevent transmission at the population level. From the perspective of control and eradication, clinical protection from disease or clinical cure are only of value to the extent that they contribute to reduction in disease transmission. Unfortunately, most of the CBPP vaccine research and some of the antibiotic research are focused on clinical impact rather than on the effect of the interventions on transmission.

In epidemiological terms, the ability of agent to spread in a population is governed by the *transmissibility* of an agent in that population, and this is described by a quantity called the basic reproductive number, or  $R_0$ . Simply stated,  $R_0$  is the number of secondary cases that will directly result when one infected animal enters a fully susceptible population. When this quantity is greater than 1, the outbreak expands. When the quantity is less than 1, the disease fades out of the population. The purpose of disease control measures is to reduce the effective reproductive number to less than 1. Thus, it is the impact of disease control measures on *transmissibility* that determines their contribution to disease elimination.

Transmission depends on a supply of infected animals, a supply of susceptible animals, and contact between the two groups. There are only a handful of disease control measures: elimination of the capacity of infected animals to transmit; elimination of susceptible animals; or prohibiting contact between the two groups.

Usually there are only a small number of infected animals relative to the size of the susceptible population. Thus, elimination of infected animals is often the most effective way of reducing transmission. In veterinary disease control, there are two ways to eliminate infectious animals: removing them through slaughter or treating them.

Reducing susceptibility in animals is accomplished by rendering them immune, most often by vaccination. The challenge with this approach is that the majority of the population needs to be rendered immune to interrupt transmission (overall *herd* immunity). Movement control and quarantine are techniques to isolate populations and prevent contact between infectious animals and susceptible animals. These groups must be kept separate until the infection fades out of the population. As CBPP has long incubation and infectious periods, control of contact rates must last months to years to be effective.



# The way forward to regain control of CBPP

The failure to contain CBPP is largely the result of the lack of a coherent and achievable policy with realistic approaches for coordinated and progressive control. It is therefore a matter of urgency to reconsider the strategic approach to CBPP in the continent and identify improved control strategies that countries can implement effectively.

For an appropriate and sustained CBPP control, there is the need for a strong political commitment that prioritizes CBPP as a major disease to convince governments, regional organizations, international bodies and funding partners to invest in CBPP control as a basis for improving food security, people's livelihoods and general well-being.

The public sector (government and international donors) may not substantially increase the funding available for CBPP control in the foreseeable future. Over the medium term (5 to 10 years), prudent policies should assume no more than moderate public investment and seek to increase the positive role of market forces. Sadly, many communities have been "trained" to be dependent on the government for vaccination, but self-reliant in the purchase of antibiotics. Although expectations regarding free vaccination exist, livestock owners already invest substantially in CBPP control through the purchase of antibiotics. The goal is to channel this investment into greater impact through the provision of effective and coordinated control measures.

The government clearly has the responsibility for coordinating control, conducting surveillance and regulating vaccines and treatments. Delivery of control interventions is best viewed as a responsibility shared between the government, the private sector and the communities. The intervention strategy should be such that it mobilizes all sectors and captures market forces to drive control to the maximum extent possible.



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*Delivery of control interventions is best viewed as a responsibility shared between the government, the private sector and the communities.*

The guiding elements of the CBPP control policy are:

- Evidence-based analysis of epidemiological and socio-economic impact of the disease and control options;
- Integration of vaccination, treatment and biosecurity actions in well-defined, validated control options;
- Effective public-private-community-partnerships for the regulated delivery of vaccination, treatment and surveillance services; and
- Strong initiatives to stimulate basic research.

The proposed policy builds on the knowledge and experience accumulated over the past years in terms of the efficacy and effectiveness of various CBPP control measures as reflected in the recommendations from the FAO-OIE-AU/IBAR Consultative Group on CBPP (FAO-OIE-AU/IBAR-IAEA, 2003; FAO-OIE-AU/IBAR-IAEA, 2006; FAO-OIE-AU/IBAR-IAEA, 2016), the OIE Standards for CBPP (OIE, 2016) and the OIE guidelines for recognition of disease-free status and endorsement of national control programmes (OIE).

## COMBINED CONTROL INTERVENTIONS

*“There is evidence that antibiotics could play a role in CBPP control, particularly where they are applied under controlled conditions, especially to replace slaughter of affected or in contact animals, and as a substitute to the ‘stamping out’ policy. There is an urgent need to conduct pilot studies as proof of concept that compare control alternatives, and particularly to demonstrate that the combination of vaccination and controlled use of antibiotics can be applied to full effect for CBPP control.*

*In countries where CBPP remains endemic, an effective vaccination policy is the only realistic method of choice at present for control of the disease, and should be encouraged. Current vaccines, despite their limitations (short duration of immunity and requirement of a cold chain for delivery), can provide sufficient protection if properly deployed, by using the correct dosage and ensuring efficient delivery of the vaccines.”*

**The Fifth Meeting of the Consultative Group for CBPP**

**(FAO-OIE-AU/IBAR-IAEA 2016)**

Available technical information and social analysis suggest that a new combined approach to CBPP control is needed. There is little public tolerance for either movement control or stamping out. Both vaccination and treatment are socially acceptable and although the data on CBPP is never crystal clear, there is sufficient information to conclude that both approaches are moderately effective when applied individually. Farmers are willing to invest in vaccination and treatment.

Epidemiological analysis suggests that the combination of treatment of CBPP cases combined with vaccination of healthy in contact animals has considerably greater impact than either treatment or vaccination alone (Mariner *et al.*, 2006).

Antibiotics are currently widely available, although vaccination is not. Action is needed to enhance access to vaccination. Research and conventional wisdom indicate that when herders prioritize CBPP they invest in its control. Specifics regarding preferences undoubtedly vary between communities. Available information suggests that although the public would prefer regular, free public vaccination, they would and do pay for control interventions in the absence of free programmes or to supplement inadequate free programmes.

## RATIONAL TREATMENT PRACTICE

International action to limit the development of AMR is of critical importance to global health. In 2015, the World Health Organisation (WHO) General Assembly adopted the Global Action Plan on Antimicrobial Resistance. A specific recommendation is the need to develop rational, *enforceable* policies for the use of antibiotics at the national and international levels. The plan calls on FAO to “to engage and support producers and stakeholders in the food and agriculture sectors in adopting good practices in husbandry and health aimed at reducing the use of antibiotics and the risk of development and spread of antimicrobial resistance”. In 2016, the OIE adopted resolution 36 which calls for an AMR strategy (OIE, 2016), and in the same year FAO launched the Organization’s an action plan for AMR (FAO, 2016). FAO’s action plan and OIE’s strategy are aligned with the Global Action Plan and both call for the importance of the One Health approach to address the issue of AMR. Rationalization of CBPP control policies considering current information and social forces is essential to reaching the goal of reducing inappropriate antibiotic use.

