Chlamydioidosis (C. Abortus)

Control Tools

Diagnostics availability

Commercial diagnostic kits available worldwide

A number of commercially available tests exist for the detection of antibodies by ELISA (also see 9.3). These include MVD-Enfer Chlamydia abortus ELISA (MVDiagnostics Ltd, Edinburgh, UK; Enfer Scientific, Naas, Co.Kildare, Ireland), CHEKIT Chlamydia Antibody Test (Idexx, Hoofddorp, The Netherlands) and ID Screen Chlamydophila abortus Indirect Multi-Species (ID Vet, France). A number of other tests are also available for the detection of genus level antigens by ELISA and using fluorescent antibodies.

GAPS:

- New tests are required for detection of latently infected animals
- Tests to detect infection at point of care on farm are required
- Multi-pathogen tests to detect infection due to the most common pathogens causing reproductive loss are required
- Commercial tests to distinguish natural infection in vaccinated flocks/herds should be developed (DIVA tests)

Commercial diagnostic kits available in Europe

See Section "Commercial diagnostic kits available worldwide".

Diagnostic kits validated by International, European or National Standards

Generally not.

GAPS:

- Test comparisons have been frequently reported in the literature, but large scale inter-laboratory comparisons are required to properly validate these tests. A big part of the problem, particularly for bovine infections is the lack of available known and validated positive and negative samples.
- Some of the commercial serological tests claim that they are valid for use with cattle, but have not been validated for such use due to a lack of known and properly validated standardised serum samples.
- Some of the commercial serological tests claim to be specific for detecting C. abortus when they are known to cross react with other chlamydial species, thus causing issues with regard to the detection of true positives.
- European wide collections of standardised validated serum of known origin should be agreed and used in large scale inter-laboratory trials to properly validate commercial tests.

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

Routine methods are described in the OIE Manual of Diagnostic Tests and Vaccines: Chapter 2.7.7 Enzootic abortion of ewes (ovine chlamydiosis) [Last updated May 2012 – see section 23]

1. Identification of the agent.

a) Staining of smears of placental cotyledons, fetal stomach contents.

b) Antigen detection ELISAs

c) PCR and real time PCR of placental and swab samples, and/or fetal tissues/organs

d) Isolation of C.abortus in embryonated chicken eggs or in tissue culture
e) ArrayTube platform

f) Immunohistochemistry

2. Serology

a) Complement Fixation Test

b) ELISA

**GAPS:**

- The CFT should be replaced as the internationally recognised diagnostic standard with a more sensitive and specific serological test
- Need better agreement and standardisation between National Reference and other testing laboratories on the procedures and methodologies used for the routine diagnosis of C. abortus.

**Commercial potential for diagnostic kits in Europe**

As disease is endemic in Europe and throughout the world, the potential for commercial development of kits is clear.

**DIVA tests required and/or available**

None of the existing serological tests can differentiate antibodies resulting from a natural infection and those induced by vaccination.

Two molecular methods (PCR-RFLP and High Resolution Melt PCR) have been developed for the differential detection of the live attenuated vaccine strain and natural wild-type isolates (differentiation of naturally infected from vaccinated animals, DIVA) based on single nucleotide polymorphisms.

**GAPS:**

- Serological tests to detect a natural infection in vaccinated flocks/herds should be developed (DIVA tests), validated through inter laboratory trials and commercialised
- A molecular DIVA test should be validated in inter-laboratory trials and commercialised.

**Opportunities for new developments**

Validation of developed tests to identify infected animals and distinguish vaccinated from naturally infected animals (DIVA). Comparison and evaluation of existing diagnostic tests on a pan-European scale.

**GAPS:**

Development of a test capable of indicating those infected pregnant ewes that are likely to progress to abortion, these animals could then be targeted for prophylactic antibiotic therapy.

**Vaccines availability**

**Commercial vaccines availability (globally)**

Both killed and live vaccines are available, although the live vaccines are not available in all countries. See also Section "Main means of prevention, detection and control - Vaccines".

**Commercial vaccines authorised in Europe**

Yes.

**Marker vaccines available worldwide**
No, although molecular markers have been identified for 1B vaccines.

**GAPS:**

This is one of the main aims in developing next generation vaccines.

**Marker vaccines authorised in Europe**

No.

**Effectiveness of vaccines / Main shortcomings of current vaccines**

- The incidence and severity of abortions in ruminants can be reduced by the use of vaccines but at present these do not confer complete protective immunity nor do they prevent shedding at parturition.
- The live vaccines have been implicated in causing abortion in some animals. However, on balance these vaccines do more good than harm and continue to be recommended until safer, effective vaccines are developed.
- The cost of vaccination is too expensive for many small and medium sized farmers.

**GAPS:**

- Requirement for new, safer, cheaper vaccines to be developed based on recombinant antigen and other technologies
- Development of a marker vaccine than can be coupled with a new diagnostic test to enable detection of natural infections in vaccinated flocks/herds
- Develop a transformation system that will enable the generation of novel vaccines based on genetically modified organisms

**Commercial potential for vaccines in Europe**

High, particularly in those countries with endemic problems and high density of susceptible species of ruminants. Pharmaceutical companies in some European countries are working with experts to design more effective inactivated vaccines.

**Regulatory and/or policy challenges to approval**

Use of genetically modified vaccines might be problematic in some countries. The field trials may need specific regulation regarding the release of GMOs into the environment.

**Commercial feasibility (e.g. manufacturing)**

Feasibility discussions are ongoing between scientific experts and some of the major animal health companies.

**Opportunity for barrier protection**

Currently used as part of a herd or flock control programme.

**Opportunity for new developments**

Development of next generation multi-component marker vaccines based on recombinant protein technology and other technologies that can be coupled with a serological test to differentially distinguish vaccinated from natural wild-type infected animals (DIVA).

