Contagious Bovine Pleuro Pneumonia

Control Tools

Diagnostics availability

Commercial diagnostic kits available worldwide

Yes, but kits for c-ELISA. Complement Fixation Test (CFT) for use in main laboratories slowly getting into disuse due to logistic challenges and variable results. Commercial diagnostic kits (c-ELISA kits) are available from different manufacturers.

GAP: Development of a pen-side test could facilitate diagnostics for CBPP outside main laboratories.

Commercial diagnostic kits available in Europe

Yes. See Section “Commercial Diagnostic kits available worldwide”.

Diagnostic kits validated by International, European or National Standards

Diagnostic kits have been validated by CIRAD/EMVT (Reference: OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals).

Diagnostic method(s) described by International, European or National standards

Routine methods are described in the OIE Manual of diagnostic tests and vaccines such as:

- Complement fixation (a test suitable for determining freedom from disease and a prescribed test for international trade)
- Competitive enzyme-linked immunosorbent assay (a prescribed test for international trade)
- Immunoblotting test.

Commercial potential for diagnostic kits in Europe

Limited market especially as CBPP is not present in Europe.

DIVA tests required and/or available

Required in Africa to enable differentiation of vaccinated cattle from infected cattle.

GAP: DIVA technology a critical gap in CBPP prevention and control tools.

Opportunities for new developments

The CF test and ELISAs can be used in screening and eradication programmes, but the highly specific Immunoblotting (IB) test should be used as a confirmatory test. However, the IB test is not fit for mass screening and may be difficult to standardise in countries with marginal laboratory facilities so IB testing should be performed in a reference laboratory.

The c-ELISA is easy to use and regarded as highly practical under the prevailing laboratory conditions. The test appears to be robust and can be used on hemolysed or "anti-complementary" sera.

The CFT performs well provided that the laboratories use it on a regular basis. Problems were encountered in the availability of reagents. At present there is no single source of reagents. The repeatability and reproducibility of the CFT is affected by the
differences in quality of the antigen and the combination of the reagents used.

A rapid latex agglutination test (LAT), which gives results in less than two minutes, using sera or whole blood, has been developed for screening cattle in the field.

PCR methodology is also used to confirm outbreaks of CBPP.

GAP:
Both CFT and c-ELISA highly specific and sensitive in detecting CBPP infection in acutely infected cattle. Detection of chronically infected cattle is weak especially with CFT.

Vaccines availability

Commercial vaccines availability (globally)
Commercially available. Attenuated T1/44 vaccines produced in Africa by a number of institutes such as the KARI veterinary vaccines production centre-Kenya, Botswana vaccine institute, national Veterinary Research institute Nigeria, Onderstepoort biological Products and the National Veterinary Institute-Ethiopia.

Commercial vaccines authorised in Europe
None.

Marker vaccines available worldwide
None.

Marker vaccines authorised in Europe
None.

Effectiveness of vaccines / Main shortcomings of current vaccines

Strain T1/44 confers protection for approximately 1 year (21), but the protection conferred by the T1sr strain may only be 6 months long. Serological conversion (CF test) takes place in some animals. The antibodies disappear 3 months after vaccination.

Current vaccines are only stable for a few hours at ambient temperatures. Freeze-dried vaccine must be stored at −20°C and at this temperature its storage life is more than 1 year. Viability may even be conserved for many years without loss of titre allowing for the constitution of emergency stocks.

Intense reactions may appear when infected animals are vaccinated, as occurred recently following emergency vaccination campaigns in East Africa. These reactions usually occur within 2–3 days. Local reactions may also appear at the site of injection after 2–3 weeks with strain T1/44 in some animals. These reactions consist of an invading oedema that leads to death if antibiotic treatment, such as tetracycline is not given. (Use of antibiotics in CBPP infection is not permitted by the OIE or FAO.

