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Annie Rodolakis, Khalil Yousef Mohamad

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Zoonotic potential of Chlamydothyla

Annie Rodolakis*, Khalil Yousef Mohamad

INRA, UR1282 Infectiologie Animale et Santé Publique, F-37380 Nouzilly

Tel 00 33 247 427 634

Fax 00 33 247 427 779

e-mail : Annie.Rodolakis@tours.inra.fr

1 **Abstract**

2 The purpose of this article is to present the diseases induced in humans and animals by the
3 different species of *Chlamydophila*, after providing an overview on the history of these
4 infectious agents and their taxonomy. The route of transmission and the available methods for
5 prevention and control in the different animal species are reviewed.

6 **Keywords:** *Chlamydophila*, zoonosis, prevention, vaccines

7 **Article outline**

8 1. Introduction

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25 8.1 in birds

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29 **1. Introduction**

30 *Chlamydiaceae* are spread globally and cause acute diseases in humans and animals.
31 They may provoke ocular, pulmonary, genital, articular, and intestinal illness, but very often
32 they induce persistent, chronic, or subclinical infections. All *Chlamydophila* species are
33 potential zoonotic pathogens, although *Chlamydophila psittaci* and *Chlamydophila abortus*
34 are the most important and best documented.

35 *Chlamydiae* are obligate intracellular gram-negative bacteria with a unique growth
36 cycle, which is initiated by the attachment to the host cell of the infectious elementary bodies
37 (EBs), extracellular dormant, particles with a cell wall quite similar to that of Gram negative
38 bacteria. Adhesion induces phagocytosis within a phagosome. After entering the cell, the EBs
39 convert into vegetative reticulate bodies (RBs), in which macromolecular synthesis takes
40 place. After multiplication by binary fission, the RBs convert back into EBs, which are
41 released from the host cell by lysis or exocytosis.

42 **2. History**

43 In the history of chlamydial infections, the description of trachoma first occurred in
44 the Ebers papyrus (1500 B.C.) and in ancient Chinese manuscripts. Pedanius Dioscorides, a
45 Sicilian physician, first used the term trachoma in 60 A.D. A century later the four stages of
46 the disease were delineated by Galen (Thygeson, 1962).

47 At the beginning of the 19th century, a relationship was suspected between an infection
48 in psittacine birds and pneumonia in humans who had been in contact with them. In 1895,
49 Morange proposed the name psittacosis for this infection, but the disease-causing agent was
50 finally isolated 35 years later during an epidemic of several hundred cases caused by infected

51 Argentinean parrots in 1929-1930 in the US and Europe. In 1930, Levinthal described
52 minuscule spherical basophilic bodies in tissues of infected parrots, and almost
53 simultaneously, Coles and Lillie made the same observation in the cells of infected humans
54 and birds. Bedson and co-workers (Bedson et al., 1930) established the etiological role of
55 these organisms in the disease. In 1932, the intracellular developmental cycle of the
56 psittacosis agent was described. Two years later, Thygeson (Thygerson, 1934) identified a
57 resemblance between the developmental cycle of the psittacosis agent and the organisms
58 observed during the replication of the trachoma and inclusion conjunctivitis agents, which
59 were first found in 1907 by Halberstaedter and von Prowazek (Halberstädter and von
60 Prowazek, 1907). EBs were detected in the brains of cattle suffering from sporadic
61 encephalomyelitis (McNutt and Waller, 1940), in the lungs of asymptomatic mice (Gönnert,
62 1941), and in cats suffering from pneumonia (Baker, 1944). In 1950, Stamp and co-workers
63 (Stamp et al., 1950) demonstrated that *Chlamydiae* caused abortion in sheep, and more
64 recently, *C. psittaci* strains were isolated from tortoises and *C. pneumoniae* from frogs and
65 snakes (Bodetti et al., 2002).

