Contagious agalactia of small ruminants: current knowledge concerning epidemiology, diagnosis and control

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Summary
Contagious agalactia of small ruminants is a syndrome which principally affects the mammary glands, joints and eyes. The main causal agents are Mycoplasma agalactiae in sheep, and M. agalactiae, M. mycoides subsp. mycoides large colony type and M. capricolum subsp. capricolum in goats. In addition, M. putrefaciens can produce a similar clinical picture, particularly in goats. Contagious agalactia occurs on all five continents and is often enzootic. The evolution of the infection tends to be chronic in affected animals and herds. Symptomless shedding of mycoplasmas, mainly in the milk, may persist for a long time. These insidious infections, associated with carriage in the ears of healthy animals, are difficult to diagnose and to control. The main mode of transmission between flocks is related to the sale of carrier animals and contact during transhumance, whereas transmission within a flock occurs through contact, suckling and milking.

This review discusses the clinical features, epidemiology, treatment, prevention and control of the disease.

Keywords

Introduction
The principal mycoplasmoses of small ruminants are contagious agalactia and caprine contagious pleuropneumonia. Contagious agalactia was the first of the mycoplasmoses of small ruminants for which clinical descriptions (notably by Metaxa in 1816) and microbiological findings suggested, in common with contagious bovine pleuropneumonia (CBPP), a mycoplasmal origin (Bridré and Donatien, 1923). Contagious agalactia should be regarded as a syndrome, caused by various mycoplasmas which share a triple mammary, articular and ocular tropism, with the additional possibility of respiratory disease. Although Mycoplasma agalactiae (Ma) is often considered the 'classical' agent, Mycoplasma mycoides subsp. mycoides large colony type (MmmLC) and Mycoplasma capricolum subsp. capricolum (Mcc) can produce similar clinical pictures. These three mycoplasmas are the principal causal agents of contagious agalactia. Under certain conditions, the secondary contagious agalactia agent, Mycoplasma putrefaciens (Mp), may be responsible for similar symptoms, and therefore cannot be excluded from this study.

This contagious syndrome, in which agalactia is not the only symptom, has successively received various names. Historically, the term ‘classical’ contagious agalactia was used to describe the Ma syndrome in Mediterraneanc countries. In this paper, ‘contagious agalactia’ covers infections caused by all four of the mycoplasmas mentioned above.

The current importance of contagious agalactia rests in its extensive geographical distribution, its often high prevalence
in localised foci (enzootics), and in the extent of economic and even genetic losses. Contagious agalactia affects all types of stock breeding, both traditional and intensive, throughout the world and its preferential mammary involvement presents a major health obstacle in the development of sheep and goat production.

Clinical aspects

Mycoplasma agalactiae

Natural outbreaks affecting sheep and goats can take various forms.

Typical forms

The typical forms of the disease have been reviewed extensively (2, 7, 10, 14, 30, 31, 38, 47, 48, 55, 61, 79).

Initial stage

This stage, particularly in the acute form (Table I), is often characterised by a brief febrile syndrome, which may follow bacteremia.

Clinical stage

The clinical stage consists of localisation of the infectious agent in the three main target organs. In lactating females, which show the most characteristic clinical signs, the udder is always affected and is usually the first sign to be observed. Symptoms observed in the mammary gland always include functional disorders, ranging from transient hypogalactia to abrupt and total agalactia. These symptoms are also generally characterised by the development of unilateral or bilateral parenchymatous or catarrhal mastitis, with hardening of the tissue, or the formation of abscesses and enlargement of the retromammary lymph nodes. Articular symptoms involving the carpal and tarsal joints may also appear in the form of arthritis or polyarthritis of varying severity, ranging from mild lameness to ankylosis and decubitus (particularly in the young and in goats). Ocular symptoms may also occur in all categories of animals, starting with conjunctivitis and leading to parenchymatous keratitis with corneal revascularisation in one or both eyes. Less frequently, abortion may occur during advanced pregnancy and diarrhoea is sometimes present.

Table I

Clinical features of contagious agalactia

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Host species</th>
<th>Mycoplasma agalactiae</th>
<th>M. mycoides subsp. mycoides LC</th>
<th>M. capricolum subsp. capricolum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Host species</td>
<td>Sheep, goats</td>
<td>Goats &gt; sheep</td>
<td>Goats &gt; sheep</td>
<td></td>
</tr>
<tr>
<td>Dominant forms</td>
<td>Sheep</td>
<td>Subacute to chronic</td>
<td>(a)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Goats</td>
<td>Acute to chronic</td>
<td>Hyperacute to subacute</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>Adult animals</td>
<td>Sheep, goats</td>
<td>0-3%</td>
<td>0-20%</td>
</tr>
<tr>
<td></td>
<td>Lactating females</td>
<td>Sheep</td>
<td>0-10%</td>
<td>(a)</td>
</tr>
<tr>
<td></td>
<td>Goats</td>
<td>0-40%</td>
<td>3-50%</td>
<td>(a)</td>
</tr>
<tr>
<td></td>
<td>Young animals</td>
<td>Sheep</td>
<td>1-10%</td>
<td>(a)</td>
</tr>
<tr>
<td></td>
<td>Goats</td>
<td>3-50%</td>
<td>10-95%</td>
<td>(a)</td>
</tr>
<tr>
<td>Morbidity</td>
<td>Adult animals</td>
<td>Sheep, goats</td>
<td>0-20%</td>
<td>5-40%</td>
</tr>
<tr>
<td></td>
<td>Lactating females</td>
<td>Sheep</td>
<td>1-50%</td>
<td>(a)</td>
</tr>
<tr>
<td></td>
<td>Goats</td>
<td>10-60%</td>
<td>20-30%</td>
<td>(a)</td>
</tr>
<tr>
<td></td>
<td>Young animals</td>
<td>Sheep</td>
<td>2-60%</td>
<td>(a)</td>
</tr>
<tr>
<td></td>
<td>Goats</td>
<td>10-70%</td>
<td>20-95%</td>
<td>(a)</td>
</tr>
<tr>
<td>Typical syndromes</td>
<td>Adult animals</td>
<td>A &gt; 0 &gt;&gt; R</td>
<td>A, R &gt; 0</td>
<td>A, R &gt; 0</td>
</tr>
<tr>
<td></td>
<td>Lactating females</td>
<td>M &gt;&gt; A &gt; 0</td>
<td>M, R, A &gt; 0, Ab</td>
<td>A, R, M &gt; 0, Ab</td>
</tr>
<tr>
<td></td>
<td>&gt; Ab &gt; R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Young animals</td>
<td>R, A, D (b)</td>
<td>A, R &gt; 0, N</td>
<td>A, O, R &gt; N</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>'Atypical' forms</td>
<td>R, G</td>
<td>G</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A: articular symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G: genital symptoms (m/f)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ab: abortion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M: mammary symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N: nervous symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O: ocular symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R: respiratory symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

References used in compiling this table are obtainable from the authors.
Within these typical forms, it is relatively rare to observe respiratory disease in adults (particularly in sheep), even though infection of the lungs, which is frequent after bacteraemia, can be confirmed by the isolation of \( Ma \) from lung lesions at necropsy. In contrast, pneumonia is more common and more severe in young animals.

**Evolution**

The evolution of these clinical signs depends on the prevailing clinical form (acute to chronic) and on the hygienic and therapeutic measures applied. A single prognosis for flocks infected with \( Ma \) is therefore impossible. Examples of full functional recovery have been reported. In contrast, and especially in newly infected flocks, the severity of the lesions may be such that many animals lose their entire economic value.

In summary, mammary, articular and ocular symptoms constitute an indicative triad, although they do not always occur in combination. While the complete syndrome may be observed within a flock, individual animals may show various combinations of symptoms. When the disease is enzootic, incomplete or even subclinical forms may occur. Over the course of several years, very discrete mammary symptoms may ensue after the initial, typical clinical picture.

All the spontaneous symptoms described above can be reproduced experimentally, with some variability associated with the route of \( Ma \) inoculation and the type of animal (see ‘Analytical epidemiology’) (4, 8, 12, 19, 33, 39, 48, 49, 61, 79).

**‘Atypical’ forms**

Pneumonia or pleuroneumonia, without any other major symptoms, has been observed in Australia, India and sporadically in various other countries, mainly in goats. Caprine granular vulvovaginitis occurs in India and Africa (34, 53, 68).

**Asymptomatic forms**

In regard to each of the four mycoplasmas responsible for contagious agalactia, it is important to distinguish between regression in severity with time in a given animal, leading to the possible absence of clinical expression, and the existence of forms which are asymptomatic from the outset (unrelated to the vestibular carrier state).

Thus, strains of \( Ma \) were recovered recently from the milk of high-yielding flocks, in an area where no case of contagious agalactia had been reported within living memory. As no clinical signs were apparent in these intensively managed flocks, it can be assumed that the strains were avirulent. An initial study of the genomic, protein and antigenic properties of these strains has been conducted (11, 12, 13, 14, 34).

**Mycoplasma mycoides subsp. mycoides LC**

This biotype affects mainly goats, but has also been isolated from clinically or subclinically affected sheep and, in exceptional cases, from cattle and wild goats (48, 53, 56).

There are two clinical differences between natural infections caused by \( MmmLC \) and those caused by \( Ma \) (Table I). The former is more often responsible for acute and hyperacute forms in adults and young animals, and exhibits greater symptom variability. This variability is linked to the greater range of target organs, the proteiform nature of the observed syndromes and the differing evolutionary courses possible (ranging from fatal septicaemia to asymptomatic infection).

**Typical forms**

**In adults**

The initial clinical picture in adults may either be characterised by a biphasic development identical to that described for \( Ma \), or be dominated from the outset by clinical mastitis with a drop in milk yield. Fatal septicaemia is possible. Arthritis or polyarthritis, often pronounced in goats, occurs with or without associated mammary symptoms.

The third major clinical localisation is pulmonary. Primary pneumonia and pleuritis due to \( MmmLC \) often occur, but again may vary in their combination with other manifestations. Some descriptions refer solely to respiratory symptoms, at least during a given lactation. This is in contrast to complete syndromes in which pneumonia is associated with several other localisations, all intermediate forms being possible. Sheep may also develop bronchopneumonia or pleuritis, resulting in up to 60% mortality.

Conjunctivitis and keratoconjunctivitis are less common. Abortion, peritonitis and localised abscesses are relatively rare.

These conditions are more likely to lead to serious sequelae than in \( Ma \) infection.

**In kids**

Acute or hyperacute generalised infections, resulting in considerable neonatal mortality, are often observed in kids. The local signs of acute and subacute forms are principally polyarthritis, pneumonia and (less often) diarrhoea and keratoconjunctivitis. The central nervous system may also be affected. The clinical picture of experimental infection in goats and sheep, obtained after inoculation of \( MmmLC \) by various routes, is similar to that described above (7, 19, 23, 34, 35, 37, 38, 51, 52, 61, 62, 65).

**‘Atypical’ form**

An important form of mycoplasmosis caused by \( MmmLC \) consists of ulcerative balanoposthitis and vulvovaginitis in sheep, particularly in Africa and Australia (53).

**Mycoplasma capricolum subsp. capricolum**

This subspecies principally affects goats, although subclinical and clinical cases have occurred in sheep and, in exceptional cases, in cattle and wild goats (48, 71, 72).
There are fewer clinical accounts of natural infection with \textit{Mcc}. However, it is clear that the two main characteristics highlighted for \textit{MmmLC} infection apply equally well to \textit{Mcc}: highly deleterious syndromes with variable symptoms (19, 23, 71, 72).

**Typical forms**

Typical forms of \textit{Mcc} in adults and young animals are discussed below (20, 32, 47, 51, 52, 71, 72).

**In adults**

Severe general signs may accompany bacteraemia in adults, particularly in lactating goats. Two main types of syndromes may be observed at the clinical stage (although intermediate forms are possible).