Commercial potential for vaccines in Europe
Commercial potential exists in African countries where the disease is endemic. Limited potential in Europe.

Regulatory and/or policy challenges to approval
No major problems apart from providing data to obtain the marketing authorisation.

Commercial feasibility (e.g manufacturing)
Possible.
Opportunity for barrier protection

Not applicable as barrier protection is less effective than control of cattle movements.

Opportunity for new developments

The sequence of the complete genome of the reference strain PG1 has been published. Further technical development will allow for a finer characterisation of strains.

Multi-locus sequence analysis of *Mycoplasma mycoides* subsp. *mycoides* identifies 3 main lineages that correlate with the geographical origins (Europe, Southern Africa, rest of Africa). It may be possible to produce modified live vaccines using various antigenic components from the *Mycoplasma mycoides* subsp. *mycoides*.

Pharmaceutical availability

Current therapy (curative and preventive)

Antibiotics used for treatment and trials have been conducted in some African countries.

Future therapy

Improved and more effective anti mycoplasma drugs may be developed.

GAPS:

- Most tests on antibiotic efficacy on MmmSC done in vitro.
- Needs more *in vivo* studies, but cost implications too high. The absence of an experimental animal model for CBPP disease a critical limiting factor.

Commercial potential for pharmaceuticals in Europe

Antibiotics which reduce the effect of disease and prevent the carrier status may become interesting.

Regulatory and/or policy challenges to approval

No major problems apart from providing data to obtain the marketing authorisation.

Commercial feasibility (e.g manufacturing)

Possible.

Opportunities for new developments

Antibiotics or specific anti-mycoplasma compounds may offer tools for the control of CBPP.

New developments for diagnostic tests

Requirements for diagnostics development

New tests are being developed with a need for improved sensitivity, specificity, reproducibility, robustness, low cost and ease of use in difficult environments. Tests to detect chronic infection and carrier animals are important requirement.

There is a need for a sensitive screening test such as ELISA to be applied for CBPP diagnosis. However, both standardised antigens and reference sera need urgently to be developed.

The CFT and cELISA are relatively expensive, slow (tests took 2-3 hours plus all the transport times/costs) and usually need to be conducted in a laboratory. New tests which are inexpensive, easy to operate and pen side in nature, are required for use in Africa. These tests need high sensitivity and specificity. The sensitivity of the Latex Agglutination test was comparable to the
internationally recognised CFT but is far simpler and more rapid to perform. This test may have great potential in parts of Africa where there are great distances between the outbreaks, usually in nomadic herds, and diagnostic laboratories enabling control measures to be implemented rapidly.

**Time to develop new or improved diagnostics**

Time and cost depend on the type of test. Several years will elapse from the time the test is developed until the time it is available for field use. Even longer for the test to become commercially available.

**Cost of developing new or improved diagnostics and their validation**

Developing a new test is costly and subsequent validation adds to that cost.

**Research requirements for new or improved diagnostics**

Pen-side tests capable of giving an instant diagnosis of the infectious state of an animal were identified as a research priority by a CBPP Expert group.

**New developments for vaccines**

**Requirements for vaccines development / main characteristics for improved vaccines**

A safer, more effective and better characterised vaccine is needed to allow more effective disease control strategies to be implemented.

The development and validation of new types of vaccines composed either of adjuvanted, subunit preparations of defined antigens or live, attenuated mutants created by specific knockout of virulence genes.

**Time to develop new or improved vaccines**

5-10 years for development, clinical trials and licensing is probable.

**Cost of developing new or improved vaccines and their validation**

Very expensive especially if based on modern molecular techniques. Cost amplified by the fact that there is no experimental model for CBPP as such, live cattle must be used in vaccine research studies. This is very expensive to carry out.

**Research requirements for new or improved vaccines**

The mechanisms involved in the invading process after the first contact of mycoplasmas with host cells are unknown. In depth study of immunopathology will not only facilitate the development of new diagnostic tests, but at the same time will yield useful information for vaccine development.