66 However the nature of these pathogenic agents was only clarified at the end of the
67 1960s. They were originally regarded as viruses because they were unable to grow outside of
68 a live cell, then as an intermediate organism between bacteria and viruses (Bernkopf et al.,
69 1962) because clear definitions of bacteria and viruses were lacking. The cultivation of the
70 psittacosis agent in the chorioallantoic membrane (Burnet and Rountree, 1935), then in the
71 yolk sac of chicken embryos (Yamura and Meyer, 1941), allowed biochemical and biological
72 studies showing that these agents are prokaryotic organisms that parasitize eukaryotic cells.
73 They retain their cellular properties throughout the growth cycle, and the RBs develop in
74 cytoplasmic vacuoles and divide by a process analogous to binary fission in bacteria. Both the
75 EBs and RBs contain DNA and RNA, and the cytoplasm is defined by a cell wall. They are

76 sensitive to antibiotics, leading to the conclusion that they share many properties with bacteria
77 (Moulder, 1966).

78 **3. Taxonomy**

79 The classification was controversial until recently, as attested to by the various appellations
80 that designated the agents of the PLT group, Psittacosis, Lymphogranuloma venereum
81 Trachoma, over the years. In 1948, they were classed in the order *Rickettsiales* and the family
82 of *Chlamydozoceae* Moshkowsky, which included three genera (*Chlamydozoon*,
83 *Myagawanella*, and *Colesiota*), since they could not be cultivated outside of living animal
84 cells. During the next 20 years, a new classification was proposed almost every year until
85 Storz and Page (Storz and Page, 1971) proposed placing them in a new order, *Chlamydiales*,
86 which contained only one genus, *Chlamydia*, characterized by the unique intracellular
87 developmental cycle. This genus included two species, *Chlamydia trachomatis* and
88 *Chlamydia psittaci* (Page, 1968) that are distinguished on the basis of sulfonamide
89 susceptibility and glycogen accumulation within the inclusion, leading to different iodine
90 staining. *C. psittaci* strains were sulfadiazine resistant and iodine-staining negative, whereas
91 *C. trachomatis* strains were sensitive to sulfonamides and iodine-staining positive. In
92 addition, the two species appeared to have a low degree of similarity in DNA sequences
93 (Weiss et al., 1970).

94 Molecular biology and phylogenetic analysis of the 16S and 23S rRNA genes changed
95 the classification of *Chlamydia* and the nomenclature of the strains again (Everett et al.,
96 1999). Now the order *Chlamydiales* contains at least four families and the family
97 *Chlamydiaceae* contains two genera, *Chlamydia* and *Chlamydophila*, with nine species: three
98 for the genus *Chlamydia*, *Chlamydia trachomatis*, *Chlamydia muridarum*, and *Chlamydia*
99 *suis*; two for the genus *Chlamydophila*, *Chlamydophila pneumoniae* and *Chlamydophila*
100 *pecorum*; and four species that corresponded to the previous *Chlamydia psittaci*,

101 *Chlamydophila psittaci* pathogen for birds, *Chlamydophila abortus* pathogen for ruminants,
102 *Chlamydophila caviae* pathogen for guinea pigs, and *Chlamydophila felis* pathogen for cats.

103 The phylogenetic trees constructed from five other genes, *ompA* coding for the major
104 outer membrane protein (MOMP), *GroEL* coding for a chaperon protein, *omp2* coding for the
105 60 kDa cysteine-rich protein, *omp3* coding for a small cysteine rich lipoprotein, and *kdtA*
106 coding for the KDO-transferase, supported this new classification (Bush and Everett, 2001).
107 In addition, this classification, which is relevant to the host range, disease syndrome, and
108 virulence, provides easy tools for identifying new strains by PCR-RFLP on the 16S-23S
109 spacer region (Everett et al., 1999) or by DNA microarray (Sachse et al., 2005). Genetic
110 studies suggested that *C. pneumoniae* and *C. pecorum* are closely related and that *C. abortus*
111 is derived from *C. psittaci* (Van Loock et al., 2003).