**Pharmaceutical availability**
**Current therapy (curative and preventive)**

Long acting oxytetracycline is the antibiotic most commonly used. Although the drug is recommended to be given as a single dose to minimize any potential development of resistance, the aim of the treatment is to suppress multiplication of the organisms, therefore further doses are often given until lambing is completed.

**Future therapy**

Potential pharmaceuticals which will eliminate the organism in the latent and carrier state.

**GAP:**

Development of natural biocides and bacteriophages as therapeutics?

**Commercial potential for pharmaceuticals in Europe**

Depends on price and demand. If more effective vaccines and health schemes develop then there should not be a major demand for new pharmaceuticals. Vaccination should be favoured due to possibility of emerging antimicrobial resistance.

**Regulatory and/or policy challenges to approval**

No specific issues.

**Commercial feasibility (e.g manufacturing)**

Feasible if demand exists.

**Opportunities for new developments**

Opportunities to improve existing vaccines and develop next generation vaccines through a range of technological approaches (also see Section "Main means of prevention, detection and control").

**GAPS:**

- For live vaccines there is a need to study the impact that co-infections could have on vaccination with the live attenuated vaccines because of possible immunosuppression.
- Inactivated vaccines could be improved through the investigation of alternate novel adjuvants to improve the immune response.
- Development of next generation vaccines.

**New developments for diagnostic tests**

**Requirements for diagnostics development**

Validation of recently developed tests to identify latently infected animals and distinguish vaccinated from naturally infected animal (DIVA).

Comparison and evaluation of existing diagnostic tests on a pan-European scale.

Serological tests: Development of host species-specific serological tests.

Requirement for proper validated control sera in order to assess diagnostic tests and determine cut-offs for positivity.

**GAPS:**

- DIVA tests should be applicable for sheep, goats, cattle, and pigs.
Molecular methods to detect latent infection in the host should be explored, as previously described in in vitro studies.

### Time to develop new or improved diagnostics

In general the development of tests is much faster and less expensive than developing vaccines. From development through validation to commercial availability will be time consuming and can take years.

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

The development and validation of new tests is time consuming and labor intensive which is costly. Costs cannot be specified as they will depend on the nature of the test and the cost of producing reagents and supplying reading or processing machines if necessary. Once validated there will need to be a commercial company willing to market the test.

### Research requirements for new or improved diagnostics

Validation of recently developed tests to identify latently infected animals and distinguish vaccinated from naturally infected animal (DIVA).

Comparison and evaluation of existing diagnostic tests on a pan-European scale.

Serological tests: Development of host species-specific serological tests.

Requirement for proper validated control sera in order to assess diagnostic tests and determine cut-offs for positivity.

### Technology to determine virus freedom in animals

Currently the technology does not exist to identify the latent carrier. This is a real technological challenge as the site of latency is unknown and may be difficult to sample routinely in a live animal. Accreditation schemes do exist where animals are monitored on a yearly basis to determine on a flock/herd basis whether infection is present on farm. This works well although anomalies do arise which can create difficulties for the farmer. Experimental studies show that following entry of infection into an animal a rise in antibody titre does occur, however this subsides as the organism latently persists in the non-pregnant animal. Catching this rise would require constant monitoring, which is impractical, but on a flock/herd basis it may be more feasible.

**GAP:**

More robust serological based testing that will detect whether animals on a farm or flock/herd basis have become infected is needed as part of an accreditation scheme.

### New developments for vaccines

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

There is a requirement for safer, more stable, cheaper alternatives to the current vaccines. These will likely be based on recombinant protein technology, as multi-component subunit vaccines.

**GAP:**

Although various virulence associated antigens have been described for C. abortus, further research is needed to obtain a better understanding of the molecular mechanisms involved in infection, including the molecular functions behind the newly described ultrastructures in the organism’s developmental cycle. This may offer new perspectives for development of novel vaccine strategies as well as for diagnosis.

### Time to develop new or improved vaccines

This would depend on the technology being employed, the identification of suitable candidate antigens, adjuvants and appropriate routes of delivery. Generally, once all of these issues have been resolved a timescale of 5-10 years to conduct
efficacy and stability trials in pregnant animals, as well as licensing and marketing, would not be unreasonable.

Employment of reverse vaccinology approaches to vaccine development could save money, time and labour and therefore enable faster movement to the clinical trial stages.

**GAP:**

The big question is what do the Pharmaceutical companies want in their next generation products, taking into consideration what is actually feasible from a scientific perspective? Discussions are ongoing between some scientific experts and the companies on this issue.

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

This is difficult to quantify as it involves, in addition to the technological antigen discovery and proof of concept work, trials in pregnant sheep to determine efficacy, reduction of abortions, pathology and shedding. A single typical sheep vaccine trials costs in excess of €400,000 and takes over 9 months to complete. Following a series of such trials, safety field trials would need to be conducted in order to enable the product to be authorised. So costs in excess of €2M would not be unreasonable.

**Research requirements for new or improved vaccines**

Identification of relevant protective antigens, through genomic, bioinformatic, proteomic, immunological and biological approaches.

Novel adjuvants that promote an effective cellular immune response should be included in inactivated vaccine formulations together with a protective antigen.

Development of new approaches to vaccine development.

**New developments for pharmaceuticals**

**Requirements for pharmaceuticals development**

No specific requirement.

**Time to develop new or improved pharmaceuticals**

Time to develop would depend on the product and the trials necessary to validate efficacy and safety. Commercial production would then take further time. Five to 10 years is a realistic timeframe.

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

Expensive but difficult to assess as it will depend on the product and the trials necessary to validate and licence.

**Research requirements for new or improved pharmaceuticals**

No specific requirement.