To study the immunopathology of CBPP and to elucidate the pathogenic mechanisms by identifying the role of the microorganism and its immunogenic components in eliciting pro-inflammatory and inflammatory reactions. The cellular elements of inflammatory nature: macrophages, monocytes, lymphocytes, neutrophils that may liberate inflammatory products such as NO2, myeloperoxidases or cytokines need to be identified. Data on the T cell responses should form the scientific basis to the development of a safe vaccine conferring long lasting immune protection.

The route of administration for the vaccines might also affect immunity: an aerosol through the nose appears more effective than the current tail or subcutaneous injections.

**New developments for pharmaceuticals**

**Requirements for pharmaceuticals development**

Potential for use of antibiotics needs to be evaluated. Development of new anti- mycoplasma drugs could be considered.
Time to develop new or improved pharmaceuticals

5-10 years.

Cost of developing new or improved pharmaceuticals and their validation

High

Research requirements for new or improved pharmaceuticals

Review of potential mycoplasmacidal agents.

GAP: In vivo studies in cattle.

Disease details

Description and characteristics.

Pathogen

CBPP is caused by the bovine biotype of Mycoplasma mycoides subsp. Mycoides - a member of the family Mycoplasmataceae. According to the new taxonomy Mycoplasma mycoides subsp. mycoides Small Colony (MmmSc) was modified as Mycoplasma mycoides subsp. mycoides as approved by the OIE Scientific Committee.

Variability of the disease

There is only one antigenic type. Recent molecular techniques were able to identify differences among strains. M. mycoides (bovine) strains can be grouped into at least three major lineages, one containing isolates from Europe and the other two made up of isolates from Africa.

Stability of the agent/pathogen in the environment

M. mycoides subsp. mycoides is very sensitive to the environment with a short survival time outside the host.

- Temperature: In saline solution susceptible to 45°C/120 min and or 47°C/2 min. In lymph susceptible to 45°C/240 min and/or 60°C/2 min.
- Inactivated by acid and alkaline pH.
- Susceptible to ether, mercuric chloride (0.01%), calcium hydroxide, phenol (1%/3 min), and formaldehyde solution (0.5%/30 seconds).
- Survives well in frozen tissues.

Species involved

Animal infected/carrier/disease

Cattle (Bos taurus), zebu (Bos indicus) are the main hosts for M. mycoides SC (bovine). Infections have also been reported in Asian buffalo (Bubalus bubalis), captive bison (Bison bison) and yak (Poephagus grunnien, formerly Bos grunnien). Wild bovids and camels are resistant. Sheep can be infected experimentally with a bovine strain of M. mycoides, subsp. mycoides as well as with ovine strains.

Human infected/disease

No.

Vector cyclical/non-cyclical

None.
Reservoir (animal, environmental)

Infected cattle are the main reservoir. Wild animals (ruminants do not play a role in the epidemiology of the disease.

Description of infection & disease in natural hosts

Transmissibility

Inhalation. *M. mycoides* subsp. *mycoides* is mainly transmitted from animal to animal in aerosols. This organism also occurs in saliva, urine, fetal membranes and uterine discharges. There is no evidence of transmission through fomites as the organism does not persist in the environment.

Pathogenic life cycle stages

Not applicable.

Signs/Morbidity

Infected animals can have peracute, acute, subacute or chronic disease. Subclinical infections also occur.

The main signs of the disease are fever and coughing with signs of chest pain. Some affected animals may lose a lot of weight and die. Others may appear to recover but continue to spread the disease to other animals in the herd. Many cattle that survive remain chronic carriers.

**GAP:** The role played by chronic carriers (lungers) is still an unclarified issue and remains a major scientific gap in the spread of the disease.

Incubation period

Incubation period is 1-6 months (sometimes longer).