112 The revised taxonomy has been adopted by most researchers working on animal
113 chlamydiosis but is still rejected by some involved in human infections (Schachter et al.,
114 2001) that contest the sharing in two genera (Stephens, 2008). In the current literature, these
115 bacteria are designed as *Chlamydia* or *Chlamydophila*, which are abbreviated as *C* and *Cp*.

116 *C. abortus* strains exhibit very little antigenic (Salinas et al., 1995) or molecular
117 diversity (Laroucau et al., 2009), but *C. psittaci* could be classified in six serovars (A to F)
118 using anti-MOMP monoclonal antibodies (mAbs) (Andersen, 1997). These serovars are
119 preferentially associated with some host species: A with psittacine birds, B with pigeons, C
120 with ducks and geese, D with turkeys, E with pigeons and ducks, and F with parakeets. The
121 serovars correlate with the genotypes defined by *ompA* polymorphisms characterized by
122 restriction fragment length polymorphisms (RFLP) or sequencing that allowed the
123 identification of type E/B in ducks (Geens et al., 2005).

124 **4. Clinical signs**

125 Table 1 gives an overview of the clinical signs induce in animals and human by the
126 different species.

127 *Chlamydophila psittaci*

128 Psittacosis is the animal chlamydiosis that presents the major zoonotic threat. *C.*
129 *psittaci* strains induce a systemic disease in psittacine birds, domestic poultry, and wild fowl.
130 People in frequent contact with domestic and companion birds at work or in their spare time
131 are the most predisposed to infection. The incubation period typically lasts 1 to 2 weeks, but
132 longer incubations periods are also reported. The symptoms are variable and unspecific,
133 resembling mild flu-like illness with fever, headache, sore throat, myalgia, and diarrhea, but
134 endocarditis, encephalitis, and severe interstitial pneumonia with non-productive cough,
135 sometimes fatal, are also reported (Petrovay and Balla, 2008). In addition, the chlamydial
136 infection is often complicated by secondary bacterial infections. With *C. psittaci* strains,
137 delays before antibiotic treatment and the age and immune status of the patient affect disease
138 development, which is more severe in elderly, young, and immunocompromised individuals
139 and pregnant women. Indeed, abortion after contamination by infected birds occurred in
140 pregnant women suffering from pneumonia and respiratory distress (Idu et al., 1998; Khatib
141 et al., 1995). However, the disease is rarely fatal in humans when it is diagnosed rapidly and
142 treated accurately. Thus, awareness of the danger is important for those at risk.

143 Disease severity in birds depends on the virulence of chlamydial strains and the
144 species of the bird. These factors are not independent because the various genotypes that
145 impact host specificity also show different virulence levels. Nevertheless, asymptomatic
146 infections can occur with strains of both low and high virulence, and many strains remain
147 quiescent in birds until activated by stress. In addition, age can affect disease course: adult
148 birds may have asymptomatic infections, while young birds have acute disease (Herrmann et
149 al., 2006).

150 Infected psittacine birds often present with hyperthermia, anorexia, lethargy, fluffed
151 feathers, closed eyes, and diarrhea with green watery droppings. Birds may also present with
152 respiratory signs, such as nasal discharge, sneezing, and open-mouth breathing, due to
153 pneumonia and airsacculitis. Conjunctivitis, with ocular discharge, together with sinusitis may
154 be observed. The liver is usually affected and unusual feather coloration from altered
155 metabolism may occur in chronically infected birds (Billington, 2005).

156 In turkeys, serovar D strains induce the most severe disease, with conjunctivitis,
157 rhinitis, sinusitis, tracheitis, airsacculitis, pneumonia, pericarditis, enteritis, and reduced egg
158 production. Mortality rates may be high without early antibiotic treatment. In addition,
159 serovar D strains are especially dangerous for poultry workers, particularly in the poultry
160 processing plant. Clinical signs of turkeys infected with serotypes of low virulence are milder,
161 including anorexia and diarrhea (Vanrompay et al., 1995b).