First, most of the original clinical accounts (from Australia or Europe) portray a characteristic contagious agalactia syndrome, more or less complete, with predominantly articular involvement. Such involvement takes the form of usually severe serous or fibrinopurulent arthritis or polyarthritis. Mammary involvement with hypogalactia or agalactia ensues. Ocular manifestations are less common, but there may be conjunctivitis or even keratitis. Finally, obvious respiratory symptoms are only rarely observed in adults, even though asymptomatic infection of the airways or lungs occurs more commonly. The respiratory tropism of \textit{Mcc} has thus been qualified as occasional.

Secondly, clinical pictures dominated by respiratory symptoms seem to be habitually observed in certain countries, such as Morocco, in both sheep and goats. These enzootic respiratory disorders are associated with conjunctivitis or keratoconjunctivitis in sheep and with arthritis and mastitis in goats. The infectious agent can be isolated from lung lesions, as has occasionally been reported in sheep and goats with pneumonia in Africa and India.

Abortion may occur in connection with these various syndromes.

**In young animals**

The disease is usually very severe in young animals, particularly in kids, and is similar to that of \textit{MmmLC}. A febrile syndrome is common, leading to death within a few hours or days. Local symptoms, when expressed, involve the joints, eyes (i.e., keratoconjunctivitis), lungs and even the central nervous system.

Experimental inoculation of \textit{Mcc} usually results in symptoms similar to those of the natural disease (19, 23, 34, 48, 52, 53, 71, 72).

'Atypical' form

Vulvovaginitis and balanoposthitis, without other symptoms, have been described in sheep (36).

**Mycoplasma putrefaciens**

This species principally affects goats, although infection and clinical disease have been described in sheep (70).

A dozen or so clinical accounts of outbreaks have been published (21, 23, 42, 70). \textit{Mp} was initially regarded as an agent of caprine contagious mastitis. The local symptoms sometimes involved only half the udder, or were very discrete in comparison with hypogalactia or agalactia.

In 1987, a very severe outbreak among goats in the United States of America (USA) confirmed suspicions of the invasiveness of \textit{Mp} and its ability to cause septicemia under certain conditions. Mastitis, agalactia, acute arthritis (adult goats and kids) and abortion were observed. Morbidity attained 90% and 700 animals died. There was no evidence of fever.

Many cases now provide evidence of the tropism of \textit{Mp} for the joints in kids and adult goats, although localisation in the udder remains dominant. The development of bacteraemia has been reported. Respiratory tropism of \textit{Mp} is suspected but this question remains unresolved. This mycoplasma has been isolated from the respiratory tract of sheep and goats, and from the lungs of sheep with pneumonia. No indication of ocular involvement has been described.

Attempts at experimental reproduction by inoculating cultures into the teats of lactating goats resulted in agalactia without any other symptoms, and the infection remained confined to the inoculated half of the udder. Intramuscular inoculation of \textit{Mp} into goats (39) and inoculation of kids by various routes failed to provoke clinical disease. In contrast, the intranasal inoculation of a kid, debilitated by intestinal coccidiosis, led to bacteraemia and arthritis (1).

Consequently, \textit{Mp} may be regarded as an opportunistic pathogen. It is capable of causing an infection which is probably intermediate in nature and severity between the primary mycoplasmoses (caused by \textit{Ma}, \textit{MmmLC} and \textit{Mcc}) and the associated mycoplasmoses (e.g., \textit{M. arginini}). \textit{Mp} is also capable of producing septicemia, and may cause mastitis-arthritis syndromes and even pneumonia, particularly if the susceptibility of animals has been enhanced by intrinsic or external factors (such as intercurrent disease, poor milking conditions and various stress factors).

**Other mastitis-causing Mollicutes**

Other members of the class \textit{Mollicutes} may cause agalactia and mastitis in small ruminants under natural conditions (73).

One of these is \textit{Mycoplasma mycoides} subsp. \textit{capri} (\textit{Mmc}). Although cross-reactions with \textit{MmmLC} have complicated serological diagnosis in the past, \textit{Mmc} now seems to be quite rare. It has been linked to mastitis in goats, with possible general manifestations and bacteraemia, and its respiratory tropism is more pronounced than that of \textit{MmmLC}. 

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The same difficulty in identification has hampered definition of the aetiological agent of oedema disease of Sparta goats, which might be \textit{MmmLC} or \textit{Mmc}. This disease occurs sporadically in Greece and Turkey, appearing as an acute or hyperacute syndrome, fatal within three to five days, with hyperthermia and the production of hot, painful, oedematous swellings (19).

Strains of \textit{M. mycoides} subsp. \textit{mycoides} small colony type (\textit{MmmSC}), the causal agent of CBPP, have been isolated in Portugal from cases of mastitis in sheep and pneumonia in goats (34). \textit{Mycoplasma} sp. PG50 has been recovered from the milk, lungs, joints and foetuses of sheep and goats (5).

These various pathological entities require additional investigation.

Finally, rare cases of caprine mastitis, seldom accompanied by other localisations, have been caused by \textit{Mycoplasma} sp. of serogroup 11, \textit{M. arginini}, \textit{Mycoplasma} sp. GM790A, \textit{Acholeplasma laidlawii} and \textit{A. modicum} (48).

In conclusion, aetiological investigations have revealed a wider diversity concerning mycoplasma causative agents in goats, which are generally susceptible to all the mycoplasmas mentioned, than in sheep. The range of clinical expression is also broader than in sheep. However, the descriptions of various sheep diseases caused by \textit{MmmLC} or \textit{Mcc} confirm that, in regard to contagious agalactia, host specificity, which was previously regarded as certain in some mycoplasmoses, is not in fact absolute.

Secondly, clinical differences which are often considerable have been noted within these four infectious agents. Many factors may be responsible for this, including possible differences in pathogenicity or tropism between different strains, the natural or vaccinal immune status of the host (particularly in enzootic areas) and external environmental effects.

Finally, and above all, behind the apparent global unity of the contagious agalactia syndrome, certain differences do exist between \textit{Ma}, on the one hand, and \textit{MmmLC} and \textit{Mcc} on the other, within the 'mycoides cluster'. The percentages of acute and hyperacute forms and morbidity rates are greater in the latter two organisms; their respiratory tropism is also, on average, more pronounced, in contrast to their ocular tropism.

Descriptive epidemiology

Geographical distribution of contagious agalactia syndrome

It is apparent from the Food and Agriculture Organisation (FAO) Animal Health Yearbook (25) and from other scientific publications that the distribution of contagious agalactia is still extensive, for the disease occurs on every continent, and outbreaks or isolations have been reported from at least 55 countries (2, 9, 19, 23, 24, 25, 30, 31, 33, 34, 35, 46, 68, 71, 79).

The region of the world in which the disease has occurred over the longest period, and in which it is most widely distributed and has been best described, is the Mediterranean Basin (in the broad sense). Contagious agalactia probably spread considerably at the end of the 19th and at the beginning of the 20th centuries. The term 'contagious agalactia of sheep and goats', attributed to Brusasco, dates from that period (1871). In addition to the 14 countries bordering the Mediterranean (Table II), the disease has also affected, or still affects, the following European countries: Portugal, Switzerland, Austria, Romania, Bulgaria, the Commonwealth of Independent States, Germany, Sweden and the United Kingdom (UK). Only sporadic outbreaks have been reported in the last three countries.

Contagious agalactia is also present on the continent of Asia. It has been reported from the Mediterranean countries of Asia Minor, in Iraq, the United Arab Emirates, Iran, Afghanistan, Pakistan, India, Nepal, the People's Republic of China, Mongolia and Indonesia.

Most African countries are probably affected by contagious agalactia. Outbreaks have been described in the following countries, in addition to North Africa: Mauritania, Senegal, Guinea, Guinea Bissau, Togo, Côte d'Ivoire, Ghana, Nigeria, Cameroon, Niger, Chad, Sudan, Ethiopia, Kenya, Mozambique and Zimbabwe.

The overall epidemiological situation on the continents of North and South America is less well known. Contagious agalactia has occurred in the USA since the 1950s. Infections or clinical cases have been described in Canada, Guadeloupe, Peru and Brazil.

Finally, there are reports of contagious agalactia from Australia and New Zealand.

Geographical distribution of the different specific infections

Evolution of the epidemiological situation

The epidemiology of contagious agalactia changed progressively from the 1970s onwards, with regard to the increased geographical spread and/or frequency of infections due to \textit{MmmLC} and \textit{Mcc} (Table II). In fact, in most countries of the northern and eastern Mediterranean, the identification of these mycoplasmas is apparently more recent than that of \textit{Ma}. Although possible reasons for this change may be distorted (due to the perfecting and wider application of microbiological techniques), two associated explanations may be proposed.
First, this diversification of the epidemiology seems in many cases to have been due to an increase in the importation and transfer of (breeding) animals, which could have spread the infections. This explanation was proposed in France (57), since 1972, with a presumably imported enzootic/epizootic infection due to MmmLC, which affects intensive dairy husbandry of Saanen goats. Outside this area of the Mediterranean, the trade in animals has also been held responsible for sporadic cases in areas previously considered free from the disease: i.e., MmmLC infections in Germany, enzootic infection of Ma in traditional flocks has co-existed, since 1977, with a presumably imported enzootic infection due to MmmLC, which affects intensive dairy husbandry of Saanen goats. Outside this area of the Mediterranean, the trade in animals has also been held responsible for sporadic cases in areas previously considered free from the disease: i.e., MmmLC infections in Germany, 