Mortality

The mortality rate may be as high as 70%. When an outbreak first occurs in an area, the mortality rate will be high but is often lower in the field following the primary outbreak. Generally 10 to 70% depending on the condition of affected animals.

Shedding kinetic patterns

Carrier cattle may shed Mycoplasma intermittently possibly related to stress and breakdown of sequestrum although this is questioned and has not been proved conclusively.

**GAP:** Shedding kinetic patterns are a gap that needs further investigation.

Mechanism of pathogenicity

Little is known about the pathogenic mechanisms of CBPP. It has been suggested that autoimmune and hypersensitive reactions are essential in the development of pathological lesions. The immunological mechanism involved during infection and ability of the pathogen to evade the immune system, must also be elucidated. This lack of knowledge has consequences for diagnostic tests, for assessing immune response and for developing an appropriate vaccine.

**GAP:** The pathogenic mechanism of Mmm still remains a critical gap in knowledge. Production of hydrogen peroxide at tissue level and its cytotoxic effects are yet to be elucidated. It is known that certain strains of Mmm organisms have different capsular contents. Whether this is related to the levels of antibody production and ability to resist infection and hence pathogenicity, are not known. Attachment organelles as have been described for other mycoplasmas such as *M. pulmonis* not yet identified for MmmSC. It is important that the pathogenic mechanisms of CBPP disease be given the highest priority in terms of research activities, so as to underpin the development of vaccines and diagnostic tools.
Zoonotic potential

Reported incidence in humans
Not recorded in humans and does not infect humans.

Estimated level of under-reporting in humans

Risk of occurrence in humans, populations at risk, specific risk factors
Humans are not susceptible to Mycoplasma mycoides subsp. mycoides.

Symptoms described in humans
Not applicable.

Likelihood of spread in humans
Not applicable.

Impact on animal welfare and biodiversity

Both disease and prevention/control measures related
Clinical CBPP is a severe welfare problem. Both Bos indicus and Bos taurus are equally affected, with significant biodiversity implications.

GAP: Reports indicate that B. taurus and crosses more susceptible to post-vaccinal skin reactions. Possible genetic predisposition?

Endangered wild species affected or not (estimation for Europe / worldwide)
No.

Slaughter necessity according to EU rules or other regions
Yes: infected herds if in a CBPP-free country. Has strong implications for the loss of valuable animal genetic resources.

Geographical distribution and spread

Current occurrence/distribution
CBPP is widespread in Africa (south of the Sahara) except in the Republic of South Africa, Swaziland, Botswana and southern Namibia. The disease is also suspected to be present in other regions of the world, including the Middle East and parts of Asia although the situation in Asia is unclear. There have been no reported outbreaks of CBPP in Europe since 1999.

GAP: Presence of CBPP in Middle Eastern countries requires verification. In parts of Asia, similarities in both clinical signs of CBPP and Haemorrhagic Septicaemia which is highly prevalent in some Asian countries may be confused with CBPP, if bacteriologic isolation of Mmm and PCR techniques are not employed to determine the cause(s) of pulmonary pathology.

Epizootic/endemic - if epidemic frequency of outbreaks
The disease is endemic in parts of Africa. Mostly a problem of nomadic areas and large ranches where there is close contact between large groups of animals especially at grazing and watering points.
Seasonal cycle (seasonality)

Only based on rainfall and availability of food. CBPP is a disease of cattle movement.

**GAP:** Seasonality of outbreaks is not clearly defined since in countries where the disease occurs; there are two basic seasons - wet and dry seasons. However, the paucity of official CBPP disease reporting to international organizations (OIE, FAO, AU-IBAR) makes the definition of this aspect of CBPP epidemiology weak.

Speed of spatial spread during an outbreak

Rapid spread of disease in drought conditions with increased movement of animals in search of food.

Transboundary potential of the disease

High where unrestricted movements occur. A particular problem in times of drought, war or civil unrest.

Seasonal cycle linked to climate

No.