162 In contrast, infected feral pigeons are asymptomatic latent carriers of *C. psittaci* that
163 shed bacteria in feces, respiratory, and conjunctival secretions (Magnino et al., 2008).
164 However, clinical signs, including anorexia, diarrhea, and respiratory signs, may occur in
165 cases of simultaneous disease, such as salmonellosis, trichomoniasis, and viral infections
166 (herpesvirus or paramyxovirus) (Longbottom and Coulter, 2003). Infections in ducks are also
167 often asymptomatic, but confinement and close contact with them may induce severe
168 pneumonia in humans (Laroucau et al., 2008). In some cases, *C. psittaci* strains may infect
169 other mammals, such as dogs (Sprague et al., 2008), horses (Theegarten et al., 2008), and pigs
170 (Kauffold et al., 2006), and induce abortions or pneumonia.

171 4.2 *Chlamydophila abortus*

172 *C. abortus* is the causal agent of enzootic abortion of ewes (EAE) or ovine enzootic abortion
173 (OEA) and is the most common infectious cause of abortion in many small ruminant-rearing
174 countries. The economic impact of these abortions is very high since one third of the pregnant

175 ewes in a flock and occasionally 2-fold more pregnant goats may abort following the first
176 exposure to *C. abortus*. This high level of abortion persists during 2 or 3 years until almost all
177 the females abort. Then the disease takes on a cyclic nature and only 1% to 5% of abortions
178 occur for several years until a new outbreak, when all primiparous females abort. This cyclic
179 evolution is due to life-long immunity following abortion that protects against subsequent
180 infection (Rodolakis et al., 1998) It is exceptional for a female to abort twice. Cattle, pigs,
181 deer, and horses may also be infected with *C. abortus*.

182 In addition to the economic losses, *C. abortus* presents a zoonotic risk, inducing mild
183 influenza-like illness or pneumonia in rare cases. Human infections associated with bovine
184 chlamydial pneumonia and bovine encephalomyelitis were recorded (Johnson, 1983;
185 Stepanek et al., 1983), and serological changes and urogenital symptoms were described in
186 men and women in contact with bovine chlamydiosis (Stepanek et al., 1983). Although *C.*
187 *abortus* is not very contagious in humans, the consequences of the infection for pregnant
188 women in close contact with infected sheep and goats are disastrous. The association of
189 human abortions with *Chlamydia* from ruminants was suspected long ago (Giroud et al.,
190 1956) by several authors (Beer et al., 1982; Crosse et al., 1971; Roberts et al., 1967; Terskikh
191 et al., 1977), but it was based only on serological data. The role of *C. abortus* was contested
192 (Hobson and Rees, 1982) until the isolation of the bacteria from the placenta and the fetus of a
193 young woman who had assisted with a lambing on her husband's farm, on which some ewes
194 had aborted (Buxton, 1986; Wong et al., 1985). RFLP characterization of the two strains from
195 human and ovine origin proved definitively that the young woman was contaminated by her
196 ewes (Herring et al., 1987). Abortions due to *C. abortus* have been confirmed in several other
197 countries, including France (Villemonteix et al., 1990), the US (Jorgensen, 1997), Switzerland
198 (Pospischil et al., 2002), Netherlands ((Kampinga et al., 2000), and Italy (Walder et al., 2005).
199 A fever with headache, malaise, nausea, and vomiting are generally the first symptoms of the

200 infection in pregnant women and are frequently associated with lower abdominal pain
201 followed by abortion and sometimes severe complications, such as acute renal failure,
202 disseminated intravascular coagulation, or respiratory distress necessitating mechanical
203 ventilation. Recovery from the disease follows termination of the pregnancy and appropriate
204 antibiotic therapy, except in one case when the patient died (Beer et al., 1982).

205 *C. abortus* infection of pregnant ewes and goats induces abortion, stillbirth, or delivery
206 of weak lambs or kids that quickly fall ill or have difficulties rising. Abortions mainly occur
207 in the last month of gestation without clinical signs until abortion is imminent. Sometimes
208 vaginal discharge is observed a few days before abortion, more frequently in goats than in
209 ewes. As in small ruminants, no clinical symptoms are observed before the onset of bovine
210 chlamydial abortion, which usually occurs during the last trimester of gestation, but may also
211 take place as early as the fourth month (Storz, 1971).