### Table II

Aetiological and epidemiological characteristics of contagious agalactia in various countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Mycoplasmas</th>
<th>Geographical extent</th>
<th>Epidemiological forms</th>
<th>Host species</th>
<th>Original description</th>
<th>Identification</th>
<th>Control strategies</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>Ma</td>
<td></td>
<td>E</td>
<td>Sheep, goats</td>
<td>1644</td>
<td>1966</td>
<td>GM</td>
<td>All four agents</td>
</tr>
<tr>
<td></td>
<td>MmmLC</td>
<td></td>
<td>S</td>
<td>Goats</td>
<td>1972</td>
<td>1972</td>
<td>GM</td>
<td>identified in the same region.</td>
</tr>
<tr>
<td></td>
<td>Mcc</td>
<td></td>
<td>S</td>
<td>Goats [sheep]</td>
<td>1972</td>
<td>1975</td>
<td>GM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mp</td>
<td></td>
<td>S</td>
<td>Goats</td>
<td>1972</td>
<td>1977</td>
<td>GM</td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>Ma</td>
<td></td>
<td>E</td>
<td>Sheep, goats</td>
<td>1981</td>
<td>1962</td>
<td>GVM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MmmLC</td>
<td></td>
<td>S</td>
<td>Goats [sheep]</td>
<td>?</td>
<td>1980</td>
<td>GVM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mp</td>
<td></td>
<td>S</td>
<td>Goats</td>
<td>?</td>
<td>1980</td>
<td>GM</td>
<td></td>
</tr>
<tr>
<td>Portugal</td>
<td>Ma</td>
<td></td>
<td>E</td>
<td>Sheep, goats</td>
<td>1958</td>
<td>1984</td>
<td>GVM</td>
<td>MmmLC isolated in Portugal.</td>
</tr>
<tr>
<td></td>
<td>MmmLC</td>
<td></td>
<td>S</td>
<td>Goats</td>
<td>?</td>
<td>?</td>
<td>GVM</td>
<td>sheep and goats</td>
</tr>
<tr>
<td></td>
<td>Mcc</td>
<td></td>
<td>S</td>
<td>Goats</td>
<td>?</td>
<td>?</td>
<td>GVM</td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td>Ma</td>
<td></td>
<td>E</td>
<td>Goats [sheep]</td>
<td>1854</td>
<td>1974</td>
<td>GM</td>
<td></td>
</tr>
<tr>
<td>Italy*</td>
<td>Ma</td>
<td></td>
<td>E</td>
<td>Sheep, goats</td>
<td>1816</td>
<td>1951</td>
<td>GVM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MmmLC</td>
<td></td>
<td>S</td>
<td>Goats [sheep]</td>
<td>1954</td>
<td>1973</td>
<td>GVM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mcc</td>
<td></td>
<td>S</td>
<td>Goats [sheep]</td>
<td>?</td>
<td>1962</td>
<td>GVM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MmmLC</td>
<td></td>
<td>S or E</td>
<td>Goats</td>
<td>?</td>
<td>?</td>
<td>GM</td>
<td>Sparta goats.</td>
</tr>
<tr>
<td></td>
<td>Mcc</td>
<td></td>
<td>S</td>
<td>Goats</td>
<td>?</td>
<td>?</td>
<td>GM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MmmLC</td>
<td></td>
<td>S</td>
<td>Goats</td>
<td>1954</td>
<td>1978</td>
<td>GM</td>
<td>Sparta goats.</td>
</tr>
<tr>
<td></td>
<td>Mcc</td>
<td></td>
<td>S</td>
<td>Goats</td>
<td>?</td>
<td>1957</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Israel</td>
<td>Ma</td>
<td></td>
<td>E</td>
<td>Goats, sheep</td>
<td>1954</td>
<td>1954</td>
<td>GM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MmmLC</td>
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<td>S</td>
<td>Goats</td>
<td>1977</td>
<td>1978</td>
<td>GVM</td>
<td></td>
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<tr>
<td>Iran*</td>
<td>Ma</td>
<td></td>
<td>E</td>
<td>Sheep, goats</td>
<td>1959</td>
<td>1962</td>
<td>GVM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MmmLC</td>
<td></td>
<td>S</td>
<td>Goats</td>
<td>?</td>
<td>1958</td>
<td>GM</td>
<td>Sparta goats.</td>
</tr>
<tr>
<td>Morocco</td>
<td>Mcc</td>
<td></td>
<td>E</td>
<td>Sheep, goats</td>
<td>1938</td>
<td>1983</td>
<td>?</td>
<td>MmmLC is common in Morocco.</td>
</tr>
<tr>
<td></td>
<td>Ma</td>
<td></td>
<td>E</td>
<td>Goats, sheep</td>
<td>1958</td>
<td>1986</td>
<td>?</td>
<td>sheep and goats</td>
</tr>
<tr>
<td>USA</td>
<td>MmmLC</td>
<td></td>
<td>E</td>
<td>Goats</td>
<td>1959</td>
<td>1972</td>
<td>GM</td>
<td>All four agents identified in a single State.</td>
</tr>
<tr>
<td></td>
<td>Mcc</td>
<td></td>
<td>S</td>
<td>Goats [sheep]</td>
<td>1954</td>
<td>1974</td>
<td>GM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mp</td>
<td></td>
<td>S</td>
<td>Goats</td>
<td>1955</td>
<td>1974</td>
<td>GM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ma</td>
<td></td>
<td>S</td>
<td>Goats</td>
<td>1959</td>
<td>1978</td>
<td>GM</td>
<td></td>
</tr>
<tr>
<td>Australia*</td>
<td>MmmLC</td>
<td></td>
<td>S or E</td>
<td>Goats</td>
<td>?</td>
<td>1957</td>
<td>?</td>
<td>Atypical forms of Ma infection.</td>
</tr>
<tr>
<td></td>
<td>Ma</td>
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<td>S</td>
<td>Goats</td>
<td>?</td>
<td>1957</td>
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<td>1957</td>
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<td></td>
<td>Mp</td>
<td></td>
<td>S</td>
<td>Goats</td>
<td>?</td>
<td>1957</td>
<td>?</td>
<td></td>
</tr>
</tbody>
</table>

* relative prevalence of MmmLC and/or Mcc unknown.

The mycoplasmas are listed in decreasing order of prevalence, and are shown only if there is a published account of their identification. References used in compiling this table are obtainable from the authors.

**Ma:** Mycoplasma agalactiae

**MmmLC:** Mycoplasma mycoides subsp. mycoides LC

**Mcc:** Mycoplasma capricolum subsp. capricolum

**Mp:** Mycoplasma putrefaciens

(): confined to certain regions

(): unlimited or unknown distribution

E: epidemiologic

S: sporadic cases

(S): exceptional sporadic cases

($Sheep$): rare or exceptional cases in sheep

GM: general disease control measures (without vaccination)

GVM: general control measures and vaccination

*: not stated by the authors.

Notes:

- France: May 1959-1977, with a presumably imported enzootic/epizootic infection due to MmmLC, which affects intensive dairy husbandry of Saanen goats. Outside this area of the Mediterranean, the trade in animals has also been held responsible for sporadic cases in areas previously considered free from the disease: i.e., MmmLC infections in Germany, 

- **Enzootic infection of Ma in traditional flocks has co-existed, since 1977, with a presumably imported enzootic/epizootic infection due to MmmLC, which affects intensive dairy husbandry of Saanen goats.** Outside this area of the Mediterranean, the trade in animals has also been held responsible for sporadic cases in areas previously considered free from the disease: i.e., MmmLC infections in Germany,
Sweden and Canada; Mcc infection in the UK (19). The question of imports and exports has also been raised in the USA and Australia. The authors could cite many examples, even on a regional scale (21, 37, 42, 73), of outbreaks occurring, sooner or later, after the introduction of new animals, particularly in the case of goats. This mode of herd contamination, although not specific, becomes very important in the case of contagious agalactia, as a result of the frequent occurrence of asymptomatic carriers.

Secondly, the change in the general epidemiology of contagious agalactia has probably been revealed by the intensification of sheep and, more especially, goat production. High-yielding dairy goats kept under intensive conditions, fed in zero-grazing systems and machine-milked, are more prone to develop severe clinical forms of infection than goats in 'mixed' herds (suckling then milk-producing), kept under the traditional extensive conditions. Since this intensification of production, the involvement of MmmLC and Mcc has been more clearly identified, and has more frequently given rise to hyperacute and acute forms than Ma infection (19, 57). Preceding examples (57), particularly from Italy (19) and California, where MmmLC has dominated the epidemiology of contagious agalactia in intensive herds of goats (37), illustrate this evolution. Similarly, in France, an area of traditional transhumance in the Alps, which has constituted an example of 'historical' enzootic Ma infection since at least 1935, may be clearly contrasted with the central western region of intensive husbandry, where only sporadic cases, caused mainly by MmmLC, have been recorded (19, 52).

Current situation
The consequence of these changes is a preponderance of Ma in most of the Mediterranean countries (except the Maghreb) and in western Asia, where this mycoplasma is responsible for enzootic diseases of variable extension (Table II). Sheep are mostly infected with Ma, whereas goats are mostly infected with Ma and MmmLC. The persistence in this region of the world of major long-standing foci of Ma infection in goats, in Spain, Portugal, France, Italy, Switzerland, Israel, Iraq, Iran, etc., should be stressed (4, 5, 19, 33, 44, 46, 48). Infection with MmmLC occurs in the same region, either as sporadic cases (19, 48, 57, 61) or in an enzootic-epizootic state (19, 57), in areas which are often smaller than those affected by Ma. Mcc is also present in most of these countries, particularly in Algeria (9), and above all in Morocco. Mcc is not only enzootic in a large part of Morocco, but seems to be the mycoplasma most often isolated from sheep, in addition to being present in goats (72). This unusual epidemiological situation, characteristic of certain North African countries, and probably of long standing, undermines the concept of Ma being the causal agent of 'classical' contagious agalactia throughout the Mediterranean Basin.

The epidemiological situation in the USA and Australia is different. All four mycoplasmas have been isolated from goats since the mid-1950s, without any previous description of a 'classical' clinical outbreak of the disease. MmmLC seems to be the most prevalent agent (23).

The occurrence of Ma, MmmLC and Mcc has been demonstrated in India (34, 51, 65, 68) and in Africa. In the latter, and in many of the countries listed previously (Algeria, Morocco, etc.), the geographical extension of infections due at least to Ma (25, 34) and to MmmLC (35) is probably considerable. Little information (consisting of only three reports) is available about the epidemiology of Mcc infection in Africa (2, 19, 71).

Since the original description of Mp in California in 1935, this infection has remained limited in frequency and extension, although its prevalence may be underestimated. Only sporadic clinical cases or isolations of Mp have been reported, even though seroprevalence attains 11% in California (in 450 goats and sheep in 45 flocks), suggesting the existence of enzootic subclinical forms. Clinical infection has been reported in at least five flocks in the USA, and the infectious agent has been recovered from the external ears of healthy goats. In France, Mp has been isolated from at least seven affected flocks. Clinical cases have also been observed in Spain and Egypt. Carriage in the ears has been confirmed in Australia (19, 21, 23, 42).

Co-existence of the mycoplasmas responsible for contagious agalactia is not uncommon in goats. This co-existence may be demonstrated within an infected herd (19, 37, 57), or even in the same clinically affected animal (19, 45, 72). MmmLC is almost systematically one of the mycoplasmas involved, and Ma is most often another.

In conclusion, the epidemiology of the various specific infections may be distinguished from their historical evolution and geographical distribution. Thus, Ma, which is widespread throughout the world, and usually present in enzootic form, is the dominant causal agent in sheep. MmmLC is without doubt responsible for the heaviest economic losses in goats (particularly dairy goats) on all five continents, and occurs in enzootic/epizootic or sporadic forms. The epidemiology of Mcc and Mp infections remains to be determined.

Evolution in an infected area

Mycoplasma agalactiae infection
Numerous reports covering several decades have indicated the number of clinical outbreaks declared each year in certain regions of Italy, Greece and France, or have described the general evolution of the disease (19, 34, 79). While such data generally underestimate the actual clinical prevalence, they do demonstrate the high persistence of enzootic contagious agalactia, interspersed with epizootic flare-ups at intervals. Certain developments have been described as 'recurrent' or 'cyclical'. Thus, after the significant spread of the disease around 1900 in countries between the Mediterranean and the Alpine chain, an increased prevalence between 1913 and 1914, in 1934, from 1948 to 1950 and in 1979 was observed in certain
regions of Italy (19, 79). In the ovine focus of infection in the Atlantic Pyrénées, present since at least 1891, phases of recrudescence of Ma infection occurred from 1966 to 1967, from 1976 to 1978 and from 1985 to 1987 (an approximate ten-year cycle). Although the disease occurred in phases of milder clinical severity between these peaks, exhibiting subacute or chronic evolution, the infection was still definitely present.

*Mycoplasma mycoides* subsp. *mycoides* LC and *Mycoplasma capricolum* subsp. *capricolum* infections

The precise evolution of the epidemiological situation in regard to these infections is less well documented and harder to define. When these infections are not geographically and/or clinically confused with Ma infection, they are often of such economic gravity that stricter measures, such as slaughter or systematic testing for infected animals, must be applied. The infection of goats with *MmmLC* may, however, assume enzootic proportions in certain regions (57).

**Evolution within an infected flock or herd**

**Incidence**

The disease may appear suddenly as an ‘explosive’ clinical outbreak, or successively affect a limited number of animals. All intermediate forms between these two possibilities can be observed. One or more discrete clinical cases would probably already have occurred, possibly during the previous lactation, but these would have failed to alert the stockbreeder (39, 52).

This often happens with *MmmLC* (19, 52) and *Mcc* (57), and has been reported for *Mp* (21). Some accounts make no mention of previous clinical manifestations in individual animals. Such outbreaks are usually caused by asymptomatic carriers or shedders and are sometimes associated with adverse environmental conditions (37). The appearance of new cases at regular intervals within a flock is also characteristic of *Ma*, particularly in areas of long-standing enzootic infection (79).