The current policies on CBPP vaccination and treatment directly contribute to the sub-optimal use of antibiotics and favour the emergence of resistance. The present situation regarding CBPP control and the risk of AMR is, in fact, a worst-case scenario, and FAO and OIE have an obligation to act. In terms of policy on antibiotic use, CBPP needs to be constructively regulated in a science-based manner that is consistent with other bacterial pathogens. Appropriate policies on the use of antibiotics in CBPP are needed to reduce the risk that essentially unregulated and uncoordinated CBPP control programmes currently pose for the emergence of AMR. Enforceable policies that effectively mitigate the impact of antibiotic use in CBPP control will be based on:

- Evidence of the benefits and risks of antimicrobial use that looks at primary data collected in well-designed studies;
- A realistic appraisal of the socio-economic drivers of antibiotic use in the control of CBPP and other cattle pneumonias in local context;
- Current market and institutional contexts for the delivery of animal health services and inputs; and
- Identification of CBPP control options that are affordable and accessible to livestock owners in *all* communities and production systems affected by CBPP.

Although additional applied research is needed to further refine treatment plans and evaluate newer-generation antibiotics, the rational use of antibiotics as a component of CBPP control is good practice. Research on antibiotics indicates that treatment aids in clinical recovery can clear infection and reduces mortality. But much more importantly in managing disease spread, antibiotics suppress transmission. Policies that ignore or negate the benefits and drivers of antibiotic use are poor policies that lead to poor practice and undesirable results.

It is essential that clear and practical recommendations be made now on the dosing schedule of antibiotic treatments for CBPP and other pneumonias, using third-generation macrolides and long-acting oxytetracycline, tylosin and danofloxacin (Lees and Shojaee Alibadi, 2002). The emphasis must be on informing responsible policies to encourage safe, effective use with available information.

Managing current treatment practices for CBPP and other cattle pneumonias of bacterial origin is an essential step in the prudent use of antibiotics. As most diagnoses are made on a clinical basis and the principle differential diagnoses for CBPP are other bacterial pneumonias, it makes sense to target the antibiotic action plan to the use of antibiotics in all cattle pneumonias. The necessary steps are:

- Documentation of current practices and quantities of drugs used;
- Identification of ineffective or high-risk practices;
- Documentation of efficacious treatment regimens and their level of effect through operational research;
- Projection of levels of future use based on programme intervention targets and future estimations of disease prevalence;
- Tailoring of policies, communication tools and regulations to create an environment that enables rational use; and
- Establishment of monitoring protocols to assess progress in control of CBPP, amounts of antibiotics used, emergence of resistance in MmmSC field strains, and level of adoption of good treatment practices.

The principal differential diagnoses for CBPP are other bacterial pneumonias. At the field level, in communities where cattle are important, farmers and veterinarians make good clinical diagnoses and identify CBPP with reasonable levels of sensitivity and specificity. Further, treatment of other bacterial pneumonias with the same antibiotics is appropriate and non-controversial (Sarasola *et al.*, 2002). Pen-side diagnostics would increase the accuracy of the differential diagnosis of pneumonias, but in routine control in endemic areas it would add significant cost without resulting in changes in the treatment plan. As the goal of the programme is to increase the use of good practice in antibiotic use (appropriate dosing, treatment schedules, etc.), the programme will mitigate the risk of AMR across a range of differential diagnoses.

### **PARTNERSHIPS AND MARKETS TO GET CBPP VACCINE INTO THE FIELD**

Given the financial constraints on public CBPP control, means must be found to leverage available resources. Countries should develop public-private-community partnerships for control. This is explicitly in line with the recommendations of the Global Action Plan on Antimicrobial Resistance, which advocates for public-private partnerships to enhance access to interventions that could reduce the prevalence of disease and the need for antibiotics.

The Fifth Meeting of the Consultative Group for CBPP (FAO-OIE-AU/IBAR-IAEA, 2016) highlighted that a strong public-private strategy should be implemented at country level. Such a strategy can be a key instrument in the policy balance between the oversight and regulatory roles of the State Veterinary Service and the regulated, subcontracted (by the State) operational role of the private veterinary sector.

Without wishing to be prescriptive, it is suggested that government consider:

- Liberalizing access to a licensed, certified CBPP vaccine supply;
- Empowering private veterinarians to deliver CBPP vaccination services;
- Measuring the impact of payment for quantity of work and payment for services;
- Including roles for community animal health workers (CAHWs) in CBPP control; and
- Public sector licensing, targeting and monitoring of compliance and progress.

Veterinary services and recognized drug control authorities should select and license reputable sources of CBPP vaccine and only permit importation of lots of vaccine with the African Union Pan African Veterinary Vaccine Centre (AU-PANVAC) certificate of quality.

Private veterinarians should be integrated into national CBPP control programmes. Creation of an accreditation process is an option where veterinarians are given a short course on the national strategy and recommended CBPP control practices.

Payment for CBPP services can have positive and negative effects. The effect is determined by what is done with the money, more than the requirement for payment itself.

The method of inclusion of partial payment for services can have dramatic effects on participation and compliance. If payments are retained at the local level to cover labour, infrastructure (such as corrals, dipping pens and water wells) and transport costs, they stimulate greater activity on the part of the service delivery value chain. On the other hand, if payments are returned to a central authority, they are in fact a form of tax and discourage activity. Payment empowers livestock owners to demand timely and quality service. The concept is on payment for quantity of work as an incentive for activity, rather than entitlement payments like per diems or field allowances that are not directly linked to the number and quality of vaccinations delivered.

CAHW have played an important role in infectious disease control and eradication in the past (Mariner *et al.*, 2012), including integration in CBPP control programmes (see box above). CBPP programmes should evaluate roles for CAHWs in CBPP vaccination and treatment programmes, under the supervision of accredited veterinarians.

Whatever system is implemented, it is critical that the public sector actively participate in the field, assessing compliance, measuring progress and providing guidance. This requires an appropriate budget allocation.

## **SURVEILLANCE AND DISEASE REPORTING**

Surveillance is essential for formulating strategy, detecting events and measuring progress.

Disease reporting systems are a core veterinary services activity. However, as private veterinarians take on an increasing role in clinical medicine and some control programmes, the contact between public sector veterinarians and livestock owners is reduced. Efforts must be made to integrate private practitioners in disease reporting systems. In the case of CBPP, if an accreditation system is implemented, reporting of CBPP cases can be easily implemented. Activity reports and receipts from livestock owners should document the number of vaccinations and the number of suspect cases treated.

Abattoir surveillance for lesions of CBPP is useful and should continue as an indicator of disease presence or absence. Prevalence of lesions at slaughter can be highly biased and should only be used in combination with information from other sources (Annex II).

Participatory surveillance using a syndromic case definition that captures CBPP cases should be implemented. Participatory surveillance teams gain insights on the attitudes and expectations of participants, which is important for guiding policy and programme design. Participatory assessments should be at the centre of the programme design process.

Serosurveillance is useful for measuring prevalence and the progress of disease control programmes. As vaccinal antibodies are short-lived, serosurveys conducted at least two to three months after vaccination programmes are excellent tools for measuring infection



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*Participatory surveillance using a syndromic case definition that captures CBPP cases should be implemented and take advantage of herders' knowledge and familiarity with their animals.*

rates. However, for chronic disease, such as CBPP, prevalence is determined by both transmission rates and the duration of infection. Serological results need to be interpreted in combination with clinical and participatory surveillance that adequately characterize the clinical course and outcome of infection.