**Disease details**

**Description and characteristics.**

**Pathogen**

*Chlamydia abortus* (formerly *Chlamydia psittaci* serotype-1 or *Chlamydophila abortus*) is an obligate intracellular Gram-negative
bacterium belonging to the family Chlamydiaceae. The family Chlamydiaceae has undergone further reclassification since 2011, and currently comprises the reunified genus Chlamydia (formerly Chlamydia and Chlamydophila) which is composed of 11 species in addition to C. abortus, including C. pecorum (affecting sheep, goats, cattle and pigs), C. suis (pigs) and C. psittaci (birds and poultry). Chlamydia abortus is one of the most common causes of infectious abortion in small ruminants (sheep and goats) throughout Europe. The organism can also infect other animal species, including cattle, horses and pigs. Chlamydia abortus is also zoonotic and poses a significant risk during pregnancy for both the unborn child and mother.

GAPS:

- Genetic diversity of the pathogen in different host species, in different geographical locations.
- Any evidence of recombination.
- Extent of co-infections with other chlamydial species and effect on disease pathogenesis.

Variability of the disease

The disease associated with C. abortus infection is variously known as ‘ovine enzootic abortion’, ‘enzootic abortion of ewes’ or ‘ovine chlamydiosis’. Host range includes sheep, goats and cattle. Farmed game, wild and zoo ruminants, and pigs, are also natural hosts. Sporadic infections have been described in the horse, mouse, guinea pig and rabbit. Chlamydia abortus infection can cause severe reproductive disease in all affected species worldwide. The pathogen can also result in spontaneous abortion or miscarriage if women are exposed to the organism during pregnancy and infection can also be fatal for the mother.

Sophisticated molecular typing tools, namely AFLP, MLVA, MLST and whole-genome specific SNPs analysis have allowed the differentiation of genotypes partly related to geographical origin, but not to host. To date a Greek LLG-variant type strain has been shown to be different (based on phenotypic, genotypic and pathotypic traits) from other C. abortus strains, even among strains circulating in the same area. This LLG-variant represents one distinct lineage evolving independently from other C. abortus strains, to such an extent that “subspecies” status has been suggested for it.

GAPS:

- Require greater information on strain and genotype diversity and how this relates to pathology.
- Only a proportion of an infected naïve flock will abort. Why do some animals appear resistant to infection and disease?
- Most research has been conducted on ovine disease. Need to determine the full host range and pathogenic potential in other domestic, farmed and wild animal species.
- Ruminants are commonly infected with C. pecorum, which complicates the diagnosis of C. abortus infection. C. pecorum infections of sheep are generally subclinical whereas C. abortus infections generally give rise to clinical disease. What is the genetic and mechanistic basis for these wide differences in pathogenicity?
- What factors underlie the geographic “specificity” of C. abortus genotypes?
- Determine whether the expansion of certain genotypes relate to some level of vaccine escape in countries where vaccination has been introduced.
- Determine population dynamics of C. abortus through genetic investigation of isolates collected locally over a long period.

Stability of the agent/pathogen in the environment

The organism is reported to be relatively stable in the environment and can survive for long periods (weeks to months) in freezing temperatures and for days during spring weather conditions.

GAPS:

- This requires further investigation due to limited published data and the importance of this question with regard to risks for transmission.
- Need to investigate the viability of the pathogen (survival and stability) in potential transmission vehicles (bedding, water troughs, water courses, pasture, soil, abortion material), as well as under different climatic conditions (temperature, humidity).

Species involved

Animal infected/carryer/disease

Chlamydia abortus is a cause of abortion, stillbirth and premature birth of weak offspring in all affected species. Among livestock, sheep and goats are more severely affected.

Infection is ‘silent’ or ‘latent’ in non-pregnant animals, with the first signs of any problem being the expulsion of a dead fetus generally 1-2 weeks prior to expected parturition. Higher rates of abortion occur in younger naïve animals. After abortion, ewes
and goats can remain persistently infected and be carriers of the organism for long periods.

**GAPS:**

- What is the role of wildlife (foxes, rabbits, rodents, wild ungulates etc) and birds ( carrion, game, etc) as carriers and/or reservoirs?
- Investigate and compare host susceptibility and its determining factors for *C. abortus* infection: sheep and goat (enzootic abortions) vs. cattle and pigs (sporadic abortion cases); goats more susceptible than sheep.
- Require further investigations to determine the site of latency or persistence.

**Human infected/disease**

Literature suggests that cases in humans are rare. However, infection can affect pregnant women resulting in spontaneous abortion or stillbirths depending on period of pregnancy when exposed. Such infections are most likely to result from direct or indirect exposure during the lambing or kidding season. There are also reports of respiratory illness in laboratory staff. Recently, one human case of pelvic inflammatory disease in a woman resulting from *C. abortus* infection has been published.

**GAPS:**

- It is unclear if cases of abortion or respiratory illness in humans are under reported. Further epidemiological evidence and seroprevalence data is required to determine the true extent of exposure in contact persons (e.g. shepherds, agricultural workers, veterinarians, laboratory staff) and links with abortion and respiratory illness.
- Epidemiological studies on human cases are needed to investigate if chronic infection with *C. abortus* may be involved in the pathogenesis of tubal infertility and chlamydial pelvic inflammatory disease similar to the human pathogen *C. trachoma*’s.
- Diagnostic tools that allow the rapid and reliable detection of *C. abortus* in human specimens are needed.

**Vector cyclical/non-cyclical**

Recent work reports the finding of *Chlamydiales* in ticks. It is not unreasonable to expect that *C. abortus* is carried at some level in ticks from infected flocks/herds, although there is no direct evidence for vector transmission (most likely mechanical transmission) of this disease. The role of ticks as vectors for transmission of *C. abortus* is considered to be negligible.

**GAPS:**

- Determine whether vectors such as ticks, mites or fleas are involved as vectors (mechanical or otherwise) for transmitting infection.

**Reservoir (animal, environmental)**

Asymptomatic carrier animals infected with *C. abortus* are the main reservoir of infection. Ewes can remain persistently infected after the initial abortion and limited evidence suggests they can excrete the organism and infect other naïve animals in a subsequent lambing/kidding season. *Chlamydia abortus* can persist in the environment for days to months, depending on weather conditions (temperature and humidity).