**Prevalence**

The evolution of prevalence in a flock or herd is governed by two major non-infectious factors: the physiological status of the females and the movement of animals linked to transhumance. It is thus possible to identify three physiological and seasonal periods of maximum clinical prevalence in dairy breeding systems where the reproductive cycles of ewes and goats are synchronised, based on the date of transfer to summer pastures.

First, the highest peak occurs after parturition (in the dams and young). This specific period of clinical expression is typical of Ma infection (57, 61, 79), and almost always occurs with *MmmLC* and *Mcc* (19, 57). It often coincides with the expression of an infection contracted during transhumance or after the introduction of an asymptomatic carrier into the herd during the previous lactation.

Secondly, the period after the onset of milking (particularly machine milking) can give rise to a second peak, as transmission occurs through the milk during milking (37, 39).

Finally, the third peak may occur during transhumance, due to the inevitable multiple contacts on the communal mountain pastures and possibly to the stress associated with the transfer to summer grazing (34, 79). The traditional practice of the mountain shepherds, in distributing flocks into different winter quarters on returning from the summer transhumance, has been blamed for certain outbreaks.

**Persistence**

The clinical persistence of contagious agalactia in a flock or herd usually lasts for at least several months if no radical control measures are applied. However, it is not uncommon for clinical recurrence to be observed in the same or different animals during the next lactation (9, 45, 61, 72), or even for two, three, four or more years (19, 52, 57). All four contagious agalactia mycoplasmas are associated with this considerably lengthy persistence. The estimated rate of ‘relapse’ from one year to another is available for the enzootic area of the French Atlantic Pyrénées. Between 1984 and 1993, the proportion of flocks which, after already having been affected the previous year, then exhibited clinical relapse, fluctuated between 10% and 30%.

Comparison of the clinical pictures in a given flock from one year to another may reveal qualitative variations in the organs preferentially affected. Transitions from mammary forms to ocular or respiratory forms, or from pneu-mo-articular forms to mammary forms, have been described (19, 72). These changes again demonstrate the proteiform nature of the symptoms of contagious agalactia. This course of disease is typical of goats infected with *MmmLC* or *Mcc*. It must be distinguished from the possible evolution of Ma infection over many years in enzootic areas, in which the clinical disease almost exclusively affects sucklings or primiparous females during the years following the initial outbreak (15, 45, 72). This second course constitutes one manifestation of the long-term, generally subacute evolution of Ma infections, corresponding in adults to infections which may remain confined to the udder.

The serological persistence of contagious agalactia within a flock was evaluated in 146 clinically affected flocks in the Atlantic Pyrénées between 1984 and 1992. ‘Recovery’ was defined as seronegativity of the flock, demonstrated by enzyme-linked immunosorbent assay (ELISA), coupled with disappearance of the symptoms. Such recovery was only obtained on average approximately five years after the initial outbreak. Prolonged serological persistence has also been noted in the Spanish Pyrénées, where the same technique has been applied to serological surveys over many years (34). An epidemiological survey in Greece showed that antibodies to Ma infection (demonstrated particularly by ELISA) could still
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be detected eight years (in goats) or three years (in sheep) after the initial disease (74).

The microbiological persistence of contagious agalactia in the flock or herd is best studied by the direct testing of bulk tank milk (tanks or churns). In 1995, bulk milk samples were taken from 115 flocks, which were classified according to clinical, bacteriological and serological status (15). Ma could be isolated from 12 of the 18 previously diseased flocks (which no longer demonstrated symptoms and were mostly seropositive), in concentrations ranging from 10⁴ to more than 10⁷ colony-forming units (CFU) per ml of bulk tank milk. The initial clinical outbreak in these shedder flocks had occurred one to eight years earlier. This again confirms the considerable persistence of occult Ma infections and the major epidemiological risk of animal movement.

A study conducted in Israel also illustrated the possibility of detecting MmmLC in bulk tank milk over two years. This study included samples from apparently healthy flocks (60).

Molecular epidemiology

**Mycoplasma agalactiae infection**

Genomic, protein and antigen variabilities have been studied since 1991 in 250 strains of Ma, isolated in ten countries of the Mediterranean Basin and Africa between 1951 and 1995 (11, 12, 13, 14, 34, 69, 75).

**Genomic and protein variability**

Genomic variability was examined by comparing total deoxyribonucleic acid (DNA) restriction profiles, and protein variability evaluated using sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE). The existence of a major restriction profile and protein profile which included about 80% of isolates was demonstrated. Approximately ten other genomic and protein profiles were also identified. It is not yet possible to distinguish clearly a link between these molecular characteristics and the geographical origin of the isolates. For example, certain specific profiles occur in France and Spain (where most of the isolates belong to the major type) and also in African isolates.

**Antigenic variability**

The antigenic variability of Ma was examined by comparing immunoblotting patterns which had been obtained with a number of field or experimental polyclonal sera (11, 14, 69). Distinct differences were apparent in France, for example, between ovine isolates from the Atlantic Pyrénées and caprine isolates from Savoy; no exchange of animals having occurred between these regions.

The existence of variable antigens was later demonstrated by using Ma-specific monoclonal antibodies (MABs) (11, 12, 13). Variations in certain antigenic determinants were apparent in successive generations of the same clone. In M. bovis, this type of diversification of surface antigenicity has been interpreted as an adaptive strategy of the micro-organism to its host, providing a certain escape from immunitory defence mechanisms or even a degree of 'specialisation' of the affinity for certain tissues. Ma is genetically, antigenically and pathologically very close to M. bovis (18, 34). Antigenic profiles were obtained by dot immunobinding and immunoblotting, using MABs which recognised epitopes that did not exhibit phenotypic variability with these methods (11, 12, 14). True antigenic differences appear to exist and eight distinct profiles were identified within the 250 isolates. There is a relatively clear link with geographical origin; one frequent profile includes most isolates from south-west France, Spain and Portugal and differs from the profiles of isolates from Savoy (France) and Macedonia (Greece). Thus, antigenic differences exist between enzootic regions within a given country (e.g., France and Spain).

These results concur with those of a German study, which demonstrated homogeneous DNA restriction profiles in 13 out of 14 Ma strains, with slight differences in protein profile (by SDS-PAGE) and clear antigenic variability (by immunoblotting with polyclonal sera) (34).

**Mycoplasma mycoides subsp. mycoides LC and Mycoplasma capricolum subsp. capricolum**

It is difficult to link strain differences with geographical origin, because these mycoplasmas exhibit greater intraspecific heterogeneity than Ma. However, genomic polymorphism has been recorded in collections of isolates from different countries, either by comparison of amplification products from polymerase chain reaction (PCR) of randomly cloned genomic fragments (see 'Diagnosis', above), or by analysis of restriction products from fragments containing ribosomal ribonucleic acid (RNA) genes. Within Mcc, comparison of Moroccan strains with isolates from Australia, Italy and France, based on SDS-PAGE profiles and immunoblotting, revealed certain protein peculiarities in the strains from Morocco (72).

Analytical epidemiology

**Sources of mycoplasmas**

Animal sources have a much more important epidemiological role than the environment.

**Sick animals**

Shedding of mycoplasmas usually precedes the appearance of symptoms. Experimental evaluation of the duration of pre-clinical shedding showed that this duration varied from approximately one to ten days, depending on the dose and route of inoculation and on the mycoplasma (68). When Ma was injected subcutaneously, shedding in milk lasted from between four to seven days (79).
Maximum shedding usually occurs during the clinical stage. It may be particularly significant and diversified following bacteraemia. Routes of excretion can include the following: milk, tears, respiratory secretions or discharge, faeces, urine, discharge from affected joints, uterovaginal secretions and even male genital secretions (21, 33, 79). Counts in the milk or urine may exceed $10^9$ CFU/ml. 

**Clinically cured animals**

**Adult lactating females**

Many studies have proved continuous or recurrent (after a new pregnancy) shedding which may be air-borne or, above all, through milk (56, 57, 79). The durations of shedding in the milk, assessed experimentally, were as follows: three weeks (Mp in goats), four weeks (Mc in ewes), two months (Ma in ewes), five months (Ma in goats), seven months (Ma in a single goat) and ten months (Ma in ewes) (33). Ma was recovered from vaginal swabs of goats for up to six weeks after inoculation by various routes (33), confirming previous reports of the local persistence of Ma for ten weeks in goats after inoculation by the vulvar route (68).

An experimental model of chronic Ma infection was studied for five years in the same lactating ewes (11). During the first lactation, 10 ewes which had been inoculated subcutaneously shed mycoplasmas in milk for an average of 82 days, in some cases until drying-off (pathological or induced). A total of 20 ewes were naturally infected by direct contact with the first ewes, or by machine milking. During the second lactation, 5 of the 30 again shed Ma in the colostrum, without exhibiting any symptoms. This lasted from one week to at least two months, after which the animals were experimentally reinfected. Thus, the shedding of Ma in the milk of these five ewes lasted between at least six and twelve months before their reinoculation. After this, shedding (always asymptomatic) was prolonged in only two ewes, for two and six weeks before drying-off. No isolate could be obtained during the third to fifth lactations. In this model, symptoms had thus disappeared by the second lambing and shedding in the milk by the third.

**Adult vaccinated females**

In adult females, vaccinated with an attenuated strain of Ma, carriage in the lymph nodes or in the joints lasted for three to nine months after inoculation (29).

From a general point of view, the major epidemiological importance of lactating animals (either vaccinated or not), which become asymptomatic shedders, must be stressed. Some of these animals merely harbour mycoplasmas (in the lymph nodes) without shedding them, at least temporarily. Taking into account the major role of milk as a vector in flocks, whether by milking or suckling, this peculiarity of mycoplasmas is an essential factor in the maintenance and spread of infection within a flock. Exacerbated by certain traditional practices, such as poorly supervised commercial transactions, movement of animals and collective milking on summer pastures, this feature may explain past failures to eradicate contagious agalactia.

**Adult males, non-lactating females, non-pregnant females and lambs**

In these animals, and sometimes in lambs, carriage or insidious shedding may persist with only discrete clinical or subclinical illness (particularly with Ma). Adult males and dry and non-pregnant females can shed mycoplasmas by rectal, nasal or even ocular and genital routes (33, 79). Experimental infection of lambs with Ma by various routes resulted in persistent but almost symptomless infections. However, rectal and ocular shedding have been demonstrated between 72 and 77 days after inoculation. The carriage of Ma, confirmed on necropsy, lasts for at least six months, particularly in the digestive tract, lasts for at least six months, particularly in the digestive tract, lasting for at least six months, particularly in the digestive tract, lasting for at least six months, particularly in the digestive tract.

More information is required on the epidemiological importance of such categories of animals as sources of mycoplasmas (the loan and sale of males is common). The occurrence or expression of infection in lambs also depends on the acquisition of passive immunity through ingestion of colostrum. In this regard, the time during pregnancy or lactation at which suckling females become infected is therefore crucial.

**Healthy carriers**

Healthy carriage essentially involves vestibular carriage. There are some reports of vulvar carriage in healthy females, but cephalic carriage in healthy or sick animals, from flocks with or without a history of infection, is more frequent and probably of greater epidemiological importance. However, the peculiarity — and the risk — of this carrier state is that it may occur independently of any clinical expression. The most frequent habitat is the external ear canal, which exhibits certain ecological and immunological peculiarities (the immune defences of the host probably being less effective).

**Goats**

All four contagious agalactia mycoplasmas have been recovered from ear swabs in goats, in the following order of decreasing frequency: MmmLC, Mc, Mp and Ma (19, 21, 22). These results were principally obtained in the USA, Australia and France, where captive contagious agalactia appears to be caused by these four mycoplasmas in the same order of frequency. Mycoplasmas have also been recovered from the tonsils, mouth, nose and middle ear. One to six different species may be present in a single swab, yielding cultures in concentrations of up to $10^9$ CFU/ml. The origin and significance of this type of carriage remain obscure. Colonisation of the ear could follow bacteraemia, either directly, or indirectly through certain blood-sucking mites which harbour the same mycoplasmas. The existence of multiple mycoplasma species in cultures from a single swab suggests the intervention of such vectors. As the external ear...
Mycoplasmas are considered delicate. Lacking a cell wall, they are examples of the ‘minimum cell’ which needs to behave like a parasite in order to multiply. They are sensitive to heat (50°C to 55°C), ultraviolet light, putrefaction, antiseptics and common detergents.