### **IMPACT ASSESSMENTS**

It is difficult to evaluate the losses due to CBPP in many African countries where the disease is enzootic because of the lack of proper reporting, knowledge of underlying conditions, and economic evaluation. Evaluation of the real epidemiological situation and economic losses of CBPP is a critical step for developing an effective control programme of CBPP. Broad-based impact assessments of CBPP and CBPP control measures are needed. It is not known how much the disease costs producers, including how much they spend on treatment and the quantities of antibiotics used. Assessments should look at epidemiological,

economic, livelihood and institutional impacts. As has been mentioned, CBPP epidemiology and impact differ significantly between agro-ecological zones. Measurement of prevalence is only an intermediate variable, and data collection is expensive. Impact assessments should seek to quantify outcome variables such as costs and livelihood impact in the context of a qualitative appreciation of prevalence.

## OPERATIONAL RESEARCH

Technical information, participatory assessment and dialogue with communities should proceed and inform the design of control packages, which should then be piloted and evaluated. There are several approaches to combining vaccination and treatment that should be tested at scale in the context of field programmes. Disease modelling suggests that the most powerful approach to clearing CBPP from a herd is antimicrobial treatment of clinical cases combined with vaccination of the remainder of the herd. Scenarios with this combination of interventions showed the greatest reduction in transmission.

There are multiple approaches to combining vaccination and treatment that should be evaluated at scale in the context of field programmes.

Operational research on control options and delivery mechanisms is the main research priority for CBPP. Operational research is defined as “the search for knowledge on interventions, strategies or tools that can enhance the quality, effectiveness or coverage of the programmes in which the research is being done” (Zachariah *et al.*, 2009). Research should be effectively designed to measure process parameters (the extent of implementation) and incentives (the economic, social and cultural reasons why stakeholders make decisions) as drivers of impact on disease, production and livelihoods. The perceptions of stakeholders and the reasons behind the decision to participate or not participate are invaluable pieces of information for informing programme design. This requires appropriate methods and it is suggested that both structured quantitative tools and participatory techniques be utilized.

## RESEARCH FOR BETTER TECHNICAL TOOLS

Basic research on vaccines with greater safety, immunogenicity and duration of immunity must continue as a priority. Important improvements in any of these three areas would be of benefit to the livelihoods of farmers and national economies. The feedback from farmers is that adverse reactions to vaccines are a major deterrent to participation (Kairu-Wanyoike, Kiara *et al.*, 2014).

The immune response to CBPP is poorly understood. It is known that inflammatory responses linked to ineffective immune responses are a major component of the pathology of CBPP. In fact, a true immune state has never been formally documented. Some speculate that the existing vaccines work to block infections and do not induce a true immune response. Naturally infected cattle that recover are said to be immune for life, but this has not been tested in a controlled setting. There is no method for demonstrating durable immunity other than response to challenge. Thus, current vaccine research, although using cutting-edge technology, is essentially empirical, as the type of immunity needed is unknown. *Basic research that demonstrates an immune state and the nature of that immunity is needed to target vaccine research.*

Research on novel vaccines is critical. For vaccines to be a truly “stand-alone” interven-

tion, high levels of efficacy >90 percent and duration of immunity (essentially life-long) will be required. This is a level of immunity equivalent to that believed to result in animals that recover from natural infection. Most probably, new vaccines will fall short of such a high standard. Strategies that combine novel vaccines with other interventions will still be needed.

Integrated strategies will benefit from improved diagnostics, especially for field-based tests and tests that detect early infection. Improved diagnostics can enhance targeting and guidance of control programmes. As the farmer's decision to intervene is largely based on cost, the cost of diagnostic tests will be an essential factor in their utility. Low-cost multiplexed assays that allow differential diagnosis are preferred. However, if the treatment decisions are unchanged by the test outcome (such as in differentiation of pneumonias), farmers and field veterinarians are unlikely to incur the added cost of a test.

A vaccine and test combination that facilitated the identification of immune cattle would be highly beneficial. Today, herds and communities can only be classified as disease-free through the absence of detection of disease.

*In vivo* assessments of third-generation macrolides have shown excellent results that include high rates of clinical cure, clearance of infection and interruption of onward transmission (Annex II). Assessment of treatment protocols and combined interventions (vaccination of healthy and treatment of sick animals) should be conducted as part of either intervention or research programmes.

# Programme implementation

The success of this policy depends on its rapid implementation. For this to happen, costs for the implementation of all the elements of the policy will need to be defined and adequate resources identified. In addition, scale-up of CBPP control will require simple indicators to monitor success in working towards strong veterinary services.

The implementation plan defines a decision-point 10 years in the future on eradication. The results of operational research implemented in the course of rolling out integrated control programmes and more basic research on improved vaccines are needed before an informed decision can be made on the goal of eradication.

## COORDINATION AND ASSESSMENT OF PROGRESS

International coordination is a necessary element in the control of CBPP. CBPP is a trans-boundary disease and many of the CBPP endemic zones span international borders. There have been repeated calls over the last two decades to restructure and reinvigorate CBPP control (Thomson, 2005); however, a coordination mechanism mandated to sustain and guide the process has been lacking. The absence of a dedicated coordination mechanism has been one of the reasons for the stagnation of CBPP control and the resurgence of the disease.

The main functions of international coordination should be to:

- Encourage learning and adaptive management;
- Develop regionally integrated control plans;
- Promote information exchange and new knowledge; and
- Stimulate innovation and high-quality applied and basic research.

FAO has traditionally taken the lead in facilitating dialogue through the FAO-OIE-AU/IBAR-IAEA CBPP Consultative Group, in which countries and regional organizations present their current situation, research developments are presented and discussed, and dialogue on the principles of CBPP control is held. The spirit of the dialogue has been frank, open and inclusive. However, there has not been a specific coordination mechanism within any of the international organizations since perhaps the 1970s. **It is proposed that FAO and OIE build on their current role and take the lead in establishing a coordination mechanism, under the Global Framework for Progressive Control of Transboundary Animal Diseases, and launch a prescient CBPP control initiative.** This policy is the first milestone of this initiative.

Progress will require strong veterinary services and effective systems of epidemiological assessment and information exchange. OIE has a critical role in defining epidemiological objectives, enhancing transparency and information exchange, and validating progress. The AU-IBAR, a platform representing African ministries of livestock, has tremendous ownership and influence in the region. They are the key partner for policy dialogue and engagement of the Regional Economic Communities (RECs) for their major role in implementation and

sub-regional coordination. The strong tradition of the Joint FAO/IAEA Division of Nuclear Techniques in Food and Agriculture in supporting diagnostic technology and networks will be needed as well as AU-PANVAC's role in assuring vaccine quality.

In addition to the conventional research funding mechanisms, consideration should be given to "pull" mechanisms such as prizes for new vaccines and diagnostic platforms that meet required criteria. The size of the market for CBPP vaccines and diagnostics has limited the participation of global pharmaceutical players. The use of prizes could help to engage powerful private sector research. The pull mechanism would need to address pricing issues to assure that the product became available to the intended beneficiaries.

As part of CBPP national control strategy, countries should establish a national CBPP control coordination mechanism under the Director of Veterinary Services. Ideally, the national epidemiology office should have a significant role, as CBPP epidemiology (and risk management) should determine strategy.