Transmission of *C. abortus* may occur between wild and domestic animals through sharing of grazing pastures.

The main sources of environmental contamination and transmission to susceptible animals are the aborting placentas, the fetuses and the vaginal discharges. Vaginal excretions have been shown to be infective for up to around 7-10 days post abortion/lambing. Weak or live lambs delivered from animals in which placental infection is lower grade, possibly play a role in the epidemiology of this disease. Aborting animals may shed the microorganism during the following per-ovulatory period and at subsequent lambing, although evidence is limited.

**GAPS:**

- Determine the site of latency/persistence of *C. abortus* in asymptomatic carrier animals (body/tissues site).
- The main period of transmission is believed to be lambing time. Transmission may also occur outside of this period but is poorly documented and quantified. Therefore, does excretion and transmission occur to any significant extent outside of the lambing period? Investigate other potential routes of excretion, such as faecal and ocular.
- In flocks that have experienced chlamydial abortion, it is common to find evidence of intermittent fecal shedding. Indeed intestinal infections have been observed, even in the absence of elevated abortion rates. This raise questions about the significance of this reservoir for animal and human health and underlines the necessity for further investigation and regular monitoring.
The main routes of transmission are through contact and ingestion of microorganisms shed with the aborted materials (vaginal fluids, dead fetuses, coats of weak and surviving lambs), as well as through inhalation of aerosols from the environment. There is also limited evidence of vertical transmission from mother to lamb, as well as transmission resulting from shedding in fecal material. Thus, horizontal transmission remains the greatest risk for other naive animals. Venereal transmission by males is not thought to play an important role in the spread of infection, although direct intra-vaginal infection of ewes has been demonstrated suggesting that it is possible, while infection of rams or semen failed to establish infection in ewes or result in abortion.

**GAPS:**
- Pathogen transmission and stability in the environment (bedding, soil, water, air) is currently unclear as well as role in the epidemiology of infection.
- Investigate other potential sources and routes of infection, for example artificial insemination, milk, colostrum.
- Further evidence for transmission through faeces.
- Further evidence for horizontal transmission of infection to lambs and disease outcome.
- Further evidence required of role of rams in transmission of infection from infected to naive ewes.

### Pathogenic life cycle stages

*Chlamydia abortus*, like other chlamydial species, undergoes a developmental cycle involving two developmental forms, the extracellular metabolically-inactive infectious form (elementary body or EB) and the intracellular metabolically active form (reticulate body or RB). Both forms play an important role in the pathogenesis of the organism. The EB attaches to the host cell, enters and differentiates to the RB within a chlamydial inclusion. The RB multiplies within this inclusion, which fills most of the cells extranuclear space. At the end of the cycle the RBs redifferentiate back into EBs and the cell is lysed releasing the infectious organisms, which go on to infect neighbouring cells and thus causing the tissue damage that is characteristic of this disease.

Specifically in the case of the disease caused by *C. abortus*, it is currently thought that infection is established first in the tonsils, from where it is disseminated by blood or lymph to other organs (possibly lymph nodes), where it may remain in a latent or persistent form until the animal becomes pregnant. Possibly key to this persistent stage is the discovery of aberrant forms of the organism. Infection establishes in the placenta and is thought to pass from the maternal to fetal side at around 60 days coinciding with the development of hemotomas at the placental villous tips. From this point infection develops and spreads from the trophoblastic chorionic epithelial cells. Ensuing tissue damage, changes in key pregnancy hormones and possible changes in immune responses ultimately lead to placental insufficiency and the death and abortion of the fetus, or the birth of weak lambs.

**GAPS:**
- Determine the role of the aberrant bodies in chlamydial persistence using in vivo models?
- What is the site of persistence in asymptomatic animals?
- What is the trigger for release of the organism from a persistent state to a replicating state?

### Signs/Morbidity

In sheep and goats, clinical signs primarily consist of abortion occurring in the last 2-3 weeks of gestation. In cattle, abortions tend to be sporadic, occurring near or at term. Infections can result in the birth of almost fully developed dead animals at term, or the delivery of weak and underweight animals which may subsequently die. In sheep, goats and cattle there is usually no overt evidence of clinical disease prior to abortion although uterine discharge can be observed 1-2 days prior to abortion occurring. In the case of goats this vaginal discharge may be observed for up to 2 weeks prior to and following the abortion. Placentas may be retained following delivery, with an increased frequency of placental retention being described for goats.

**GAP:**

What is the role of chronic/subclinical *C. abortus* infections in cases of infertility in both pigs and cattle?

### Incubation period

Sheep and goats infected early in pregnancy (generally prior to 110 days in the case of sheep) abort late in the same pregnancy. However, infection of non-pregnant females (lambs, kids) or females in late pregnancy (last 5-6 weeks) will most
likely lead to the development of a latent or sub-clinical infection, where the animals appear to be uninfected until the subsequent pregnancy. In an extended lambing season it is possible for a naïve pregnant ewe to pick up infection from an aborted ewe and then abort in the same season.

**GAPS:**
- The localization of the pathogen (body/tissues site) during the incubation period should be investigated.
- What is the situation in cattle and pigs? This is currently unknown and should be investigated.

**Mortality**

Mortality of infected ewes and goats is very low and if it occurs it is usually associated with retained placentas and the development of secondary bacterial infections. This is principally a disease of offspring, with up to 30-40% of pregnant ewes and 60% of pregnant goats affected during an abortion storm resulting in abortion, stillbirths and weak progeny. Following an abortion storm the disease becomes enzootic in nature, with an annual abortion incidence of 5-10% occurring in younger females and replacement naïve animals.

**Shedding kinetic patterns**

* C. abortus is excreted in large numbers in the vaginal fluids and products of abortion, as well as contaminating the coats of weak lambs and surviving offspring. Infectious organisms may also be shed in the faeces of animals (also see 2.4), although it is unclear as to the extent of such shedding and the role this might play in the epidemiology of infection. The organism has also been found in goats milk, but again it is unclear as to the significance of this in terms of spread of infection.