Under experimental conditions, mycoplasmas can survive for one to two weeks at room temperature, for one to several months in cold conditions (4°C to 8°C), and from six months to several years at -20°C. Resistance diminishes at temperatures above 30°C. MmmLC survived for more than 70 days in goat milk kept at 5°C. Similarly, M. bovis survived in normal milk for two months at 4°C and two weeks at 20°C. Survival was considerably reduced in mastitic milk (less than one day at 20°C).

In conditions similar to those in the field, M. bovis survived for longer in the shade than in sunlight, and for longer at 20°C than at higher temperatures. When placed on various inorganic substrates (such as metal, glass or synthetic sponge), this mycoplasma survived for 1 to 18 days. M. bovis survived storage for 18 days in drinking water and 236 days on unsterilised dung. Experiments conducted in France to determine the survival of Ma on organic substrates (bracken, straw, dung, soil, tissues, wood, ewe’s milk and water; sterilised and unsterilised) at room temperature gave survival times of up to seven days after seeding on wood or in water (sterilised or unsterilised), and in sterilised soil or milk. No mycoplasma could be recovered from any substrate after 15 days (P. Lebret and F. Pédaillé, unpublished findings).

Hence, the environment can serve as a transient reservoir of mycoplasmas.

**Modes of infection**

**Routes of penetration**

**Oral route**

*From the nature of observed outbreaks*, it can be seen that the oropharyngeal route is the most important route for penetration by mycoplasmas. This is especially the case when taking into account the ‘natural’ modes of infection, such as contact and communal feeders, and exempting human intervention through milking. The small intestine would be the privileged site of adhesion and possible invasion (33, 79). The severe infection in unweaned kids during various clinical outbreaks of contagious agalactia due to MmmLC, Mcc, Ma or Mp probably resulted from invasion by mycoplasmas present in the colostrum or milk (21).

Supporting experimental evidence confirms the importance of this route. Infection and disease can be reproduced by the oral route both with MmmLC and Mcc in kids. The same applies to lambs inoculated with Mcc. The outcome is also dependent on the virulence of the strain and on passive immunity conferred by the colostrum. Oral acquisition of infection by weaned, in-contact lambs has also been suggested by the isolation of Ma from rectal swabs and the small intestine at necropsy. The oral administration of Ma to non-pregnant adult goats and a ram induced asymptomatic infections, characterised by prolonged periods (two weeks) of intestinal bleeding. Ma was subsequently recovered from the faeces, blood and nostrils, at slaughter, it was recovered from blood and testes. Subacute enteritis was confirmed by histopathological findings (33).

**Respiratory route**

*Under natural conditions*, the actual importance of this route is difficult to determine. A distinction should be made between the respiratory tropism of MmmLC and Mcc, and that of Ma and Mp. The infection of adults by this route is favoured by close contact, whereas it could take place during suckling in young animals.

Various attempts to reproduce the disease experimentally by the respiratory route have been made, revealing two categories of symptoms. The first group consists of persistent infections with discrete symptoms or no symptoms at all, and occurs after nasal or bronchial instillation of Mcc into goats, nasal instillation of Mp into goats, and nasal or tracheal infection of lambs and goats with Ma. The second group consists of clinical illness obtained after bronchial inoculation of MmmLC into young or adult goats or lambs, Mcc into lambs, and Ma into goats (23, 24).

**Mammary route**

*From the epidemiological aspect*, this can be considered as the main route of infection in milked females. In view of the intensity and duration of shedding in milk, microbial pressure exerted on the teat sphincter during milking results in ascending infection following the deposition of mycoplasmas on the teats, with or without active transport by the ‘impact’ phenomenon during machine milking. This type of mammary colonisation is encouraged by defective milking technique or faulty equipment, and by the general absence of teat-dipping in small ruminants (21, 23, 37).
From a physiopathological aspect, mammary infection may easily be obtained by inoculating into the teat, resulting in hypogalactia. Experiments have been conducted with Ma, Mcc, MmmLC and Mp. Mammary infection with mycoplasmas in ewes and goats is used as an experimental model to study pathogenicity or therapeutic efficacy. Many mycoplasmas have been tested for this purpose, some of which do not exhibit any major tropism for the udder (23, 33, 72).

The oral, respiratory and mammary routes constitute the principal means of penetration for mycoplasmas under natural conditions.

Ocular route
In infected flocks, ocular penetration may occur during close contact, on the emission of infectious aerosols, or by insillation of contaminated dust or fodder particles.

Experimentally, clinical disease has been reproduced on rare occasions with Ma, with MmmLC in goats and with Mcc, which produced a generalised, fatal infection in a lamb. Recently, several experiments have been conducted in France in an attempt to develop a model of the early stages of Ma infection, using the conjunctival route (64). The resulting almost symptomless infection was accompanied by colonisation of lymph nodes draining the inoculation site on the 7th and 14th day post inoculation (p.i.) (depending on the titre of the inoculum). Extensive spread to other lymph nodes and to the spleen revealed the existence of bacteraemia. All the cephalic lymph nodes were still infected after 60 days p.i., suggesting the long persistence of Ma. This simple and reproducible model can be used for comparing strain pathogenicity and assessing the protection conferred by immunisation.

Genital route
In the field, the actual epidemiological importance of this route is probably confined to 'atypical' genital forms (34, 53, 68). Nevertheless, sporadic cases may occur. Infection or disease caused by Ma, Mcc, MmmLC and MmmSC involves the genital organs of the male (33, 39, 53) and/or female (33, 34, 53, 68).

The experimental production of granular vulvovaginitis with Ma in goats led to long-lasting clinical infection (68), in contrast to that of Mcc in ewes.

Other routes
Under natural conditions, certain minor routes of penetration, such as subcutaneous or intradermal inoculation (during shearing or through wounds), may be effective (79).

Experimentally, the subcutaneous route is often used (7, 11, 33, 79). Intradermal, intramuscular, intravenous, intraperitoneal, intra-articular and intracerebral routes have also been tested (33, 71).

**Modes of transmission**

**Vertical transmission**
- Transmission during pregnancy from dam to foetus has been seriously suspected, since the isolation of MmmLC from the internal organs of aborted calves, and of Ma, MmmLC and Mcc from swollen joints of neonate kids and lambs born at full term (48, 72). Such transmission has been demonstrated for M. bovis in cows. The abortions observed in certain outbreaks confirm that the placenta may be affected after bacteraemia. However, young animals separated from their infected dams at birth do not necessarily develop infection (19).
- Transmission at parturition cannot be ruled out, in view of the risk of vaginal infection.
- Transmission by suckling is probably the essential mechanism because milk constitutes an early, major and persistent route of shedding of Ma (23), MmmLC (19), Mcc (19, 72) and Mp (21, 23).

**Horizontal transmission**

**Direct horizontal transmission**
Direct horizontal transmission from animals in the clinical stage of infection does occur. Although environmental sources cannot be excluded, this type of transmission has been strongly incriminated in controlled experiments by the infection of ‘in-contact’ animals (11, 33). Its effectiveness, however, depends firstly on the main source of shedding. When mammary shedding is the prime source, either from the onset of or during chronic infection, there is limited direct transmission between adults. This is not so during respiratory shedding, for instance, when coughing animals emit infective aerosols. Secondly, the population density of the breeding units is a factor, albeit non-specific, in this type of transmission because overcrowding promotes contagion by direct contact.

**Indirect horizontal transmission**
Indirect horizontal transmission may occur in at least four ways, of unequal importance.
- The possible intervention of vectors, principally parasites, has been suggested but their actual role has yet to be determined. The principal vectors are mites which inhabit the ears and are known to carry mycoplasmas and to move from one animal to another (22). Ticks may also be infected with Mm sp. Finally, fleas may act as vectors of MmmLC (50). Most of these cases concern goats.
- Transmission from the environment may occur in certain circumstances but its true importance is not well known. Observations and a few experiments have in fact provided contradictory results for Ma (79). Many factors may be involved, distorting certain observations, such as the actual significance of reservoirs of mycoplasmas (bacterial load, conditions of survival, etc.), susceptibility of the animals (physiological status, age, sex, immune status, etc.), and the permanence of exposure (degree of confinement, etc.). This
question is of practical importance in certain regions (e.g., communal grazing, summer pastures, farms divided into several parts).

A partial answer is provided by non-lactating ewes exposed to Ma in a naturally contaminated sheep house. The first stage of the experiment, aimed at contaminating the sheep house (25 m²), consisted of inoculating ten lactating ewes and verifying their shedding state by detecting Ma, and checking the transmission to in-contact lactating ewes. The second stage was to replace these shedding ewes with 15 new, healthy, dry ewes. No clinical, bacteriological or serological modification could be detected for two months (D. Bergonier, unpublished findings).

- The role of manual and, more especially, machine milking is much clearer. It is due to the importance of milk-borne shedding, the role of machine milking in weakening the primary defences of the teat (at the sphincter), and the tropism of contagious agalactia mycoplasmas for the udder. The significant role of milking in the transmission of contagious agalactia has frequently been emphasised (21, 23, 37, 61, 79).

- The intervention, probably incidental, of transmission during shearing, or via shoes or wheels, has been mentioned.

Susceptibility factors

Animal factors

*Host species*

Rigorous experimental determination of the variations in host species sensitivity is difficult because of a certain host specificity for MmmLC, Mcc and Mp, and the existence in experimental infections of confounding factors (such as age, sex and physiological status) which limit comparisons. It is therefore valid to underline certain differences, particularly in the case of Ma. It is generally observed, in natural and experimental infections, that clinical expression is more pronounced in goats than in sheep. This does not seem to be specific to mycoplasmoses (33, 71, 72, 79).

*Breed*

Firm conclusions cannot be drawn at present, regarding the existence of variations in susceptibility attributable to breed. On the one hand, Ma, MmmLC and Mcc are considered major (or primary) highly virulent agents of mycoplasmoses, for which the variability between individuals or breeds is of little significance. Outbreaks have often in fact spread between flocks or herds of different breeds (19, 57). On the other hand, there appear to be variations in the susceptibility of breeds to MmmSC, the agent of CBPP, implying that similar variability cannot be discarded for contagious agalactia. A study conducted in Mongolia suggests that the local breed of sheep is not very susceptible to Ma (24).

The clear variations in symptoms expressed by various breeds throughout the world in response to the same mycoplasma provide an intermediate response. For example, MmmLC regularly produces mastitis and arthritis in Europe and North America, but goats in Nigeria and some breeds in Oman seem to be more resistant to articular involvement (23, 34, 38). In this type of example, however, the variability associated with strain pathogenicity and the immunitary and environmental factors should be taken into account.

*Age*

The greater susceptibility of young animals, particularly kids, to MmmLC and Mcc has frequently been reported. In natural outbreaks, hyperacute clinical disease with a fatal outcome is common in this age group (57, 58, 72). In regard to experimental inoculation, inoculation by various routes in young animals is more likely to result in bacteraemia and very severe disease than in adults. In the case of Ma, the effect of age is probably less pronounced, particularly in lambs (species-related bias), in which the difficulty in reproducing clinical contagious agalactia by various routes may be due to endocrine peculiarities (33, 64).

*Sex and physiological status*

Adult males and non-lactating, non-pregnant females are usually less severely affected than pregnant or lactating females. Comparisons of experimental infection in male and female goats and sheep have shown that rams present the most discrete symptoms, independent of species susceptibility (79). Lactation may facilitate the multiplication of mycoplasmas in the udder, and their clinical manifestation in this major target organ. The importance of pregnancy in exacerbating infection has recently been confirmed (33).