### **A TIME-BOUND, PHASED IMPLEMENTATION PROGRAMME**

This policy is a practical call to action. More than two decades have passed since CBPP control slipped into decline, leaving no vision for the way forward for CBPP. Enough information is available now to empower reform and renewed action. The principle of adaptive management maintains that the best strategy based on existing information should be put in place while assuming that future learning will justify new changes. Learn more by doing and make research and learning part of the plan.

Critical evaluation of action research on new combined technical strategies involving multiple interventions, service delivery partners and financing strategies will indicate just how far existing technologies can take control. In the meantime, research may give rise to better options. Three phases leading to a decision point on eradication in 10 years are suggested.



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*The primary beneficiaries from the investment in search of new technologies to tackle the disease must be the herders themselves, such as this cattle keeper in Mingkamen, South Sudan.*

### Phase 1: scaling out integrated control (3-5 years)

The initial phase will be a period of regional, national and local assessments leading to the development and roll-out of regional and national strategies. Part of the strategic roll-out will be operational research that evaluates new approaches to integration of control measures and institutional arrangements for the delivery of services. This may lead to the prioritization of clusters of countries where early emphasis will leverage impact and deliver results in terms of rapidly rolling back disease or preventing further spread.

The specific objectives of Phase 1 are to:

- Define the regional systems of infection that affect multiple countries and the development of coordinated programmes of control based on regional disease ecology;
- Define the national epidemiological zones and development of a phased national strategy for progressive control;
- Integrate an abattoir surveillance, particularly in at-risk areas, supported by laboratory confirmation in endemic areas;
- Analyse the CBPP impact to inform programme design and identify incentives to drive participation;
- Develop and pilot integrated control plans that address both technical tools as well as delivery systems that create incentives for appropriate actions;
- Train and accredit service personnel; and
- Establish monitoring systems and baseline data on antimicrobial use and AMR.

The regional and national assessments will seek to define epidemiological zones and characterize the differing CBPP situations within a country and across borders. Field assessments that examine the epidemiology, production and control practices, attitudes towards treatment and vaccination, and levels of service infrastructure will be undertaken. Their purpose will be to identify critical control points and opportunities to enhance access to vaccination and surveillance. Different control and service delivery strategies may be required within one country.

During this period, countries will continue to seek to control CBPP, but under the assumption that new approaches will be tried and validated. New control strategy initiatives will need to be fully articulated and communicated to service delivery actors and livestock owners. This will require user-friendly communications that describe the roles and responsibilities of different actors as well as provide a clear description of the appropriate manner of application and integration of control tools. For example, in the face of an outbreak, criteria for determining which animals to treat and which to vaccinate should be stated using a plain language. The financial arrangements for cost-sharing must be clearly elaborated and communicated. Financial contributions from livestock owners should be utilized to cover some of the delivery costs such as fuel, vaccination material and manpower. Ideally, farmer contributions should be utilized as incentives for personnel conducting the vaccination campaigns. This creates a quantity-based incentive for field personnel to be present on the field and work effectively.

This period will see the elaboration of recommended control options, development of accreditation systems and training of key actors in the delivery of the system. The learning will include experience with new mechanisms for financing CBPP control that channel current public and livestock owner investment into coordinated control.

Specific actions will be taken to improve the utilization of antibiotics in bovine pneumonias, reduce under- and over-dosing, and provide information on effective courses of treatment. Current levels of antibiotic usage will be quantified as well as resistance levels through isolation and testing of MmmSC strains. National importation data as well as field research will be used to establish baselines. Guidance will be provided on appropriate standards for licensing and extension messages on common pneumonias and their management, treatment and prevention. One goal will be to reduce the range of potencies of antibiotic formulations on the market to allow straightforward recognition and guidance on dosage.

Impact assessments that quantify changes in disease burden due to disease control actions will be collected. Antibiotic usage will be monitored and the impact of the CBPP on the risk of AMR will be reassessed annually in light of data and programme goals. Information on the indirect impact of control activities on livelihoods of livestock owners and service providers is also needed to optimize control packages. The collection of information on the drivers of participation in the programme should be part of the assessment, as well as current expenditure on disease treatment. The collection of information should include both positive and negative factors affecting livestock owners' participation, which shape delivery choices.

The international community has a critical role to play in stimulating innovation and facilitating the sharing of experiences on new methods. FAO, OIE and AU/IBAR will be at the centre of efforts to channel change towards more effective control and measurement of progress.

### **Phase 2: aggressive control (5-7 years)**

During the aggressive control phase, governments will conduct surveillance (particularly abattoir surveillance), continuously monitor implementation, and conduct annual assessments to refine strategies in light of changes on the ground. Implementation will continue through public-private-community partnerships. Livestock-owner perceptions of benefit will be crucial to guiding the programme.

The specific objectives of this phase are to:

- Suppress the incidence and impact of the disease across its range;
- Optimize antibiotic use to reduce the total quantity of antimicrobials used to 10 percent of current levels and the risk of the emergence of AMR; and
- Eliminate disease from defined zones.

The strategy for defining epidemiological zones within a country and achieving progress within zones will be essential. Surveillance, particularly abattoir, will be a pivotal tool in implementing this strategy. The creation of permanent, institutionalized control is not the goal. Programmes that reach control plateaus stagnate and lose support. National and international coordination will have the task of setting goals and challenging stakeholders to aspire to further improvements.

The impact of the programme on antibiotic usage and progress toward achieving a 90 percent reduction will be reviewed annually with participation of stakeholders tasked with oversights AMR initiatives.

**Phase 3: the decision point on eradication (at 10 years)**

Although learning and strategic review should be an integral part of the ongoing programme, a time-bound goal is essential to effectively measure programme progress.

At the end of 10 years, the programme will be evaluated on the extent it has:

- Suppressed of the incidence and impact of the disease across its range;
- Optimized antibiotic use to reduce the total quantity of antimicrobials used to 10 percent of current levels and the risk of the emergence of AMR; and
- Eliminated disease from defined zones.

It is envisaged that these general goals will be explicitly defined in spatial and temporal terms as a first step in implementation to enhance programme monitoring and evaluation.

With facilitation from FAO and OIE, the international community and national authorities will review progress against these goals, the efficacy of national control programmes and new technologies that have become available, and decide on a feasible time plan for eradication.



## Conclusion

CBPP control and elimination are achievable with existing tools. Although the tools available for control of CBPP have not changed significantly in the last 30 years, social conditions have changed. Markets for veterinary services and pharmaceuticals have evolved dramatically and are much more liberal today, systems of governance have changed, and livestock owners are much more empowered and able to purchase a wide range of services. In addition, there has been a considerable reassessment of the epidemiology of CBPP considering modern evidence-based approaches to assessing risk. Documented risk of transmission from animals with sequestered infection is negligible and it is now recognized that the net effect of antibiotic treatment is most likely to reduce the overall number and risk of pulmonary sequestra in a population. CBPP control requires modernization of policies to fit the current social conditions and technical information.

Policies on CBPP control have not evolved with market forces and animal health institutions. CBPP vaccination remains one of the few government monopolies and has not been effectively implemented since the use of bivalent rinderpest and CBPP vaccine was discontinued with the elimination of rinderpest from most regions in the 1990s. The widespread but unregulated use of antibiotics in CBPP is a direct result of the failure of the public sector to implement vaccination in the context of generally liberalized animal health markets and provide guidance on how to use antibiotics appropriately. The solution is to eliminate this anachronism and harmonize CBPP policies with the general state of today's animal health markets.