212 Usually, aborting females recover rapidly without ill effect. Placental retention is rare
213 in ewes but is more frequent in both cows and goats. This may lead to metritis, which is fatal
214 in a very small number of cases. Arthritis, conjunctivitis, and pneumonia may affect calves,
215 kids, and lambs born live from infected females. The fetus does not show specific
216 macroscopic lesions.

217 In non-pregnant females, the infection generally develops towards an asymptomatic
218 form, which may induce abortion during later gestations only in a small percentage of animals
219 (Waldhalm et al., 1971). Male fetuses can be contaminated *in utero* (Rodolakis and Bernard,
220 1977) and adult males by mating with infected females. The infection can reach the seminal
221 vesicles, causing epididymitis, and testicles, affecting the semen quality with shedding of the
222 bacteria in the sperm.

223 In pigs, *C. abortus* may be isolated from cervical swabs and genital tracts of sows with
224 repeated return to oestrus, abortions, and small litters with weak piglets (Thoma et al., 1997,

225 Hoelzle et al., 2000, Camenisch et al., 2004;). However, *C. suis* and *C. pecorum* seem to
226 dominate in porcine abortions.

227 4.3 *Chlamydomphila felis*

228 In cats, *Chlamydomphila felis* causes conjunctivitis associated with severe swelling of
229 the lid, mild rhinitis, ocular and nasal discharges, fever, and lameness, as shown by
230 experimental infections (Masubuchi et al., 2002; TerWee et al., 1998) In addition. *C. felis*
231 may reach the genital tract, producing chronic salpingitis leading to persistent oviduct
232 infections.

233 Due to the close contact between cats and their owners, *C. felis* was suspected of
234 causing human disease, particularly follicular conjunctivitis (Ostler et al., 1969; Schachter et
235 al., 1969) or atypical pneumonitis (Cotton and Partridge, 1998). Endocarditis with secondary
236 glomerulonephritis (Regan et al., 1979) and severe liver breakdown in an
237 immunocompromised patient (Griffiths et al., 1978), both probably caused by a feline
238 conjunctivitis agent, were reported based on serological investigations. However, *C. felis* was
239 only isolated from conjunctivitis. The *Chlamydomphila* recovered from the HIV positive
240 patient's eye suffering of chronic conjunctivitis was indistinguishable of that isolated from the
241 cat's eye (Hartley et al., 2001). *C. felis* can induce conjunctivitis in people who are in close
242 contact with infected cats, but the risk is extremely low, as indicated by the comparison of the
243 seroprevalence in cats and their owners (Yan et al., 2000). However, some precaution is
244 warranted when handling affected cats.

245 4.4 *Chlamydomphila caviae*

246 *C. caviae* in guinea pigs produces asymptomatic infection or clinical signs ranging
247 from mild to severe conjunctivitis, with profuse purulent ocular discharge sealing the eyelids.
248 Conjunctival chemosis, follicular hypertrophy, and pannus may develop as early as five days
249 after experimental infection. Keratoconjunctivitis is self-limiting and clears up within three to

250 four weeks. It may also cause infection of the genital tract, inducing symptoms comparable to
251 those caused by *C. trachomatis* in humans. Infection of guinea pigs with *C. caviae* is widely
252 used as an experimental model of *C. trachomatis* genital tract infection in humans (Batteiger
253 and Rank, 1987).

254 PCR analysis allowed the detection of *C. caviae* in a conjunctival swab of the owners
255 of symptomatic guinea pigs (Lutz-Wohlgroth et al., 2006). He reported mild serous ocular
256 discharge, suggesting a zoonotic potential for *C. caviae* similar to that of *C. felis*.
257 Symptomatic and asymptomatic guinea pigs may harbor *C. caviae*. As some are pets in close
258 contact with young children, it would be interesting to investigate more accurately if *C.*
259 *caviae* could be responsible for conjunctivitis in humans.