Immune status

A certain resistance to reinfection exists in contagious agalactia. The immunity which develops after primary infection may attenuate the subsequent clinical severity, even if reinfection cannot be avoided. The immune mechanisms and effectors are largely unknown (63).

Note that intercurrent infections may be responsible for greater susceptibility (72, 79).

Environmental factors

*Husbandry factors*

The importance of the type of husbandry in the epidemiology of contagious agalactia has been emphasised; certain types of flock or herd management possibly affect animal susceptibility. Apart from machine milking (21, 37), housing (construction, microclimate, hygiene) and high population density may also enhance the susceptibility of animals in cases of respiratory involvement, especially under the conditions of certain intensive systems. Certain nutritional factors may also have an important role (21).

*Climatic factors*

Various situations of environmental stress may promote the development of infection, such as sudden changes in climate and/or premature shearing, which are believed to aggravate certain clinical manifestations (51). Goats seem to be more
sensitive to such factors (21), which are probably more important in the case of *Mp* infection.

**Synthetic epidemiology**

Descriptive and analytical data first demonstrated the differences between sheep and goats. The increased trade in breeder goats, on an international scale, may promote the spread of contagious agalactia. Transmission, particularly in goats, may then occur from the ears or even parasite vectors. Finally, this species is generally more sensitive to infection and to environmental factors than sheep. The greater variability in aetiology, symptoms and even epidemiology of contagious agalactia in goats should therefore be emphasised.

The epidemiological cycle of contagious agalactia can be determined from the information mentioned above (Fig. 1).

**Diagnosis**

A hint of the presence of contagious agalactia is usually provided by the observation of certain epidemiological and clinical features. The symptoms and evolution of the disease are more or less characteristic, depending on the mycoplasma species, animal species and longevity of infection. At one extreme, the picture may be pathognomonic, with an explosive outbreak occurring in an area hitherto free from contagious agalactia and caused by *MmmLC* or *Mcc* in an intensive breeding herd of dairy goats at the onset of lactation, for example. It may, in contrast, be very discrete in traditional

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*Fig. 1*

**Epidemiological cycle of contagious agalactia (principal modes of transmission)**
Fig. 2
Origin of outbreaks of contagious agalactia caused by Mycoplasma agalactiae between 1984 and 1994 in the Atlantic Pyrénées Department of France (250 clinical foci)

In regions where Ma is enzootic, under these conditions, and in view of the existence of other clinical entities, which must be differentiated from contagious agalactia (such as lentiviral infections, certain forms of classic mastitis, etc.), the systematic application of an aetiological diagnosis is essential.

**Aetiological diagnosis**

**Isolation**

The culture media and isolation techniques for mycoplasmas have been extensively described elsewhere (39). Briefly, the species involved in contagious agalactia can readily be grown on the culture media used to isolate mycoplasmas of ruminant origin, such as 'DE medium and its variants. The maintenance of constant quality from one batch of a culture medium to another is at least as important as its composition. The addition of thallium acetate (1 ml of 10% solution per litre) and ampicillin (2 g per litre) will considerably reduce contamination with other bacteria, although samples should still be collected under strictly aseptic conditions.

For isolation in broth medium, four or five decimal dilutions should be prepared to significantly reduce contaminants and inhibitors, particularly in the case of milk samples. Solid media should be freshly prepared and sown directly with the sample or, better still, after the broth stage. Cultures should be incubated at 37°C in a moist atmosphere (for agar). Anaerobic conditions are best for an initial isolation (19). Growth will appear after one to two days for MmmLC and Mcc and after two to five days for Ma, as more or less intense turbidity in broth and typical colonies on agar (19).

**Conventional identification**

Purification by cloning before identification is not recommended, except for biochemical testing and the growth inhibition test. In fact, cloning and subculture take too much time and preclude the detection of mixtures of mycoplasmas. In addition, following the demonstration of highly variable antigens in certain mycoplasmas, such as Ma (11, 12, 14), this could result in the selection of antigenic phenotypes far removed from the original isolate. This risk, however, must be evaluated for each species.

**Biochemical identification**

Biochemical tests which are time-consuming and difficult to interpret have lost much of their value. Routine identification now relies on serology (39).

**Serological identification**

*Traditional serological identification* is based on growth inhibition, metabolic inhibition, immunofluorescence and the immunoperoxidase test applied to colonies. The relative advantages and disadvantages of these techniques have been determined (39).

*Dot immunobinding tests* applied to broth cultures have been introduced recently. These are conducted on filtration membranes (0.2 µm) with low protein affinities and are at least as specific as earlier tests when polyclonal hyperimmune sera are used. This technique has the advantages of practicability and high output and can be used by non-specialist laboratories as a standardised procedure. The test is applied directly to fresh or stored cultures and takes two to three hours. Its sensitivity is good, it incorporates intraspecific variations and can detect mixtures of mycoplasmas.

It is easy to identify Ma and Mp serologically, except for weak cross-reactions between Ma and M. bovis, which are closely related phylogenetically (34). It may prove difficult to identify MmmLC and Mcc, which both belong to the 'mycoides cluster'. This 'cluster' is composed of ruminant mycoplasmas which share numerous genetic, protein and antigenic properties, although the diseases they cause are very different epidemiologically and pathologically. Their precise identification may require a distinction of biotype, which is hindered by the existence of close antigenic relationships, and complicated by the considerable intraspecific heterogeneity of MmmLC, Mcc and Mmc. There are numerous cross-reactions. It may prove difficult to distinguish between MmmLC and Mmc because of their close genetic, protein and antigenic similarities and the existence of numerous intermediate strains (19). Mcc is also heterogeneous (23, 24) and the type strain is poorly representative of the field isolates usually...
encountered (23), many of which are intermediate between the reference strains Mcc California Kid and Mycoplasma sp. PG50 (19).

These difficulties in identifying members of the 'mycoides cluster' will be overcome in the near future by using MAbs for certain mycoplasmas or gene amplification techniques for the cluster as a whole. MAbs have already been produced and characterised for Ma (11, 12, 14).

Genomic detection
Nucleic acid probes
These probes were developed for detecting contagious agalactia mycoplasmas from 1990 onwards. Such probes were complementary to segments of chromosomal DNA or 16S ribosomal RNA (rRNA) (34, 74). Although their specificity was high, and they represented a considerable advance in diagnosis, research was soon under way to develop PCR, which seemed more sensitive.

Polymerase chain reaction
PCR techniques and their application in mycoplasma detection have been reviewed recently. The PCR systems proposed for contagious agalactia have been undergoing development, mainly during the past three years.

Two strategies for defining target sequences for amplification are apparent from published data. Certain primers have been chosen for amplifying randomly cloned DNA fragments of variable specificity. Several systems for detecting Ma or MmmLC and Mcc have been proposed, some of them combining an amplification step with two pairs of different primers, and an identification step based on the analysis of restriction profiles of the PCR products. Sensitivity, in cultures added to milk, attains 10^3 CFU/ml (25, 76).

PCRs based on 16S rRNA fragments have also been proposed (13, 18, 34). These systems detect variable sequences in the evolution of mycoplasmas, some being specific to clusters or to species, while other sequences have been strictly preserved. Primers have thus been proposed for detecting Ma. Cross-reactions occur only with M. bovis or strains closely related to M. bovis (13, 18, 34). Comparison of the 16S rRNA sequences of these two species has revealed only eight different nucleotides. The sensitivity of these systems may be very high. The detection limit for Ma in cultures has been brought to 2 x 10^2 CFU/ml (18).

Regarding detection of mycoplasmas in clinical specimens, several groups are currently working on procedures which would be as sensitive as PCR performed from cultures. The main problem is the complex composition of milk, which is the best sampling material for detecting contagious agalactia mycoplasmas, particularly in chronic infections. Various substances present in milk, particularly proteins, can inhibit or limit amplification reactions.

PCR offers great promise as a tool for detecting contagious agalactia mycoplasmas. In addition to its high sensitivity, future improvements should permit more rapid diagnosis than with conventional techniques. The detection of mycoplasmas in animals treated with antibiotics may also become easier. However, these advantages must not obscure the risk of false positive results due to possible contaminants. Thus, PCR cannot at present be considered suitable for routine diagnosis in field laboratories requiring high output and reliability.

Serological diagnosis
Various techniques have been tested in the past (immunofluorescence, slide agglutination, tube agglutination, growth inhibition, immunodiffusion, etc.) (39, 43, 77). Two have successively undergone important development, namely the complement fixation (CF) test and ELISA.

Complement fixation test
The main research on CF commenced in the 1970s for Ma and in the 1980s for MmmLC and Mcc.

The techniques for preparing antigens were based on lysis by sonication or by repeated freezing and thawing of whole cells, sodium lauryl sulfate lysis followed by dialysis of cells with phosphate buffer, or boiling and use of the culture supernatant. CF is generally considered difficult to perform and difficult from which to obtain suitable reliability (43, 79).

Detailed evaluation of the CF test is the subject of few published reports. In fact, there was no reference technique for comparison with the CF test, because this was the first test to be widely adopted. Attention was very soon brought to the problem of specificity, however. Many false positive or cross-reactions have been noted, due to the complete antigen used in the test which includes cytoplasmic antigens of poor specificity. False positive reactions involve mainly Ma, whereas cross-reactions involve MmmLC and Mcc (9, 43). Some workers tried to solve these problems by choosing a relatively high positive threshold, which thus gave rise to erroneous negative results and the non-detection of certain healthy carriers. Under these conditions, the CF test has often been considered as having poor sensitivity (43, 79).

The kinetics of the antibodies detected by this test are available from some publications. Serum antibodies are detectable from the first appearance of symptoms, 3 to 15 days after inoculation of adult animals with Ma and from the fourth week in lambs. Such antibodies persist for several months or even for more than a year. Similar results have been reported from outbreaks caused by Ma or Mcc (79).

Finally, the CF test has been proposed as a diagnostic aid to be used in addition to epidemiological and clinical data, at the herd or flock level, but not for individual animals (43, 79 and others).
Enzyme-linked immunosorbent assay

Immuno-enzymatic techniques were introduced for contagious agalactia in 1982 and have been applied mainly to Ma and M. mycoides. A trivalent test for Ma, M. mycoides and M. capricolum has been proposed (9, 17, 40, 41, 45, 57, 77).

From the technical aspect, these 'first generation' ELISAs do not include a competition step. The authors are not aware of any publication describing improvement of the technique by the use of MAbs. Antigen is prepared by sonication in carbonate buffer, or by the action of non-ionic detergents, formaldehyde or polysorbates (TWEEN 20) (45, 47, 67). The crude data are expressed as optical densities. In order to limit the variability inherent in the conditions of equilibration and performance of each reaction, it was proposed that the results be expressed in units by reference to control sera of known titres for each test plate. This improves the reproducibility of the test (39, 40).

Evaluation of these techniques, in comparison with the CF test, has shown that ELISA is more sensitive (9, 40, 47). Such evaluation has also frequently revealed certain problems of specificity. These have arisen from comparison of the CF test and ELISA, titrations of sera in multiple antigen plates (with and without heterologous mycoplasmal antigens) (9, 45), and field observations. In the last case, false positive results may frequently be obtained from flocks and regions free of specific infection (45). In regard to contagious agalactia, this problem of specificity seems more obvious in the case of Ma but may also hinder the serological testing of other major mycoplasmosis in ruminants. Associated infections may occur in the case of contagious agalactia in goats, particularly with M. mycoides and Ma. However, in most cases, such false positive results may be due to cross-reactions in the absence of mixed infection. It has been shown by immunoblotting that rabbit sera raised against M. mycoides recognize certain protein bands present in homologous and heterologous mycoplasmas, including Ma PG2 (44). Certain ovine sera also react with bacterial or parasitic antigens, independently of any case history. This type of non-specific positive result is regarded as 'background' reaction.