The need for coordinated action is urgent. Communities note that the direct effects of CBPP on their livelihood and food security is a primary concern. The valid need to address the threat of CBPP is a major driver of antibiotic usage. The current policy failures directly create one of the greatest hazards for the emergence of antibiotic resistance within the context of African livestock agriculture. The policy of officially banning or discouraging widely available antibiotic usage for a common, treatable microbial disease is unenforce-



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*Community Animal Health Workers, trained and promoted by FAO, such as the one in a cattle camp outside Rumbek, South Sudan, are an essential resource to be used in controlling the disease.*

able. The approach described in this document seeks to eliminate CBPP as a driver of inappropriate antibiotic use and reduce the overall use of antibiotics to 10 percent of its current levels.

The way forward depends on public-private-community partnership for implementation of control measures under good government coordination and regulation. Strict quarantine, movement control and stamping out are not feasible at scale. Market forces favour coordinated treatment and vaccination interventions, and evidence suggests that both approaches have reasonable impact. Animal identification is a powerful tool in the control of populations, prevention of stock theft and the tracing of cases in surveillance schemes. However, in most of Africa, animal identification is not yet practiced and there are major hurdles, both economic and cultural, to the implementation of identification schemes. Identification schemes should be supported and may be important elements of CBPP control where they are feasible.

The international animal health community and national governments need to move forward to implement and validate new control options and delivery mechanisms that capture biological and economic realities.

The map to the future requires significant technical and institutional change supported by applied action research to sort the successes from the failures. This is not the first attempt to revitalize CBPP control, and the process will require concerted international leadership from FAO, OIE, AU-IBAR, IAEA and the RECs to reach fruition. As the full potential of impact of the new approaches to utilization of the available biological and institutional tools has yet to be seen, it is premature to set an eradication date. However, after a 10-year period of innovation and aggressive control, sufficient information should be available to make an evidence-based decision on the completion of eradication.

## Annex I

# The evolution of CBPP control until the present

There is a rich history concerning the world's efforts to control and eliminate CBPP. The disease has probably been with us since ancient times. Detailed descriptions from Germany date from 1693. The disease spread widely in Europe from about the time of the Napoleonic Wars and the expansion of cattle trade thereafter. It subsequently spread to most of the world through colonial activities and trade. CBPP was present in North America in the 19th century and persisted in Europe, parts of Asia and Australia until recent times. Like rinderpest, CBPP was accidentally introduced to Africa during the colonial period through importation of exotic cattle.

Today, the disease has been eradicated from the developed world. There have also been important examples of successful eradication in Africa, as well as breakdowns in control and reinfection of free areas. This section will briefly outline some of the major control strategies used in CBPP in the context of socio-cultural conditions and suggest lessons for the future.

### **ELIMINATION PROGRAMMES WITHOUT VACCINES AND DIAGNOSTIC TESTS**

CBPP was the first disease eliminated in North America and in large parts of Europe in the second half of the 19th century. Eradication was completed without the aid of diagnostic tests or vaccines, which suggests that eradication is about effective methods rather than technology. At times, subcutaneous inoculation procedures with virulent material were carried out which provided solid immunity for animals in endemic areas.

CBPP entered the United States in 1843. It was eradicated from Canada in 1876 but persisted in the USA. In 1879, the United Kingdom restricted importation of cattle from the USA because of the widespread incidence of CBPP in the USA. The decision was made to embark on the eradication of CBPP, which led to the formation of the Bureau of Animal Industries in 1894, the precursor to the US Veterinary Services. The Bureau was empowered to purchase and destroy sick animals in 1887 and to implement quarantines in 1889. CBPP was eradicated from the USA in 1892 by clinical identification, elimination of suspect cases and disinfection of premises.

The United Kingdom of Great Britain and Northern Ireland eradicated the disease by 1898. CBPP was eliminated throughout most of the rest of Europe prior to the First World War. This was largely accomplished through movement control and slaughter of infected and in-contact cattle. Sporadic cases appeared in Europe during various periods and have been attributed to gaps in surveillance and enforcement of control procedures. There have been no reports in Europe since 2000.

Elimination required intense commitment combined with rigorous enforcement of movement control and stamping out procedures.

### **DIAGNOSTICS, VACCINATION AND STRICT MOVEMENT CONTROL**

With the advent of the complement fixation test (CFT), test and slaughter programmes became feasible. The development of somewhat safe and effective vaccines enabled programmes of vaccination and strict movement control.

The example of Australia illustrates the impact of technologies for diagnosis and immunization. CBPP was introduced to Australia in 1859 in cattle imported from the United Kingdom. Australia has a federal system of governance, and methods used within states varied. A range of production systems and ecologies exist across the country, with the northern states being more arid and with predominantly extensive systems of cattle husbandry. Various combinations of identification of infected animals, slaughter of infected animals, vaccination and movement control were used in the different states. Surveillance included visual inspection, abattoir surveillance and laboratory testing. One commonality was very strong actions at state borders to limit cattle movement (Newton, 1992).

A principal procedure was the identification of infected animals, slaughter of infected animals and vaccination of the remainder of the herd. Prior to the advent of the CFT test in the 1930s, suspect CBPP cases were identified in Victoria State based on a case definition of poor productivity and a temperature of more than 40°C. The suspects were slaughtered and the remainder inoculated. It has been said that this procedure virtually eradicated the disease from the state by 1914. After the CFT was available, a common approach was to test herds, destroy the reactors, vaccinate the rest and retest in five months. Early versions employed test and slaughter without vaccination, but this was found to be less successful.

In northern Australian, cattle were trekked hundreds to over a thousand kilometers to market. Over the course of the eradication programme, a basic shift to motorized transport occurred and this is believed to have been an enabling change for the completion of national eradication (Newton *et al.*, 1992).

Australia made the decision to move from control to eradication in 1959. In 1968, the federal government established a uniform system of criteria for classification of epidemiological zones as infected, protected and disease-free. A national system was put in place to help all regions of the country attain disease-free status. All areas on the country obtained disease-free status by 1973 and no evidence of disease was found after 1968. The disease was declared eradicated from Australia in 1973.

Similar models to those used in Australia based on identification and slaughter of infected animals were employed in southern Africa in the colonial and early post-colonial periods. As the CFT became available, herds were isolated and mobile CFT teams conducted tests on the spot. Positive animals were immediately slaughtered.

The United Republic of Tanzania is perhaps the best documented example of elimination of CBPP through vaccination and movement control (Hammond *et al.*, 1965). The challenges of quarantine and early vaccination efforts in the Masailand were recorded in detail. The struggle lasted decades. Disease management measures tracked individual herds, and a period of two years without disease was required for herds to be released from quarantine. In some cases, infected herds were relocated to confined areas where contact could be

more closely supervised. The importance of adapting quarantine measures to local communities' needs and the adoption of supervised sale programmes where veterinary department personnel travelled with the sale animals trekked to slaughter were described. The level of commitment of the staff and their attention to detail were remarkable. Hammond and Branagan close their discussion with the conclusion that elimination from the Masailand of The United Republic of Tanzania could only be achieved as part of coordinated cross-border programme that included Kenyan Masailand.