**GAPS:**
- Faecal shedding of C. abortus should be investigated quantitatively and over a longer time period as well as a potential role in causing infection and abortion.
- The role of the GI tract as a potential reservoir for genital re-infection should be investigated (analogous to C. trachomatis rectal infection in humans as a source of genital re-infection).
- Data on shedding for cattle and pigs is required.
- Evidence has been found in goats milk, but again it is unclear as to the significance of this in terms of spread of infection.

**Mechanism of pathogenicity**

The destruction of the chorionic epithelium and associated placental damage and vascular thrombosis impair the functional integrity of the placentomes that are responsible for the maternal-fetal exchange of nutrients and oxygen, as well as affecting hormonal balance. Progesterone which is responsible for the maintenance of pregnancy is produced by the trophoblast cells of the chorionic epithelium in the latter stages of pregnancy and these are the cells targeted and destroyed by the pathogen. The production of TNF-alpha and other pro-inflammatory mediators, probably triggered by chlamydial lipopolysaccharide, has also been postulated to be responsible for placental inflammation and damage. All of these changes combine ultimately to result in the death and subsequent expulsion of the foetus.

**GAPS:**
- It is necessary to increase our understanding of the role and influence of reproductive hormones on the pathogenicity of C. abortus.
- Is there any effect of different C. abortus strains and different transmission routes on pathogenicity?
- Studies have shown that low doses of organisms can result in classical disease and pathology. But what is the lowest infectious dose that elicits these effects?
- Why does the disease present differently in different animal species, sheep vs. goat vs. cattle vs. pigs?
- What differences are there in mechanisms of pathogenicity?

**Zoonotic potential**

**Reported incidence in humans**

While *C. abortus* is recognised as a zoonotic agent, reports of human cases are rare.
An epidemiological survey in hospitals of areas in which chlamydial abortion is endemic could reveal the incidence amongst pregnant women or other persons engaged in sheep production, in comparison with other types of farming or non-agricultural activities (also see section 2.2).

Prevalence is possibly underestimated as the disease is not notifiable in humans. It would be worthwhile investigating human abortion cases and respiratory infections (occupational disease) in humans.

**Estimated level of under-reporting in humans**

As this is a rare condition in humans the level of under reporting is probably very low. Although, as the disease is not notifiable it is possible that prevalence is underestimated.

**GAP:**

Investigate true prevalence in humans (abortions in pregnant women, respiratory symptoms in in-contact males and non-pregnant females).

**Risk of occurrence in humans, populations at risk, specific risk factors**

Human infection can result from contact with infected sheep and goats. The risk of infection from contact with cattle is less clear. The risk to humans is mainly limited to pregnant women who have contact with *C. abortus* through assisting pregnant sheep or goats especially during the lambing or kidding season. Indeed, there are several reports of human abortion resulting from contact with lambing/aborting sheep and although relatively few cases occur annually, the potential danger to the pregnant woman and her developing fetus is considerable. Infection can occur as the result of direct contact with animals and their secretions, the inhalation of aerosols from contaminated material or the accidental ingestion of contaminated material through poor hygiene practices.

**GAPS:**

- Investigate the zoonotic risk arising from *C. abortus* infection in cattle and pigs.
- Identify risk populations (farmers, veterinarians, laboratory workers, abattoir workers, etc.): determine their exposure risk by serology.
- Investigate risk and association with respiratory diseases resulting from zoonotic infections in both males and non-pregnant females.

**Symptoms described in humans**

There are a number of reports of pregnant women having severe infections, including spontaneous abortion, stillbirth and septicemia, following exposure to animals infected with *C. abortus*. These are likely to follow several days of acute influenza-like illness. Infection in pregnant women also typically causes renal failure, hepatic dysfunction and disseminated intravascular coagulation, and may result in death. In males and non-pregnant women chlamydial respiratory disease has been reported on a number of occasions.

**GAPS:**

Investigate cases of respiratory infections in humans and any association with exposure to *C. abortus*.

**Likelihood of spread in humans**

The likelihood of human-to-human spread of *C. abortus* is unknown. However, evidence from reported cases would suggest that human-to-human transmission is rare or unlikely. Reports also suggest that there is no evidence of persistence in humans as occurs in sheep.

**GAP:**

As human-to-human transmission has been recently confirmed to occur with *C. psittaci* it would be worthwhile to investigate possible cases of transmission involving *C. abortus*. 

**Risk of occurrence in humans, populations at risk, specific risk factors**

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**GAPS:**

Investigate cases of respiratory infections in humans and any association with exposure to *C. abortus*.
Impact on animal welfare and biodiversity

Both disease and prevention/control measures related

Aborted, stillborn or weak lambs/kids/calves/piglets that fail to survive are considered welfare issues for the mothers.

GAP:
Any behavioural changes in the animals as a result of the loss of their young.

Endangered wild species affected or not (estimation for Europe / worldwide)

This is not known, but is probably of low importance.

Slaughter necessity according to EU rules or other regions

It is not usually necessary to slaughter animals that have aborted, although some livestock keepers choose this as a method of controlling spread of infection.

Geographical distribution and spread

Current occurrence/distribution

Chlamydial abortion resulting from C. abortus infection occurs in most sheep- and goat-rearing countries worldwide. It is currently not thought to be an issue in Australia and New Zealand.

GAP:
There are suggestions that C. abortus is present in Australia, although to a much lesser extent than C. pecorum. This should be thoroughly investigated.

Epizootic/endemic - if epidemic frequency of outbreaks

As the name implies ("enzootic abortion"), the disease exhibits an enzootic character. After the introduction of C. abortus to a fully susceptible breeding flock, infection can spread to other naïve ewes resulting in an abortion storm. Thereafter the disease becomes enzootic in nature with an annual incidence of 5-10%, principally among younger females and new flock entrants (see 3.5). A similar picture is observed in goats but not in cattle where infections are more epizootic in nature.