An initial solution to this problem was to treat each serum with several antigens to produce corrected titres. As the results of ELISA can be expressed quantitatively, several authors proposed subtracting a heterologous titre from the specific titre (45).

A thorough analysis of the different stages in the immune-enzyme reaction which may lead to false positive results has recently been conducted. Only the use of a monoclonal conjugate (or recombinant protein G) was able to eliminate false positive results without affecting the true positive results provided by polyclonal conjugate (41).

The kinetics of serum antibodies detectable by ELISA have been studied in kids vaccinated against M. mycoides, and in adults inoculated with Ma. In the latter case, an initial study showed that immunoglobulin G (IgG) could be detected for at least 13 months after inoculation, while immunoglobulin M appeared earlier but disappeared sooner (47). In another experiment, subcutaneous inoculation of Ma into ten ewes was followed by seroconversion after six to nine days. This seroconversion, which was concomitant with the development of agalactia, lasted for approximately nine days, after which peak titres were observed. The subsequent 'plateau' phase (mean titre of 340 units, compared with a mean titre of 31 units in the healthy controls) lasted at least until the end of the subsequent pregnancy (nine months). The main non-infectious factor affecting the antibody titre is the physiological cycle: parturition is usually preceded by a fall in titre and sometimes followed by an increase. Similar kinetics were obtained in 20 naturally infected ewes. Monitoring the chronic infection in subsequent years revealed that the antibodies could persist for more than three years. In this experiment, a conjugate capable of detecting IgG was used (13; D. Bergonier, unpublished findings). Antibody kinetics depend in particular on the titre of inoculum and route of inoculation.

ELISA techniques are used mainly for flock diagnosis (39, 77). On the individual scale, they can be considered only as a screening tool (and not a diagnostic tool), leading to a rough classification of animals into three classes, as follows:

- infected
- doubtful
- presumed healthy.

Thresholds have been proposed (40). These techniques have provided valuable information at flock level. In the case of Ma, the French control system is based on annual estimation of a flock serological index, calculated from a sample of individual sera. The number of animals to be sampled is calculated from the flock size and estimated prevalence; it is important to take into account the stage of lactation and parity at the time of sampling. Calculation of the index used for flock classification may be based on various ways of combining the individual results, depending on the prevalence and control objectives (40, 41).

This application of an improved ELISA test (elimination of false positives) to sufficiently representative samples of animals may provide a valid basis for a regional control programme, taking advantage of its simplicity and high efficiency.

Finally, it must be emphasised that, as regards serology, ELISA constitutes a technique of the future for contagious agalactia and an indispensable tool for studies of seroprevalence and for control programmes. The actual epidemiological situation in most of the countries affected by the different specific infections remains little known. The wider use of these serological tests and their technical improvement should therefore be encouraged (53).
Treatment

Antibiotics and suitable therapeutic protocols

The first medicinal treatments of contagious agalactia were based on arsenical compounds, notably the sodium or zinc salts of acetarsol. Antibiotics are now widely used, but little information has been published on their use. Such antibiotics should possess the following characteristics: activity against bacteria without a cell wall, long persistence in the plasma, efficient diffusion into tissues, passage of high concentrations from the blood to milk (even becoming concentrated in the mammary gland), and very low minimum inhibitory concentrations (MIC) (80). Thus, the main antibiotics used are the tetracyclines, macrolides, florfenicol, tiamulin and the fluoroquinolones (Table III) (3, 6, 16, 28, 32, 55). The therapeutic protocols given in Table III are indicative; most of the studies solely concern MIC, particularly against \textit{MmmLC}. In most cases, only systemic treatments are envisaged, although, in view of the importance of mammary

Table III

Activity of some antibiotics used in treating contagious agalactia

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC µg/mL</th>
<th>Source</th>
<th>Conditions</th>
<th>Dose (mg/kg)</th>
<th>Duration (days)</th>
<th>Route</th>
<th>Result</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxytetracycline</td>
<td>0.32-8.0</td>
<td>(3)</td>
<td>\textit{MmmLC, Mcc, OBS}</td>
<td>5-10</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>(52)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>40-200</td>
<td>(3)</td>
<td>\textit{MmmLC, Mcc, OBS}</td>
<td>25</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>(52)</td>
</tr>
<tr>
<td>Spiramycin</td>
<td>0.1-2.0</td>
<td>(56)</td>
<td>\textit{MmmLC, Mcc, OBS}</td>
<td>25</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>(52)</td>
</tr>
<tr>
<td>Tylasol</td>
<td>0.32-8.0</td>
<td>(3)</td>
<td>\textit{MmmLC, Mcc, OBS}</td>
<td>20-25</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>(52)</td>
</tr>
<tr>
<td>Lincomycin</td>
<td>0.1-5.0</td>
<td>(80)</td>
<td>\textit{MmmLC, OBS}</td>
<td>150</td>
<td>6</td>
<td>i.m.</td>
<td>CC+, BC-</td>
<td>(38)</td>
</tr>
<tr>
<td>Tiamulin</td>
<td>0.006-0.4</td>
<td>(10)</td>
<td>\textit{Pharmacokinetic study}</td>
<td>20-25</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>(52)</td>
</tr>
<tr>
<td>Florfenicol</td>
<td>10-25</td>
<td>(80)</td>
<td>Pharmacokinetic study</td>
<td>20-25</td>
<td>?</td>
<td>i.m.</td>
<td>?</td>
<td>(80)</td>
</tr>
<tr>
<td>Enrofloxacin</td>
<td>0.17-0.22</td>
<td>(28)</td>
<td>\textit{Mae, OBS}</td>
<td>2.5</td>
<td>4</td>
<td>s.c.</td>
<td>CC+, BC±</td>
<td>(59)</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>1-10</td>
<td>(80)</td>
<td>Pharmacokinetic study</td>
<td>10</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>(80)</td>
</tr>
</tbody>
</table>

MIC: minimum inhibitory concentration
a): minimum mycoplasmicidal concentration
b): combined with doxycycline (by mouth at 10 mg/kg for 10 days) and dexamethasone (by mouth at 0.25 mg/kg for 5 to 7 days)
i.m.: intramuscular route
i.v.: intravenous route
s.c.: subcutaneous route
cc+: clinical cure
cc-: partial clinical cure
bc+: bacteriological cure
bc-: no bacteriological cure
bc±: partial bacteriological cure
obs: clinical observation
exp: experimental infection
M > P: mammary gland concentrations were greater than those of blood plasma
?: not indicated by the author
localisation, particularly in chronic forms, certain authors recommend an intramammary treatment at drying-off (19, 27).

Value of antibiotic therapy in the control of contagious agalactia

Therapeutic efficacy
The efficacy obtained under field conditions limits its interest. In practice, the sole objective of antibiotic therapy is to reduce mortality, to improve the state of sick animals and perhaps to obtain their clinical recovery with resumption of milk yield. Many authors feel that a bacteriological cure is an illusory objective (e.g., 19, 21, 56). This conclusion is based mainly on clinical observation and, less frequently, on controlled therapeutic trials (systemic administration). There are various reasons for these therapeutic failures. The sensitivity of contagious agalactia mycoplasmas to antibiotics is not known with accuracy. Very high MICs have been reported for certain strains (10, 48, 56, 70), in comparison to those obtained for the better-known M. bovis; acquired resistance to antibiotics is suspected in the case of this latter mycoplasma. The antibiotic pressure applied to small ruminants is, however, much lower. In general terms, estimates and comparisons of MIC should be treated with caution, first because no standard techniques are available for the determination of MIC for mycoplasmas, and secondly because resistance varies from one mycoplasma to another.

Treatment failures may also be due to underdosage (55), or to poor diffusion of the molecule within the inflamed udder, because of its physicochemical properties or because of histological changes associated with the infection (80). Some antibiotics (e.g., tetracyclines) exhibit only bacteriostatic activity, permitting resumption of multiplication after treatment has stopped. Too short a period of treatment, or the late application of treatment, favours the emergence of chronic carriers, thus providing a permanent source of mycoplasmas (56).

Practicability and innocuity
The antibiotic must be easy to administer, in view of the large numbers of animals which may have to be treated. Repeated injections and the administration of intramammary infusions to dozens of animals represent a great deal of work. Intramammary injections may be complicated by poor hygiene. Systemic injections run the risk of local reactions (pain, voluminous oedema) at the injection site, although such reactions are temporary (19, 27, 39, 57).

Antibiotic therapy cost
The costs of treatment of a flock must be limited. The average cost per animal is high in comparison with its culling value and there is no guarantee either of functional recovery or of sterilisation of the animal. However, treatment of the entire flock, and not merely the sick animals, is generally recommended (19, 27, 39, 57). The cost-benefit ratio of such a practice must be considered.

Prophylaxis

Vaccination
The currently used strategies for vaccination against contagious agalactia rely on conventional live attenuated vaccines or inactivated vaccines. The authors are not aware of any immunogenic preparation based on antigens or subunit proteins. Although most research has been devoted to the development of vaccines against Ma, some work has also been conducted on MmmLC. Several reviews of traditional vaccines against contagious agalactia, particularly against Ma, have been written (33, 40). The authors will consider principally the more recent publications.

Inactivated vaccines
Mycoplasma agalactiae
Numerous vaccines have been developed and applied, particularly in Mediterranean countries and eastern Europe, since the middle of the 20th century.

The protocols for vaccine preparation and administration have changed little. Inactivation techniques usually rely on formaldehyde or heating. Excipients and adjuvants comprise aluminium hydroxide (19, 79) and oil emulsion (66), although some vaccines have no adjuvant (27). The titres of the initial cultures are high (10<sup>6</sup> to 10<sup>10</sup> CFU/ml). These cultures may be derived from laboratory strains or, more often, from the tissues of naturally or experimentally infected animals or from mastitic milk. One traditional practice is to use an autogenous vaccine prepared from milk. It is usually recommended that vaccines be prepared from isolates associated with the local outbreak, or at least from the same area. Autogenous vaccines prepared from brains or, more recently, from purified cultures have been widely used. The use of an autogenous milk vaccine followed by a stock vaccine prepared from a local strain has been recommended in Italy. It is also possible to combine several Ma strains of different origins. In parallel to these preparations produced by regional institutes, commercial vaccines prepared from wild strains of a wider distribution are also available (19, 20, 79).

Most vaccination protocols involve several booster doses. The boosting of immunity is recommended at each lactation or even every four months in goats. One source recommends that goats be given three doses of vaccine before each parturition and one dose afterwards (44). These vaccines are used in enzootic regions, particularly in herds or flocks where contagious agalactia is chronic. They may also be used for healthy flocks or herds in these regions, as part of a systematic vaccination programme (19, 20, 27, 44, 78, 79).

The evaluation of inactivated vaccines is imperfect, particularly under field conditions, but raises important doubts as to the efficacy of this immunoprophylaxis. Experimental station trials have shown that such vaccines cannot prevent the installation of infection following challenge, even though the infection may remain localised and the symptoms may be
attenuated (19, 66). There is a risk of masking natural infections and favouring the occurrence of subclinical shedders, although shedding may be temporary or intermittent. Under field conditions, where infective doses may be smaller but repeated, there may be a protective effect of brief duration, observable by the lack of symptoms shown by the flock, but no cessation of shedding (79). This protection might last for three to four months but in most cases there has been no controlled trial to prove it. Recent research in Spain, covering six successive lactations in goats, showed that it is very difficult, even when multiple booster doses are given, to control a chronic outbreak clinically and even more so bacteriologically. Moreover, such vaccination may not provide protection against surinfection of exogenous origin (44). Protection efficacy would be best in healthy or recently infected herds.

The innocuity of inactivated vaccines is generally assured with regard to generalised reactions or reactions in target organs, with the exception of booster doses given at very short intervals which may induce hypersensitivity. A reaction is sometimes seen at the site of subcutaneous injections (27, 79).