In the 1970s, Bisec, a bivalent vaccine that combined rinderpest and contagious bovine pleuropneumonia, was developed (Provost *et al.*, 1970) which greatly facilitated annual mass vaccination campaigns in West and Central Africa. In the Sahelian regions of West and Central Africa, mass vaccination was the preferred approach. Given the nature of production, movement control was not feasible. It has been said that when annual mass vaccination was applied repeatedly, it greatly suppressed the disease. Use of the combined vaccine continued into the 1990s. The completion of rinderpest eradication required the cessation of vaccination, and the use of Bisec was discontinued. Without significant funding dedicated to CBPP, vaccination rates for CBPP fell significantly.

### THE REALITY TODAY

The re-emergence of CBPP has been documented (Masiga *et al.*, 1996; Nicholas, *et al.*, 2000). Although the official reporting of CBPP is not very reliable, from a low of about 15 infected countries in the late 1970s, there is on the order of 30 infected countries today. This has been ascribed to a decline in vaccination, funding and movement control. It has also been stated that a decline in the quality of public veterinary services has contributed to the rise of CBPP. Overall though, access to veterinary services (public and private) has probably increased during the period of CBPP's resurgence.

Stamping-out was successfully used in Botswana to eliminate CBPP when it was re-introduced in the mid-1990s as part of the regional resurgence of the disease. With Botswana's ability to export to international markets, there were incentives to invest heavily and clear justifications to take drastic actions to re-establish freedom in as short a time as possible. Analysis of the lessons learned from the programme noted that stamping-out "*cannot be carried out by many countries currently affected by CBPP due to the high financial cost, the widespread nature of disease, animal welfare considerations and the potential loss of a valuable genetic resource base*" (Amanfu, 2009).

For the most part, countries indicate that CBPP control is primarily a public good and that implementation should reside with the public sector. Further, the majority of countries with diverse ecologies and production systems have defined epidemiologic zones. Within endemic areas, the predominant policy is that mass vaccination should be carried out on an annual basis by the government and that treatment with antibiotics is discouraged. For the most part, when vaccination is offered, it is free of charge. There is often a policy that movement between zones is restricted and an inspection, testing or permit system exists to some extent. In some situations, private veterinarians are contracted to deliver CBPP, but CBPP is not available for purchase and farmers cannot order CBPP vaccination as a service for a fee. Farmers must wait passively for vaccination, which is irregularly available at best (Kairu-Wanyoike, Kiara *et al.*, 2014).

Unfortunately, governments lack the resources to reliably implement free annual mass vaccination, and at best only limited portions of the endemic areas are covered each year. Donors are reluctant to invest in an open-ended control programme. In most countries, movement restrictions are only partly enforced and in some of the worst cases are purely an opportunity for collection of informal fees.

Research has shown that farmers are willing to invest in CBPP control (Mariner *et al.*, 2006; Kairu-Wanyoike, Kaitibie *et al.*, 2014). The question is: what options are available for purchase?

Currently, antibiotics are the only potential CBPP control intervention freely available for purchase; as a result, antibiotics are widely used to control CBPP. Various formulations and strengths of oxytetracycline are the most available and commonly used. In some regions, CBPP is suspected to be the most important driver of antibiotic sales. Treatment is reality.

Treatment is carried out on an ad hoc basis without any specific recommended regime. Animals are injected until a clinical improvement is seen (often after a single injection). If symptoms recur, the animals are retreated. The popularity of treatment is not new (Orue *et al.*, 1961). However, today antibiotics are widely available and vaccination is not.

Most countries permit a range of concentrations of oxytetracycline to be imported (3 percent to 20 percent). Determination of the appropriate dose for the size of an animal is challenging for many farmers, and the wide range of concentrations permitted for importation probably contributes to under- and over-dosing.

Two points should be noted:

- Although vaccination is recommended, the current policies on vaccination delivery limit farmer access to vaccination and stimulate the use of available antibiotics.
- The lack of an appropriate policy and public guidance on antibiotic use precludes effective management of antibiotic use, and contributes to sub-optimal use in a manner that maximizes the risk of the development of antibiotic resistance.

*The current situation is an acute policy failure.* The goal of the policies in place is to encourage control through public vaccination programmes and discourage antibiotics. The actual outcome of the policies in place is the opposite: high levels of unregulated antibiotic use and limited vaccination. Appropriate guidance and regulation on antibiotic use in the treatment of CBPP and other pneumonias would increase the impact of antibiotics and the cost-effectiveness of treatment and, most importantly, reduce the risk of the development of AMR.

## Annex II

# Tools available today for CBPP control

Much has been written about CBPP and CBPP control over the years. There are many statements of conventional wisdom in the literature on CBPP that are not traceable to primary evidence. In addition, specific actions that were strongly urged in the past have lost their relevance in modern society. Current students of CBPP suggest that an evidence-based approach to a review of the literature, which looks at the data in support of statements, is required to separate fact from opinion.

### **MOVEMENT CONTROL, ABATTOIR SURVEILLANCE AND ANIMAL IDENTIFICATION**

Strict movement control is effective in CBPP control and was an integral part of vaccination and stamping-out programmes. However, the key word is “strict” and this meant no movement for periods of months to years. As the combined duration of the CBPP incubation and infectious periods may exceed six months, the duration of movement restrictions need to be longer than six months to be effective.

As an example of the severity of measure used, the community of Loliondo in northern Tanzania was under complete quarantine for more than five years in the 1950s. This meant that no cattle could be sold. Colonial inspectors noted that the effect of the CBPP quarantine on the livelihoods of the community created “near famine conditions” (Hammond and Branagan, 1965). Clearly, the untoward effects of the measure were not appropriate in the larger social picture, and fortunately this level of movement control would not be possible to implement today.

Abattoir surveillance, particularly in at-risk areas, can serve as a powerful surveillance tool to estimate the prevalence based on pathological findings (Noah *et al.*, 2015; Marobela-Roborokgwe, 2011). This method, however, has its drawbacks due to potential bias and low numbers of animals that are actually slaughtered in formal abattoirs compared to backyard slaughtering.

Animal identification is a powerful tool in the control of populations, prevention of stock theft and the tracing of cases in surveillance schemes. However, in most of Africa, animal identification is not yet practiced and there are major hurdles, both economic and cultural, to the implementation of identification schemes. Identification schemes should be supported and may be important elements of CBPP control where they are feasible.

Today, communities have a much greater voice in government and there is broader recognition of the utility and appropriateness of pastoral systems. Mobility and flexible use of resources, even cross-border, are now recognized as the key to sustainable productivity in arid and semi-arid systems. Movement control is largely no longer feasible at the level

required for meaningful impact on the epidemiology of CBPP in most parts of Africa. There are exceptions in southern Africa, but for the most part these interventions were initiated decades earlier and it would be extremely difficult to expand such approaches to new areas today. Zambia had success with eliminating CBPP from areas in 1994 (Muuka *et al.*, 2013) using schemes that rely on movement control, animal identification and test and slaughter. It is not appropriate to try to prescribe a general rule for all areas.

## STAMPING OUT

Stamping out (depopulation and repopulation of a premises) is of historical importance and, if feasible, is a highly effective means of control. When properly implemented, by removing the infected animals, stamping out has much more rapid impact than vaccination. To be effective and fair, stamping-out programmes should include timely compensation for the market or near market value of the livestock destroyed.