**GAP:** Little or no information available.

Distribution of disease or vector linked to climate

No.

Outbreaks linked to extreme weather

No.

Sensitivity of disease or vectors to the effects of climate change (environmental changes/land use)

Yes, indirectly based on feed and water available for cattle.

Route of Transmission

**Usual mode of transmission (introduction, means of spread)**

Aerosol, mostly by direct contact; droplets emitted by coughing animals, saliva, and urine. Transmission up to several kilometres has been suspected under favourable climatic conditions. Inapparent carriers are a major source of infection. Possible breakdown of sequestra.

**GAP:** Breakdown of sequestra in the transmission of CBPP in experimental studies have shown that transmission does not occur by this route. However, studies need to be extended to the field.

**Occasional mode of transmission**

Transplacental infection can occur.

**Conditions that favour spread**

Cattle movement is important in the spread of the disease.

**Detection and Immune response to infection**


Mechanism of host response

Complex host response which is not fully understood involving humoral and cellular immune responses.

**GAPS:**
- The pathogenic mechanisms of CBPP for understanding the immune response and development of vaccines and diagnostic tools.
- The role of IgA immune response in CBPP.

Immunological basis of diagnosis

Antibodies against *Mycoplasma mycoides* subsp. *mycoides* are used for diagnosis.

Main means of prevention, detection and control

Sanitary measures

- Strict import policy
- Effective disease notification and disease reporting
- Effective surveillance – clinical in acute cases; abattoir/slaughter house inspection of lungs; and serological tests

In free areas control is based on early detection of outbreaks, control of animal movements and a stamping-out. Control of cattle movements is the most efficient way of limiting the spread of CBPP, but a very difficult proposition.

Mechanical and biological control

In disease-free areas: quarantine, serological tests (complement fixation and c-ELISA) and slaughtering of all animals of the herd in which positive animals have been found. Detailed epidemiological investigations.

In endemic areas diagnosis and vaccination with movement controls and slaughter of infected animals.

Diagnostic tools

Identification of the agent

- Isolation of pathogen and identification by metabolic and growth inhibition tests
- Indirect fluorescent antibody test
- Fluorescent antibody tests
- Agar gel immunodiffusion test
- Dot immunobinding on membrane filtration
- Polymerase chain reaction

Serological tests

- Slide agglutination test can be used as pen-side test in active outbreaks at the herd level. However non-specific agglutination reactions occur in the field due to dust and low humidity. Test could be conducted preferably in a tent.
- ELISA can be used to process large series of sera during screening campaigns.

**GAP:** Development of an effective pen-side test capable of detecting both acute and chronic infections is a critical gap in diagnostic tools for live animals.

Vaccines

In Africa control of the disease is based on vaccination campaigns using attenuated strains such as T1/44 and T1/SR. Current vaccines, which are freeze-dried live and attenuated, are unstable and cause post-vaccinal reactions in some animals. Consistent application of CBPP vaccines has been known to reduce the prevalence of CBPP to low levels in some countries.

**GAP:** There is a strong scientific debate regarding


- Development of a new generation of potent CBPP vaccines/subunits or
- Improvements in the current vaccines with regards to the biology of the vaccine strains and/or adjuvants and pH adjustments. Sometimes, tissue reactions have been related to faulty injection techniques - e.g. intramuscular instead of subcutaneous injection and contaminated injection equipment and diluents.

**Therapeutics**

Cattle owners often use antibiotic treatments and are reluctant to declare the disease. No therapeutic treatment is effective; however, farmers resort to heavy antimicrobial treatment in an attempt to reduce disease damage and mortality rates. Recent work has shown that antibiotic treatment of cattle may greatly reduce the transmission to healthy contacts but this requires treatment of all affected cattle in a group.

**GAP:** Demonstration of efficacy of commonly available antibiotic treatment *in vivo*, can facilitate the consideration of the official policy of non-use of antibiotic therapy in CBPP disease.