GAP:
Infection kinetics should be investigated in cattle and pigs (in comparison to sheep and goats).

Seasonal cycle (seasonality)

Any seasonality is related to the breeding cycle of the affected animals.

Speed of spatial spread during an outbreak

Spread of infection can be rapid depending on the amount of infectious material in the environment. However, the consequence of infection is not seen until the next pregnancy.

GAP:
What is the situation in cattle and pigs.
Transboundary potential of the disease

Spread by infected incubating ruminants or carrier recovered animals. Some reports show high anti-C. abortus antibody titres in wild ungulates, but little is known about their role as carriers or reservoirs of infection.

**GAP:**
What is the role of wildlife species as carriers or reservoirs of infection.

Seasonal cycle linked to climate

There is currently no evidence for this, although changes in climate will likely affect persistence of the organisms in the environment.

**GAP:**
Investigate the persistence of the agent in the environment.

Distribution of disease or vector linked to climate

There is currently no evidence for this.

**GAP:**
If vectors are involved in transmission, and vector populations vary in different regions/countries depending on climate or changes in climate, then this could affect infection rates. This should be investigated.

Outbreaks linked to extreme weather

There is currently no evidence for this.

**GAP:**
Weather could impact on persistence of organisms in the environment, with cooler weather resulting in organisms remaining viable for longer. Thus, persistence and viability of the pathogen in the environment under different climatic conditions should be investigated.

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

There is currently no evidence for this.

**GAP:**
• The organism is affected by weather and temperature, therefore this is likely to impact on disease, but to what extent is currently unknown.
• If vectors are involved in transmission and vector populations vary in different regions/countries depending on changes in climate, then this could affect infection rates. This should be investigated.

Route of Transmission

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

Ingestion or inhalation of infectious organisms, through contact with infected animals, products of abortion and vaginal fluids.

**Occasional mode of transmission**

Possible mechanical transmission from infected to naïve ewes by the ram. Faecal-oral and rectal-genital transmission might be
possible. There is no evidence for venereal transmission, although this cannot be completely ruled out and may occasionally occur.

**GAP:**

Investigate other non-classical routes of transmission and estimate impact on epidemiology of infection.

**Conditions that favour spread**

The introduction of asymptomatic *C. abortus* carriers into a naïve unvaccinated flock or herd can result in the rapid spread of infection. Lambing indoors with close contact between animals at lambing increases risk of spread of infection to naïve animals. Poor hygiene at lambing, kidding or calving can also allow spread of infection.

**GAPS:**

- What is the effect of different management and housing systems on the spread of infection.
- What impact does inter-species transmission (sheep-goat, cattle-goat, cattle-sheep and vice versa, pigs) have on spread of infection.

**Detection and Immune response to infection**

**Mechanism of host response**

Both innate, as a first line of defence, and adaptive immune responses are important in the control of chlamydial infections. Following infection in the non-pregnant animal, the pathogen persists until the animal becomes pregnant. This persistence is thought to be mediated through the cytokine interferon-gamma. Protective immunity following abortion in sheep results from the high levels of antigenic stimulation due to *C. abortus* replication in the placenta. Both cellular and humoral immunity have been demonstrated, although cellular responses appear more important in terms of a primary infection. The primary infectious dose appears to be an important factor that determines disease outcome.

**GAPS:**

- Is immunity and immune responses similar in goats and sheep?
- Requirement to investigate immunity in both cattle and pigs.

**Immunological basis of diagnosis**

Diagnosis of infection is generally based on antibody responses at the time of abortion, which correlate very well with infection in sheep. This also applies to goats, but the situation in pigs and particularly cattle is much less clear.

**GAP:**

Determine whether antibody is a good correlate of infection in cattle and pigs, which will aid the development of specific diagnostic tests for these species.

**Main means of prevention, detection and control**

**Sanitary measures**

Effective biosecurity (also see section 9.6)

Care in the purchase of replacement stock from known disease free sources, for example from accredited flocks/herds.

Keep a flock/herd closed.

Vaccinate all replacements, although it should be remembered that vaccination of animals already infected may not protect them from disease and shedding of infectious organisms.

**GAP:**

Determine sanitary measures for cattle and pigs.
Mechanical and biological control

When chlamydial abortion occurs attention must be paid to reduce the risk of within-flock transmission by

- Removal and destruction of the products of conception as well as contaminated bedding by burning or incineration
- Cleaning and disinfecting the area where the abortion occurred
- Isolating ewes which have aborted for 2-3 weeks, or at least until vaginal discharges have dried up (organisms in fluids have been demonstrated to be infective for up to 7-10 days post-partum). If the number of aborting animals is large, they may be retained for further breeding, preferably as a separately managed group.
- Operating basic standards of hygiene (e.g. hand washing) and personal protective equipment (clothing, boots, gloves) to prevent spread of infection

The use of long-acting tetracyclines can be administered as an emergency treatment to reduce other potential losses, but should not routinely be used as a means of controlling infection due to issues of potential antibiotic resistance. Antibiotics should not be used in combination with the live vaccines.

Initiate a vaccination programme for the next breeding season where abortion has occurred in a flock, if infection becomes established in a flock or where there is a high level of infection in neighbouring farms (although this depends on provision of adequate biosecurity measures).

GAP:

What are the recommendations for cattle and pigs?

Diagnostic tools

A range of tools are available for diagnosing C. abortus infection in sheep and goats and these are well documented in the OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals (also see section 15):

- Serological tests – CFT, ELISAs
- Detection of organism – chemical staining (e.g. mZN), immunohistochemistry, PCR, real-time PCR, High Resolution Melt PCR (HRM), ArrayTube

There are advantages and disadvantages to the use of some of these tests. Some serological tests (CFT, some ELISAs) detect antibodies induced by infection with other chlamydiae, including C. pecorum, a non-abortigenic chlamydial species which can be widespread in ruminants and can result in false positives. Recently a new ELISA that is more sensitive and specific has been developed and commercialised (MV-Enfer Chlamydia abortus ELISA kit).