However, stamping out carries high social costs and is poorly tolerated in many locations. In agri-business, stamping out may be a pure business decision, as the owners often have little direct relationship with their animals. On the other hand, livestock-owning households in both the developed and the developing world have a direct relationship with their livestock that includes complex and closely held values and attachments.

Stamping out is of limited applicability in endemic areas today. The principle constraints are the difficulty in supporting the high cost of compensation, the administrative and legal challenges associated with the ethical management of large payments to the private citizens, and the unwillingness of communities to destroy their herds. Perhaps the one exception where stamping out may be an acceptable option would be in the case of a very limited introduction or foci of disease where the slaughter of a small number of livestock could pre-empt a prolonged outbreak or establishment of the disease.

## VACCINES

The currently available live attenuated CBPP vaccines were developed more than 60 years ago. The less attenuated strains are more immunogenic but pose greater problems of residual virulence. Despite research, little progress has been made in developing more effective vaccines. The T1/44 strain is currently the recommended strain.

CBPP vaccine efficacy tests lack reproducibility due to the biology of the agent and methods of assessment. This makes objective documentation of vaccine efficacy challenging, as repeat experiments often generate very different outcomes. As a result, the clinical efficacy of the recommended T1/44 vaccine strain is a perennial topic for discussion. A complex qualitative, non-parametric method developed by Hudson and Turner (Hudson *et al.*, 1963) is used for scoring vaccine efficacy trials. The Hudson and Turner method scores indicators of disease and infection in vaccinates relative to controls but does not evaluate the impact of the vaccination on agent shedding or transmission.

A review of the T1/44 vaccine strain efficacy trials has shown that several studies evaluated the vaccine at three to six months post-vaccination (Masiga *et al.*, 1978; Gilbert *et al.* 1970; Karst, 1971; Masiga, 1972; Masiga, Rurangirwa *et al.*, 1978; Thiaucourt *et al.*, 2000; Wesonga *et al.*, 2000). In these studies, the reported efficacy scores for protection against macroscopic pathologic lesions (Ep) ranged between 33 and 95 percent. Additionally, a

recent study supported by Global Alliance for Livestock Veterinary Medicines (GALVmed) has shown an 87 percent reduction in lesions six months post-vaccination. Other studies reported Ep values between 66 and 78 percent from challenge experiments conducted at 12 to 15 months post-vaccination (Gilbert *et al.*, 1970; Masiga *et al.*, 1978; Wesonga *et al.*, 2000). One study, however, found an Ep of 80 percent for the T1/44 strain in cattle challenged two years post-vaccination, although 5 of the 16 (31.3 percent) vaccinated animals developed infected sequestra as a result of in-contact challenge (Windsor *et al.*, 1972).

The results mentioned above suggest an average efficacy rate of about 67 percent for protection against clinical disease over the first-year post-vaccination.

The two-year post-vaccination study is difficult to interpret within the body of evidence, as the two-year study found protection rates to be higher than almost all the 10 other studies. A conservative appraisal could be that if the vaccination leads to immunity, it may persist for up to two years.

Some experts argue that revaccination has a potentiating effect that results in high levels of solid herd immunity. It has been said that this effect accounted for the apparent suppression of CBPP in West and Central Africa when regular annual campaigns were carried out using the bivalent RP-CBPP vaccine, *bisec*. In one study, revaccination with T1/44 at 12 months post- primary vaccination rate results in a protection score of 95 percent (Wesonga *et al.*, 2000). This was essentially a primary and booster vaccination strategy. However, given the norm of 80 percent coverage in mass campaigns, the probability of revaccination in two sequential annual campaigns would be 64 percent (80 percent x 80 percent) at best.

The T1/44 vaccine is associated with significant levels of post-vaccinal reactions and some Africa breeds are exquisitely sensitive. Post-vaccinal mortality has reached as high as 30 percent. In certain breeds around the Great Lakes region, vaccination is categorically contra-indicated. It has been said that reactions result from poor technique; however, the severity of reactions observed is not experienced with other common veterinary vaccines used under similar circumstances.

Control by vaccination alone is difficult due to the low efficacy of the vaccine and the resistance of livestock owners in areas where post-vaccinal reactions have been experienced. Interest in vaccine research continues, but as yet no vaccine candidate has successfully passed the proof of concept stage.

Epidemiological analyses of the impact of available vaccines in the absence of strict movement control indicate that even well-applied annual mass vaccination programmes are unlikely to eradicate CBPP. Even at the level of individual large herds, well-managed vaccination alone is not a reliable approach to elimination of CBPP (Mariner *et al.*, 2006). Certainly, this finding agrees with the current outcomes in the field with existing vaccination practice.

## DIAGNOSTICS

CBPP serology-based diagnosis is challenging. The half-life of antibodies to CBPP vaccination and active infection are measured in weeks. Infection in protected sites such as sequestra often does not sustain an antibody response. There is no serological test that can adequately detect all forms of infection. All tests have low sensitivity for infected sequestra (~70 percent). In the past, conventional wisdom maintained that infected sequestra were

an important reservoir and source of infection, but modern evidence-based methods have failed to demonstrate a link between sequestered infection and disease outbreaks. Future efforts in diagnostic test development should focus on detection of the epidemiologically significant stages of the disease associated with transmission.

The two principle methods for CBPP serology are the CFT and the competitive enzyme-linked immunosorbent assay (ELISA). The sensitivity of these two tests for established active clinical infection has been stated to be quite high, on the order of 98 percent. The specificity of the tests is high, probably greater than 99 percent. There are problems with the detection of early cases and animals that are recovering yet still infected.

Polymerase chain reaction (PCR) methods have enhanced the ability to diagnose field cases and determine the source of infection. Moving forward, PCR should help to demystify some of the epidemiological uncertainties concerning the origin of CBPP outbreaks.

Candidate pen-side diagnostics do appear to be in the pipeline and these should facilitate control programmes. The candidate tests are expected to have performance statistics similar to current laboratory technologies, as the antigens being examined are similar. It is interesting to note that the field version of the CFT, which fell into disuse due to the resources, skills and attention to detail required for its operation, was one of the technologies that enabled progress against CBPP during the 1960s.

Better diagnostics, particularly field diagnostics, would enable more effective control.

## **SURVEILLANCE**

The principal available methods for surveillance are:

- Abattoir surveillance;
- Serosurveillance with the competitive ELISA or CFT; and
- Participatory surveillance.

Abattoir surveillance consists of inspection for classic lesions of CBPP. In endemic areas, visual inspection and reporting of suspect lesions is sufficient. In disease-free areas or areas under active control, laboratory support for isolation or PCR is appropriate to confirm rare cases. Selective marketing of sick animals biases abattoir surveillance. Where pricing or regulatory practices would discourage presentation of suspect animals, abattoir surveillance would underestimate prevalence. In other cases, conditions may drive owners to sell suspect animals and CBPP would be over-represented in the slaughterhouse population.