**Biosecurity measures effective as a preventive measure**

A quarantine period before new cattle are introduced to a farm is important for disease prevention.

**Border/trade/movement control sufficient for control**

Import of live animals prohibited from endemic areas/countries. Movement controls imposed in case of outbreaks. Serological tests in exporting countries e.g. CFT.

**Prevention tools**

- Controls on imports of live susceptible species
- Movement controls.

**GAP:** Serological tools for early detection including e.g. a Pen-side test that is specific and sensitive.

**Surveillance**

Surveillance of infected zones and surrounding areas

Surveillance to demonstrate freedom for CBPP for countries with eradication programmes.

**Past experiences on success (and failures) of prevention, control, eradication in regions outside Europe**

Successfully eradicated from Europe and other parts of the world. Less success in Africa with the spread of disease over the past 20 years. This is mainly due to uncontrolled animal movements, lack of enforcement and reduced vaccination in some areas.

**Costs of above measures**

Difficult to assess due to incomplete reporting.

**Disease information from the OIE**

**Disease notifiable to the OIE**

Yes. CBPP was recorded in 19 African countries in 2014 (AU-IBAR Annual Year Book -2014). The outbreaks were experienced mostly in West and Eastern Africa. In some cases only infection was reported and in others clinical disease. CBPP is restricted to specific regions in some countries e.g. Namibia.

**GAP:** Effective diagnostic tools especially isolation of organism and application of currently available serological tests.
CBPP is currently one of the most serious diseases of cattle in Africa, causing estimated losses of over US$ 2 billion per annum through loss of animals, reduced production of meat and milk.

Direct impact (a) on production

CBPP is currently one of the most serious diseases of cattle in Africa, causing estimated losses of over US$ 2 billion per annum through loss of animals, reduced production of meat and milk.

Direct impact (b) cost of private and public control measures

The cost of national veterinary programmes against CBPP including costs serological tests, vaccination and depopulation where carried out.

Indirect impact

High economic, social impact in countries with a high incidence. CBPP infected cattle have indirect effects on human activities, e.g. ploughing for crop agriculture, traction of farm produce, reduction in milk production and meat production etc. Cattle used for several social occasions such as marriages may be lost through outbreaks of the disease. Other indirect impact include:

- Loss of exports
- Disruption to development of cattle industry in African countries especially where animals need to be moved from production areas for further fattening.
- Impact on food supply with loss of cattle.

Trade implications

Impact on international trade/exports from the EU due to existing regulations

Trade in live cattle prohibited from endemic areas.

Impact on EU intra-community trade due to existing EU regulations

Movements restricted from infected areas and zones.
Impact on national trade due to existing regulations

Severe restrictions on movements related to the protection and surveillance zones.

Main perceived obstacles for effective prevention and control

Difficulties in identifying carrier and sub clinically infected cattle. In Africa inability to enforce movement controls for a variety of reasons. Inadequate vaccine potency. Poor diagnostic facilities. Financial constraints and lack of compensation for slaughter of whole infected herds.

GAP: Critical gap is the development of a pen-side test in live animals to support the use of other ancillary actions in CBPP prevention and control.

Main perceived facilitators for effective prevention and control


Risk

Potential movement of infected cattle poses a risk to countries in Africa which border non-infected countries.

Main critical gaps

Conclusion

There is a need for further research on CBPP, especially with regard to the establishment of infection (pathogenicity factors, immunopathology, virulence factors, genomics) and the persistence of infection in chronically affected animals (e.g. reservoirs). The search for new diagnostic tests with high sensitivity and high specificity should be continued as should the objective of developing safe and efficacious vaccines.

Sources of information

Name of expert group leader

Names of expert group members are included where permission has been given.

William Amanfu, consultant (ex-FAO), Ghana [Leader]

Name of reviewers

Project Management Board

Date of submission by expert group

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