260 4.5 *Chlamydophila pneumoniae*

261 *C. pneumoniae*, as all *Chlamydophila* species, induces asymptomatic and chronic
262 infections. It was first considered an exclusively human pathogen responsible for respiratory
263 diseases, such as pneumonia, chronic bronchitis, and asthma, but also chronic diseases, such
264 as atherosclerosis. However, strains of *C. pneumoniae* are widespread in the environment.
265 They have been found, by molecular methods in a range of reptiles (snakes, iguanas,
266 chameleons, turtles) and amphibians (frogs), and also in the respiratory tracts of horses,
267 koalas (Bodetti et al., 2002), and western barred bandicoots (Kutlin et al., 2007). *C.*
268 *pneumoniae* DNA may be found in ocular and urogenital samples of asymptomatic or
269 symptomatic koalas, but in the latter case it is associated with *C. pecorum*, suggesting that *C.*
270 *pecorum* is responsible for the clinical signs (Jackson et al., 1999). Three biovars have been
271 described (Everett, 2000): the human biovar, also designated TWAR, the equine biovar, and
272 the koala biovar. The genotyping of *C. pneumoniae* DNA from human and non-human origin
273 revealed that most of the strains infecting humans were similar, unlike those from animals.
274 The koala genotype was identified in the carotid plaque of one human (Cochrane et al., 2005)

275 and strains very similar, if not identical to the human respiratory strains, were found in
276 reptiles and amphibians (Bodetti et al., 2002). Although the zoonotic potential of *C.*
277 *pneumoniae* remains unclear, *C. pneumoniae* is now so prevalent in human that it is unknown
278 if animals or humans were the “original” reservoir.

279 4.6 *Chlamydophila pecorum*

280 Only three *Chlamydophila* species, *C. pecorum*, *C. pneumoniae*, and *C. psittaci*, may
281 be isolated from the brain tissue of infected hosts; however most *C. pecorum* and *C.*
282 *pneumoniae* strains are not considered highly virulent. Indeed, most healthy ruminants harbor
283 *C. pecorum* in their intestinal tract (Jee et al., 2004) despite the fact that, in addition to
284 encephalomyelitis, this bacterium may induce several clinical signs, such as pneumonia,
285 arthritis, conjunctivitis, enteritis, urinary tract disease, metritis, and fertility disorders, in small
286 ruminants, cattle, swine, and koalas (Table 2). For koalas, *C. pecorum* seems more pathogenic
287 than *C. pneumoniae*.

288 This species presents many antigenic and genomic variations, particularly on the
289 MOMP (Denamur et al., 1991; Fukushi and Hirai, 1992; Kaltenboeck et al., 2008; Kuroda-
290 Kitagawa et al., 1993; Salinas et al., 1995). Pathogenic (isolates from clinical samples) and
291 non-pathogenic (isolates from the intestinal tracts of healthy ruminants) strains differ
292 genetically (Yousef Mohamad et al., 2008a). Phylogenetic analysis could distinguish them
293 based on the sequence of three potential virulence genes, *ompA*, *incA*, which encodes an
294 inclusion membrane protein, and an ORF including a 15-nucleotide variant coding for a
295 tandem repeat (Yousef Mohamad et al., 2008b). However, its potential zoonotic risk is still
296 unknown.

297 **5. Route of transmission.**

298 *Chlamydophila* is shed in feces, urine, respiratory secretions, birth fluids, and
299 placentas of infected symptomatic and asymptomatic animals, and in saliva and feather dust

300 of birds. As EBs do not survive very long, close contact is needed with infected animals to
301 become infected. Two factors affect the transmission of the disease: the virulence of the
302 strains and the number of bacteria that infect the host. The minimal infecting dose of the
303 different strains are still unknown, but some serovars of *C. psittaci* are considered very
304 contagious for humans, unlike *C. abortus*, but the quantity of bacteria shed in the placenta of
305 an aborting ewe or goat is much higher than that shed by birds.