Serosurveillance using either the ELISA or CFT can be appropriate for specific purposes. As these tests primarily detect infection, sample sizes need to be calculated accordingly. It is often said that prevalence estimates are needed to assess impact. However, prevalence depends on the duration of the infective period. Ongoing infection with lingering mild strains may result in higher herd prevalence than severe strains that cause more fatal illness of short duration. Thus, the level of prevalence can be inversely related to mortality rates and impact. If the goal is to assess impact, then it is best to directly measure outcome variables such as mortality and livelihood effects.

Participatory surveillance has been used widely to study CBPP and to characterize the impact of CBPP within the context of the range of disease that affects livestock (Catley *et al.*, 2002; Bett *et al.*, 2009; Onono *et al.*, 2013). Generally, communities in East Africa have clinical terms for CBPP, are aware of the epidemiology of the disease, and can describe how

the disease affects their well-being. Considerable insight on the CBPP situation, current practices and information for designing successful control programmes can be gained using participatory surveillance.

## TREATMENT

Historically, treatment was a popular practice that was discouraged by authorities, as it was purported to favour sequestra formation and contribute to persistence of CBPP in the populations. These opinions were strongly expressed by Orue *et al.*, which may have been the source of the controversy (Orue and Memery, 1961). The belief that antibiotics contributed to sequestra formation became part of the conventional wisdom regarding CBPP control. However, evidence-based reviews of the literature have failed to identify data that support this opinion. Sequestra formation is part of the normal healing process in CBPP, and sequestra are found in a high percentage of all animals that recover. Further, animals with sequestra have never been shown to be a source of outbreaks, and attempts to reactivate sequestra and induce shedding have not been successful (Windsor *et al.*, 1977).

There are several early papers that demonstrate a positive impact for antibiotics and some interesting information on the corporal distribution of infection post-treatment. In a series of evaluations, it was reported that Novarsenobensol resulted in marked to complete clinical improvement and a reduction in mortality in cases of CBPP. Autopsy and culture results noted the presence of classic lesions of CBPP and mycoplasma up to six months after treatment. Non-treated control groups were not included for comparison, and it is not possible to know if these observations represented an increase or decrease in lingering lesions and infection. Hudson and Etheridge found that tylosin resulted in clinical improvement and eliminated bacteremia, but did not clear infection from necrotic tissue (Hudson *et al.*, 1965). Camara evaluated four antibiotics in the treatment of CBPP and found that three (bronchocilline, aureomycine and sanclomycine) were safe and resulted in high rates of cure (Camara, 1971). He concluded that treatment of ill animals was an appropriate intervention to compliment vaccination.

In recent years, there have been several *in vitro* and *in vivo* studies examining drug sensitivities and the efficacy of antibiotic treatment on the clinical response and impact of treatment on shedding and transmission. At least three of the *in vivo* publications evaluated treatment with long-acting oxytetracycline, which is a mycoplasmastatic antibiotic. The long-acting oxytetracycline studies found higher survival rates and lower rates of sequestration formation (Yaya *et al.*, 2003; Niang *et al.*, 2006; Niang *et al.*, 2010). In one experiment, there was no transmission from treated animals to in-contact controls.

A study with danofloxacin found a statistically significant reduction in transmission to in-contact controls but found no significant difference between treated animals and controls in terms of clinical course or lesion formation (Huebschle *et al.*, 2006). In a subsequent application of danofloxacin to control a field outbreak (Nicholas *et al.*, 2007), suppression of the outbreak with substantial reduction in clinical symptoms, mortality, seroprevalence and severity of lesions was noted.

All *in vivo* reports note that antibiotics resulted in clinical improvement and improved survival rates, except the controlled trial with danofloxacin. Current and historic evidence indicates that treatment discourages the severity of chronic lesions and circulating infec-

tion. The suppressive effect of treatment on the presence of mycoplasma organisms in circulation and peripheral tissues could explain the suppression of transmission in the danofloxacin and long-acting oxytetracycline studies.

Building on the summary of Niang *et al.* (Niang, 2015), *in vivo* work with antibiotics (long-acting oxytetracycline and danofloxacin) has shown:

- Important reductions in the severity of clinical disease and increases in recovery rates;
- Reductions in the rate of sequestra formation;
- Incomplete or delayed clearance of infection;
- Suppression of bacteremia; and
- Reductions in the rate of transmission.

Recent *in vitro* studies have looked at third-generation macrolides such as tulathromycin (Mitchell *et al.*, 2012) and gamithromycin (Mitchell *et al.*, 2013) used in the treatment of bovine respiratory disease due to agents such as *Mycoplasma bovis*, *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*. One interesting finding was that addition of biological factors, such as serum, potentiated the effects of some antibiotics and decreased the impact of others. For example, the minimum inhibitory concentration for tulathromycin was 330-fold lower in serum than in media (Mitchell *et al.*, 2013). This suggests that *in vitro* studies can be misleading and that emphasis should be placed on funding *in vivo* evaluations.

One current regulatory gap is the importation of oxytetracyclines in a wide range of concentrations (3 percent or less, to 20 percent). This situation makes it extremely difficult to provide appropriate guidance to livestock owners on correct dosages and timing of administration and leads to under-dosing. Importation for ruminant applications should be restricted to 10 percent and 20 percent formulations and require distinctive labelling that facilitates easy recognition in local markets.

Research sponsored by GALVmed has examined the efficacy of these third-generation macrolides (tulathromycin and gamithromycin) and oxytetracycline in live cattle. They found that the three antibiotics reduced lung lesion scores by 80 to 90 percent in animals infected with the Afade strain of MmmSC. In the case of the Afade strain, infection rates were controls, tulathromycin, gamithromycin and oxytetracycline treated animals were 92.3, 7.7, 15.4 and 42.9 percent, respectively. The reduction in infection rates was statistically significant for all three treatment groups. In animals infected with the Caprivi strain of MmmSC, treatment with tulathromycin or gamithromycin resulted in a 100 percent reduction in lung lesions scores, whereas oxytetracycline caused a 77.5 percent reduction in scores. This is solid evidence that treatment with standard antibiotics recommended for cattle pneumonias in developed countries clears CBPP infection.

Transmission to sentinels placed in contact with non-treated control groups and third-generation macrolide- and oxytetracycline-treated groups demonstrated that treatment reduced transmission to levels consistent with elimination of infection. Modelling studies indicated that programmes to detect and treat clinical cases with third-generation macrolides could eliminate infection from a community population within six months (Mariner *et al.*, 2018).

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Contagious bovine pleuropneumonia (CBPP) is an insidious disease that lingers in herds, causing significant morbidity and mortality. The policies to address the control and management of CBPP are in disarray at both the national and international levels. There has not been significant improvement in the efficacies of available vaccines or diagnostic assays for several decades. Classic strategies of mass vaccination and strict movement control that once were perceived as successful in rolling back the disease have largely fallen due to high costs, concerns of declining impact and growing public resistance. Officially, treatment with antibiotics is discouraged or prohibited, yet their use is widespread. CBPP is by all means an enigmatic disease, whose control probably requires a new paradigm or out-of-the-box thinking and executing approach. The purpose of this document is to provide an evidence-based policy for the implementation of sound control of CBPP by all stakeholders at all levels – global, regional and national. It describes a road map to CBPP control that is cognizant of the situation on the ground. While not being prescriptive, the document includes examples of combinations of interventions and control measures that should offer the opportunity to improve impact and hence offer better livelihoods to livestock producers.

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