Molecular detection of organism DNA is generally superior over serology, being more sensitive and specific, although requiring more specialist equipment and is generally more expensive.

A molecular DIVA has been developed based on PCR-RFLP and another based on High Resolution Melt (HRM) PCR that differentiates the live vaccinal 1B strain from wild-type strains.

None of the current tests can detect latent carriers.

GAPS:

- Develop diagnostic tools that are able to detect latently infected animals
- Need to develop species-specific serological tests for diagnosing infections in cattle and pigs
- Develop serological tests for differentiating between vaccinated (live and inactivated vaccines) animals and those naturally infected
- Develop point-of-care tests for diagnosing infections in the field
- Develop and validate approved tests for certifying animals free of disease for export purposes
- Develop and evaluate tests for use with other farmed species (e.g. European bison, water buffalos, yaks, zebus, reindeer).

Vaccines

Currently both inactivated and attenuated live vaccines are available for use in sheep and goats but not cattle [not officially recommended but cattle can be administered twice the dose of live vaccine given to small ruminants] (also see section 16).

- The live attenuated vaccine (temperature-sensitive mutant C. abortus strain 1B) is commercialized (Enzovax, MSD Animal Health & Ceva Chlamydia vaccine, CEVA Animal Health) in several countries worldwide. This must be
administered at least 4 weeks prior to mating and not in combination with antibiotic treatment. Vaccination should be repeated every 2–3 years.

- Inactivated vaccines are also commercialized (e.g. Mydiavac; Benchmark Animal Health). These vaccines can be administered during pregnancy, but not until 4 weeks after breeding. Vaccination should be repeated annually.

**Disadvantages**

i. Both vaccines do not completely eradicate the shedding of infectious organisms at lambing

ii. Some vaccinated animals can still abort (either as a direct result of using the live vaccine or possibly due to the vaccine being administered over an existing infection)

iii. Inactivated vaccines require large amounts of chlamydia and thus may not be cost effective for sheep producers

iv. The live vaccines have been shown to cause abortion in some animals within a vaccinated flock

v. It has been shown that some inactivated vaccines commercially available nowadays are not fully effective to control the abortion in the flock.

vi. Production issues for the live vaccines that have led to availability issues across Europe.

vii. Safety concerns in using the live vaccines (potential infection in animals as well as human handlers) and inactivated vaccines (use of oily adjuvant and potential for self-injection)

viii. In general, vaccine design and development is an inherently laborious process

Modern vaccine research should be focused on the development of next generation vaccines that are efficacious, but safe and more stable and cheaper to produce. Improved computational techniques and combined integrative strategies have the potential to simplify the process greatly. These techniques also have the potential to identify candidate proteins that would be overlooked by conventional experimentation. In particular, reverse vaccinology has proved effective in the discovery of antigenic subunit vaccines that would otherwise remain undiscovered. If methodology of reverse vaccinology is applied appropriately in vaccine design, it can save enormous amounts of money, time and labour.

**GAPS:**

- Develop next generation vaccines that are safer, cheaper to manufacture, more stable and easier to produce
- Investigate differences in immunity induced by inactivated versus live attenuated vaccines to aid in the development of new vaccines
- Develop a transformation system that will enable the generation of novel vaccines based on genetically modified organisms
- The development of a subunit vaccine comprising antigens different from a corresponding diagnostic antigen will allow the detection of infected animals within a vaccinated flock.

**Therapeutics**

Long acting tetracyclines given at the correct period (in late pregnancy) will reduce the severity of infections and reduce the number of abortions depending on when administered. However, *C. abortus* may still be shed at lambing and thus pose a risk of transmission to other naïve ewes. Antibiotic treatment has been considered as the most practical measure for control of disease in cattle where abortions are more sporadic.

**GAP:**

- Based on the emergence of tetracycline-resistant (TetR) *Chlamydia suis* isolates in pig herds in several countries, it is of importance to investigate how the use of tetracyclines in ruminants could contribute (or has contributed) to the emergence and persistence of tetracycline-resistant *C. abortus* strains.

**Biosecurity measures effective as a preventive measure**

As *C. abortus* is a particular risk to pregnant women they should avoid involvement with lambing ewes and should not handle contaminated clothing from those working with lambing ewes or newborn lambs.

Immunocompromised or immunosuppressed individuals should avoid contact with potentially infected animals or contaminated material.

Care should be taken in the use of live vaccines.

Preventative measures should be put in place to limit the spread of infection from aborting animals and products of abortion to naïve animals.
Adequate personal hygiene procedures including the use of protective equipment should be put in place to additionally reduce the risks of transmission.

Replacement animals should be purchased from accredited sources.

Consider operating a closed flock to keep disease out.

**GAP:**

What recommendations can be made for cattle and pigs?

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


**GAP:**

Define recommended tests and sampling sites to prove that animals are free of chlamydiosis for trade, export etc.

**Prevention tools**

Vaccination, diagnostics, husbandry, biosecurity and health education (eg leaflets focussing on occupational hazards to pregnant women).

**Surveillance**

Serological surveillance to assess the status of flocks/herds. This must be coupled with flock history as antibody is not a measure of current infection.

**GAP:**

Develop recommendations for direct pathogen detection and sampling site.

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

Vaccination is effective at reducing the clinical picture but is not suitable for the eradication of infection. Nevertheless vaccination is the best option to control the disease.

There is information on non-response to oxytetracycline administration in herds with confirmed chlamydial abortion in Southern Greece.

**GAP:**

It is necessary to work on improving the currently available vaccines and/or to design new vaccines.

**Costs of above measures**

Usually controls are related to the herd/flock and are not implemented at a national or regional level. Costs are related to vaccination, diagnostic investigations and to possible treatment, as well as associated costs of dealing with abortions, losses in lamb production and in purchasing more expensive premium replacement livestock from accredited sources.