306 Transmission of *C. psittaci* and *C. abortus* from animals to humans generally happens
307 through inhalation of infectious dust and aerosols inducing infection of the mucosal epithelial
308 cells and macrophages of the respiratory tract (Table 1). The bacteria eventually spread
309 through the blood stream to involve epithelial cells and macrophages of various organs,
310 including the placentas of pregnant women. *C. psittaci*, *C. abortus*, and *C. pneumoniae* may
311 be detected in the PBMCs (peripheral blood mononuclear cells) of infected humans or
312 animals, whereas *C. felis*, *C. pecorum*, and *C. caviae* tend to cause local infection of the
313 mucosa. The rate of the clearance of *C. abortus* in the blood depends on the initial inoculum.
314 *C. felis* may be transmitted from infected cats to humans via the fingers of the owners
315 contaminated by the ocular discharges or infected dust in the fur of the pet.

316 In addition to the respiratory and ocular routes, the oral route is also important for the
317 transmission of *C. psittaci* and *C. abortus* in animals. Drinking infected water could be a
318 source of contamination for many avian species, while predators and scavengers may become
319 infected by ingestion of infected carcasses and water. In addition, transmission from the
320 parent to young birds may occur at the time of feeding by regurgitation (Harkinezhad et al.,
321 2008).

322 In ruminants, the infection often originates from the ingestion of placenta or grass
323 contaminated by vaginal discharge and placenta. Goats and ewes are more liable to abort
324 when they are infected within 100 days of gestation. However, in intensive lambing

325 conditions, contamination at the time of lambing can lead to abortion during the following
326 gestation (Wilsmore et al., 1984).

327 Vertical transmission, which promotes the persistence of the infection in ruminant
328 herds, also occurs in birds. The infection of eggs leads to embryonic death or to the hatching
329 of live infected young birds. A major route of infection for neonatal kittens is from the
330 mucosal surface of the reproductive tract of their mother at birth.

331 The venereal transmission of *C. abortus* is possible as the bacteria are found in the
332 semen of bulls, rams, goats, and boars. Males become infected *in utero* or after mating of
333 infected females. However, during post-abortion ovulation, no or very few DNA copies may
334 be detected by PCR (Livingstone et al., 2008). In addition, venereal transmission to females
335 leads to sterility and early embryonic mortality rather than late abortions.

336 In the nest, *C. psittaci* may be transmitted by lice, mites, and flies (Longbottom and
337 Coulter, 2003). A similar role for other arthropod vectors has never been demonstrated for
338 other *Chlamydophila* species. Birds appear to be excellent vectors for the distribution of
339 chlamydial infection because they feed on and have access to the feces and carcass of infected
340 animals and are highly mobile (Everett et al., 1999). Although the isolation *C. abortus* from
341 birds is extremely rare (Herrmann et al., 2000), it has been isolated from cats and dogs on
342 farms with infected ruminants (Salinas et al., 1995).

343 **6. Diagnostics**

344 Definitive diagnosis is obtained by identification of the organism. This can be
345 achieved by microscopic examination of stained smears, by detection of Chlamydial antigen
346 by immunofluorescence or by ELISA, whereas Chlamydial DNA can be detected by the
347 polymerase chain reaction (PCR) or by microarray. Several commercial PCR kits are
348 available.

349 The possibilities for diagnostic detection of chlamydiae improved considerably
350 following the introduction of PCR, which permits direct identification from clinical
351 specimens and differentiation of species. The methodologies and technologies used currently
352 in diagnosis of chlamydial infections in animals have recently been reviewed (Sachse et al.,
353 2008b).

354 The determination of the *Chlamydophila* species and the genotype for *C. psittaci* by
355 PCR and microarray (Sachse et al., 2008a) is important because the species do not present the
356 same zoonotic risk.