Compatibility with serological testing is the third criterion of evaluation. An epidemiological study in Navarre showed that antibodies due to vaccination, detectable by ELISA, may have been responsible for increases in the serological indices of herds.

*L. mycoides* subsp. *mycoides* LC and *Mycoplasma capricolum* subsp. *capricolum*

There is little information on vaccines. The epidemiology of these infections has not implied the same need for vaccination as with *Ma*. The same procedures for preparation are followed.

In experimental terms, protection trials in weaned and unweaned kids showed that vaccines were more effective when a booster dose was given three weeks after the primary vaccination. The resulting serum kinetics of antibodies (determined by ELISA) showed two peaks. In this case, clinical expression was controlled, but colonisation of the liver, kidneys and lungs could still occur (7).

Vaccination against *Mmm*LC and even *Mcc* is practised in many Mediterranean countries, using the same kind of protocols developed for *Ma*. An outbreak in goats in Spain was controlled by an autogenous vaccine injected twice, at an interval of three weeks. The prompt use of locally produced stock vaccines is recommended in Italy. In Portugal, monovalent or bivalent vaccines (against *Ma*, *Mmm*LC or *Mcc*) are also prepared from local isolates (4, 5, 19, 20).

It is not possible at present to evaluate the field efficacy of these vaccines against *Mmm*LC or *Mcc*.

In view of the modest performance of these different vaccines (against *Ma*, *Mmm*LC and *Mcc*), their sole purpose is to reduce clinical and economic losses in enzootic regions. They are often combined with antibiotic therapy and may help to control chronic infections, although these infections remain contagious and interfere with regional prophylactic control programmes. As such practices do not permit disease eradication, they are controversial. They are merely palliative measures to be used in the absence of better prophylactic procedures.

**Live attenuated vaccines**

Two important series of vaccines were developed in Romania and Turkey. Trials were also conducted in Israel and Mongolia (78). Other research workers assessed the risks and abandoned their use (79). These vaccines were widely used, mainly in central Europe, the Balkans and the Mediterranean region (and are still in use in certain areas), but are now prohibited in many countries (27, 39).

Their partial evaluation has been reviewed (39, 78). Briefly, from the aspect of efficacy, they provide better protection against clinical expression than inactivated vaccines but can produce transient infection with shedding. Booster doses are necessary, because the conferred protection lasts only a few months.

In regard to innocuity, clinical manifestations of variable severity may occur, necessitating strict respect of the conditions of use: maximum inoculum not to be exceeded and contra-indications associated with age (young animals) and certain physiological states (lactation). As the stability of attenuation may fail when the vaccines are used in different field conditions and breeds, all the herds or flocks within the infected area should be vaccinated.

Incompatibility with serological testing and antibiotic therapy seems to be obvious with this type of vaccination (39).

In conclusion, the usefulness of the different types of traditional vaccination is questionable even though their application is still on the increase (30, 31, 53). The merely relative efficacy of these vaccines means that they should only be used in enzootic regions. Recourse to this type of immunoprophylaxis is often imposed by the socio-economic context and the absence of a structured breeding system. In fact, it may prove difficult to assemble the various technical, psychological and financial conditions essential to an effective prophylactic programme or an eradication campaign. When vaccination cannot be avoided, it is still important to apply or increase disease control measures so as to limit pathogen pressure. A need has been expressed for a new generation of vaccines in areas where eradication is not as yet an objective. From the immunological aspect, knowledge of spontaneous and induced immune responses remains inadequate. The efficacy of vaccination must be reviewed in the light of current and future knowledge of antigenic variability.
**Disease control**

Disease control measures provide the only means of gradually achieving disease-free status, even eradication, and should be applied whenever possible. The literature contains few references to appropriate measures, very little information on regional control schemes and no cost-benefit evaluation of such programmes.

All control procedures are based on two fundamental criteria: the detection of infected animals and herd classification on the one hand, and the reduction of prevalence by culling, isolation and protection on the other. The microbiological and serological tools available in regard to the first point have already been described (see 'Diagnosis'). Asymptomatic carriers, in particular, should be identified by the detection of mycoplasmas (in target organs and ears) and by serology, especially when the number of animals permits (purchases and sales).

**Control of contagious agalactia in an infected flock**

When an outbreak occurs, it is recommended, whenever possible, that the entire flock be slaughtered. Owing to the importance of chronic carriers and shedders, there is little likelihood of eradicating the disease by merely eliminating the clinically affected animals. The flock will, in addition, remain contagious during its own replacement and for neighbouring flocks, so that movement will have to be limited. Individual detection by exhaustive testing of entire flocks is, in general, financially impracticable, particularly by bacteriological examination, and remains uncertain. Total herd slaughter is generally accepted in disease-free areas but is difficult to apply in enzootic regions. The genetic value of certain animals may also discourage this course (19). The following measures should be adopted in such cases.

**Reduction of mycoplasma sources**

The reduction of sources within a flock is aimed mainly at animal reservoirs but also at environmental sources.

In regard to animal sources, numerous authors have described the application of partial slaughter. This is often followed by culling animals, at the end of lactation or at the onset of the next lactation, which have failed to regain their former productivity. In enzootic areas, repeated and careful clinical examination, particularly of the udders in the milking parlour, may limit the number of chronic shedders by indicating which animals to cull. A long-term trial of partial slaughter, based on exhaustive ELISA serological tests, was conducted in the French Atlantic Pyrénées. It did not lead to the recommendation of this technique because the fall in serum antibody titres was not objectively correlated to infectious and contagious status.

Environmental sources should be reduced by disinfecting material, equipment and housing. Disinfection followed by a period without animals is essential after total slaughter, and should also be applied to specific accommodation in other cases (lambing, within-herd isolation) (19, 20, 52, 57).

**Limitation of disease transmission**

Limitation of transmission within a flock will be based on its various modes, i.e., between adults or from dam to offspring.

It is essential to reduce transmission between adults during milking, for this can continue long after the initial clinical outbreak. Conventional measures, such as ensuring the correct functioning of the milking machine, avoiding practices which lead to irregular vacuum fluctuations ('impact') and improving milking hygiene, should be respected. Teat-dipping is recommended. Animals should be milked in a fixed order, with those presumed to be healthy being milked first (20, 21, 37). Such within-flock grouping should of course be continuous. Suspect animals should be isolated, while awaiting culling, in a separate building. The early drying-off of such animals is strongly recommended.

Preventing transmission from the dam to newborn offspring has been proposed by several authors, through separation at birth, and feeding the neonate with heat-treated colostrum (56°C for 20 minutes) or bovine colostrum, and subsequently with pasteurised milk. Oral antibiotic therapy is also feasible. These relatively laborious and expensive measures are mainly suited to well-organised dairy goat farms (19).

**Control of contagious agalactia in an infected region**

**Principle**

The objective in regions where the disease is enzootic may initially be the progressive restriction of infection to certain areas, with a later attempt at eradication. Such progress can only be achieved by means of a collective and concerted disease control programme which is long-lasting and well-financed. This type of action must be based on two prior conditions which permit the constant monitoring of prevalence, as follows:

- the compulsory notification of clinical cases
- a thorough annual assessment of flock status, usually by serology.

The spread of infection is progressively limited by implementing a dual control: the management of individual and flock or herd movement.

**Application**

First, the movement of individual animals should be supervised, based on flock status and, where possible, individual testing. The security of purchases, sales and loans should thus be guaranteed. Health certificates or standard guarantees may be issued in certain regions (4). The quarantine of introduced animals is difficult to implement in practice, but is regularly suggested. The value of such a measure is increased at the time of parturition (41).

Secondly, any movement of flocks or herds must be managed in relation to health status. Such movements may comprise the following: access to nearby communal grazing, the housing of all or part of the flock in winter quarters and, above all,
transfer to summer pastures. Various ways of limiting the risk of contagion have been proposed: transhumance to collective pastures after drying-off, transhumance to special quarantine pastures or the complete prohibition of transhumance. The need to isolate affected flocks is obviously emphasised by many authors (4, 19, 20, 34, 52). Such restrictions to traditional husbandry practices will require the consent of the community (19, 57) and will be based on regional or national legislation (20). The extent of financial support for these programmes will often govern their effectiveness, at least in the early stages, by covering extra feeding costs and encouraging the instigation of segregation or slaughter (20). A programme of this type has been operating in the French Atlantic Pyrénées since 1988 and has considerably reduced the level of infection.

The precautions to be taken in disease-free areas have been mentioned above. Defensive prophylactic measures based on the strict control of introduced animals and on quarantine must be applied. Periodic serological surveys are also recommended (19).


Agalactie contagieuse des petits ruminants: connaissances actuelles sur l'épidémiologie, le diagnostic et le contrôle

D. Bergonier, X. Berthelot et F. Poumarat

Résumé
L'agalactie contagieuse des petits ruminants constitue un syndrome principalement mammaire, articulaire et oculaire. Il est surtout causé chez les ovins par Mycoplasma agalactiae et, chez les caprins, en plus de cette espèce, par M. mycoides subsp. mycoides larges colonies et M. capricolum subsp. capricolum. Accessoirement, M. putrefaciens peut provoquer, surtout chez les caprins, un tableau clinique du même type.

L'agalactie contagieuse est largement présente aujourd'hui sur les cinq continents, où elle sévit fréquemment à l'état enzootique. L'évolution de ces infections présente fondamentalement un caractère de chronicité pour l'animal et le troupeau touchés. L'excrétion asymptomatique de mycoplasmes, principalement galactophore, peut alors persister longuement. Associées à de fréquents portages sains auriculaires, ces infections insidieuses constituent une des difficultés majeures du diagnostic et du contrôle de l'agalactie contagieuse. La vente de ces animaux et les contacts en transhumance sont les principales modalités de transmission entre élevages, alors qu'à l'intérieur de ceux-ci l'infection s'étend par les contacts directs, la tétée et la traite.

Les auteurs décrivent le tableau clinique et épidémiologique de la maladie, ainsi que les traitements et les mesures de prévention et de contrôle.

Mots-clés
Agalaxia contagiosa de los pequeños rumiantes: estado de los conocimientos sobre su epidemiología, diagnóstico y control

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Resumen
La agalaxia contagiosa de los pequeños rumiantes afecta de modo predominante a las glándulas mamarias, las articulaciones y los ojos. Los principales agentes causantes de esta enfermedad son, en la oveja, *Mycoplasma agalactiae*, y en la cabra *M. agalactiae, M. mycoides subsp. mycoides* en su tipo de colonia grande (large colonies, LC) y *M. capricolum subsp. capricolum*. *Mycoplasma putrefaciens*, por su parte, puede inducir un cuadro clínico similar al de la agalaxia contagiosa, en especial en la cabra.

La agalaxia contagiosa se da en los cinco continentes, es con frecuencia endémica y afecta de modo crónico tanto a individuos como a rebaños. La secreción asintomática de micoplasmas, sobre todo en la leche, puede persistir durante mucho tiempo. El diagnóstico y control de estas infecciones malignas, cuyos focos se instalan y difunden a menudo desde el oído de individuos sanos, resultan extremadamente arduos. La venta de ejemplares portadores y el contacto entre animales durante la transhumancia constituyen los principales modos de transmisión entre rebaños. En cuanto al contagio en el seno de un mismo rebaño, éste se produce por contacto, o bien a través de la lactancia o el ordeño.

Los autores pasan revista a los rasgos clínicos, epidemiología, tratamiento, prevención y control de esta enfermedad.

Palabras clave

References

This paper is a revised version of the original document published in French in Volume 15 (4), December 1996, of the Scientific and Technical Review of the Office International des Epizooties. A total of 464 publications on the contagious agalactia syndrome are reviewed. The complete list of references is obtainable from the authors. Selected references to recent, important and/or original articles, chosen from as wide a geographical range as possible, are listed below.