**Disease information from the OIE**

**Disease notifiable to the OIE**

Enzootic abortion is an OIE listed disease, although no epidemiological events are officially reported as the disease is endemic in most European countries. Some European countries however operate their own disease surveillance systems with annual
incidence figures provided. However, even then disease incidence is under reported. In the UK, around 44% of cases of ovine fetopathy due to an infectious cause are diagnosed as being caused by C. abortus. Figures are likely to be similar in other European countries.

**GAPS:**

- Improved monitoring of disease incidence is required.
- Epidemiological data is not available for all European countries and would be beneficial. Availability of data depends on disease surveillance systems in respective countries.

**OIE disease card available**

No.

**OIE Terrestrial Animal Health Code (reference)**


**OIE Terrestrial Manual (reference)**

Enzootic abortion of ewes:

[http://www.oie.int/fileadmin/Home/eng/Health_standards/tahm/2.07.06_ENZ_ABOR.pdf](http://www.oie.int/fileadmin/Home/eng/Health_standards/tahm/2.07.06_ENZ_ABOR.pdf)

Avian chlamydiosis:

[http://www.oie.int/fileadmin/Home/eng/Health_standards/tahm/2.03.01_AVIAN_CHLAMYD.pdf](http://www.oie.int/fileadmin/Home/eng/Health_standards/tahm/2.03.01_AVIAN_CHLAMYD.pdf)

**Socio-economic impact**

**Zoonosis: Impact on affected individuals and/or aggregated DALY figures**

Not known but will be low.

**GAP:**

Requires better data on incidence

**Zoonosis: cost of treatment and control of the disease in humans**

Not known but will be low as infections are considered to be rare.

**GAP:**

Requires better data on incidence to calculate costs of treatment.

**Direct impact (a) on production**

When introduced into non infected flocks/herds abortion may occur in up to 30% of the ewes and as many as 60-90% of pregnant goats.

**GAP:**

Impact for cattle and pigs is unknown.
**Direct impact (b) cost of private and public control measures**

Costs associated with diagnostic testing as well as use of vaccines and application and use of antibiotics contribute to the costs. Such costs can be prohibitively expensive for some small ruminant farmers.

**GAP:**

Impact for cattle and pigs is unknown

**Indirect impact**

Reduced production of lambs and kids affecting food supply chain and food security.

**GAP:**

Indirect impact for cattle and pigs is unknown

**Trade implications**

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

International standards for trade are contained in the OIE Terrestrial Animal Health Code. These specify the recommendations for the importation of sheep/goats into a breeding flock/herd to minimise the risk of introducing infection, the mechanisms to confirm freedom in the herd/flock and the rules for the movement of semen.

Some countries such as Russia and China demand strict serological controls for the importation of *C. abortus* free sheep and pigs.

**GAP:**

Impact not known for cattle or for wild and farmed ruminants (e.g. European bison, water buffalos, yaks)

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

None

**Impact on national trade due to existing regulations**

None

**Main perceived obstacles for effective prevention and control**

1. Detecting the presence of the organism in subclinical persistently infected non-pregnant animals is not currently possible.
2. Identifying infected ewe lambs that will go on to abort is difficult.
3. Vaccine does not give complete protection
4. Vaccinated animals may still excrete *C. abortus* at lambing.
5. Vaccination will not eradicate infection from a flock.
6. Live vaccine is capable of inducing abortion
7. Vaccines are not licenced for use in cattle and pigs

**GAPS:**

- Better detection of latently/persistently infected animals
• Improved vaccines
• Improved diagnostics
• Develop diagnostics and vaccines for use in cattle and pigs

Main perceived facilitators for effective prevention and control

1. Improved diagnostic tests
2. Better understanding of the immune response to infection and to vaccines, in particular the protective elements of the immune response.
3. Recognition of latent infection.
4. Improved second generation vaccines

GAPS:
• Improve our understanding of the immune correlates of protection (cellular and antibody)
• Improve existing inactivated vaccines with new adjuvants to enhance an effective cellular immune response.
• Feasibility of screening tests for assessing infection at herd/flock level (define specimen type, number of samples, tests)

Risk

Risks to production and rare risk of infection in humans. Across the world the infection poses problems in the main sheep and goat rearing areas and can also impact on cattle, pigs, other farmed species and wild ungulates.

GAP:
Risks for cattle, pigs, other farmed species and wild ungulates requires greater research and assessment.

Conclusion

Better diagnostic tools are required, especially to identify the latent carrier. Improved vaccines which prevent shedding and which give 100% immunity are needed. The next generation of vaccines will be based on multi component recombinant antigens. These studies will be helped by a greater understanding of pathogenesis, understanding the extent of diversity across Europe and developing tools to identify and manipulate targets for vaccine development studies.

GAPS:
• Greater understanding of the extent of genetic diversity of C. abortus strains
• Greater understanding of disease pathogenesis in cattle, pigs and other farmed and wild ruminant species
• A greater understanding of the mechanistic basis of latency and persistence, including determination of the site of latency
• Evaluation of the resistance of the pathogen under different environmental conditions
• Investigations of other potential sources for transmission of infection, including faeces, milk and water samples
• Role of wildlife and vectors in transmission of infection
• Improve epidemiological evidence of infections in humans
• Improve diagnostic tools for: other animal species (cattle, pigs, wild ungulates and farmed animal species); detecting latent/persistent infections; identifying naturally-infected animals in vaccinated flocks/herds; detecting co-infections; and point-of-care use. This will require greater standardisation of fully defined sera of known origin as well as pan-European inter-laboratory trials.
• Vaccine development studies: define immune correlates of protection; improve inactivated vaccine efficacy through the use of novel adjuvants to promote an effective cellular responses; determine effect of co-infections on efficacy of vaccines; and develop a stable transformation system for C. abortus.
• Development of safer, cheaper, more stable next generation marker vaccines, which will likely be based on subunit recombinant antigens.

Sources of information

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References