357 Serological analyses can help confirm the molecular diagnosis or in epidemiological
358 studies or if the identification of the agent is not feasible. The standard serological test for
359 chlamydial antibodies is the complement fixation test (CF) using a group-reactive
360 lipopolysaccharide antigen present in all strains. The occurrence of high CF titer in the
361 majority of individual in a flock is presumptive evidence of active infection. The
362 demonstration of a four fold increase in titer in an individual bird is considered to be
363 diagnostic of a current infection. In ruminants, CF test lacks specificity due to its antigen
364 common to *C. pecorum*. Several ELISA tests *C. abortus*-specific have been developed in
365 order to improve chlamydial serology (Vretou et al., 2007). However, whatever the
366 serological test it cannot identify carriers and potential shedders

367 In human infection is generally diagnosed by seroconversion on paired acute and
368 convalescent phase sera, although a single acute phase titer in the setting of clinically
369 compatible illness is significant. Low positive titers are common in people in contact with
370 animals. False positives may occur in *C. pneumoniae* and *C. trachomatis* infections. Specific
371 micro-immunofluorescent (MIF) test must be used to improve the diagnosis. However a
372 recent study demonstrated the weakness of MIF test for diagnosing human psittacosis
373 (Verminnen et al., 2008).

374 **7. Antibiotic Therapy**

375 Tetracycline is generally used for the treatment of animal chlamydiosis. *Chlamydiae*
376 are sensitive to several antibiotics, such as cyclines, quinolones, and macrolides. However,
377 these antibiotics are not bactericidal and the therapeutic levels of the drug should remain for a
378 long time (several weeks) to eliminate the infection and avoid the risk of transmission to
379 humans. These long-term treatments are generally too expensive and not used for ruminants.

380 Most human patients respond to orally administered doxycycline or tetracycline
381 hydrochloride, however the treatment must continue for at least 10 to 14 days after fever
382 abates (<http://www.nasphv.org/Documents/Psittacosis.pdf>).

383 *.7.1 Chlamydophila psittaci*

384 As there are no vaccines available, antibiotic treatment usually with tetracycline is the
385 only way to limit the infection. Treatment needs to be maintained for extended periods of
386 time. For pet birds, 45 days is often recommended (Vanrompay et al., 1995a). Antibiotics
387 may be given with food (chlortetracycline 500-5000 ppm according to the bird species and the
388 type of food, doxycycline 1000 mg/kg, or enrofloxacin 250-1000 ppm) (Gerlach, 1999) or in
389 water (doxycycline 200-800 mg/L according to the bird species) but it is necessary to verify
390 that no other source of water is available for drinking. Better results are obtained with
391 doxycycline in water, since it is more stable in water than food and generally more accepted
392 by birds, except for psittacine birds, which do not drink enough. In addition, parrots may be
393 very suspicious of anything added to their water (Billington, 2005). For individual pet birds,
394 direct treatment allows better control of the level of antibiotic in the blood. Intramuscular
395 injections of doxycycline provide the best results. After antibiotic treatments, bacterial
396 clearance should be checked at the end of the treatment and periodic re-sampling is advisable
397 to monitor relapse.

398 Treatments must be used only to cure sick birds. Preventive regular use of antibiotics should
399 be avoided to prevent antibiotic resistance. Although no resistance has been found in *C.*
400 *psittaci* strains, tetracycline-resistant *Chlamydia suis* have been isolated from pigs in several
401 countries (Di Francesco et al., 2008; Dugan et al., 2004).

402 *7.2 Chlamydophila abortus*

403 In ruminants, antibiotic treatment consists of two injections of tetracycline (20 mg/kg)
404 during the last month of gestation to reduce the number of abortions and the quantity of *C.*
405 *abortus* shed at parturition (Rodolakis et al., 1980). However, the infection is not cured and
406 the shedding of the bacteria persists as well as the threat for pregnant women. This kind of
407 treatment must be used only to prevent a high rate of abortion at the time of the first disease
408 outbreak in the flock, and then the animals must be vaccinated.

409 *7.3 Chlamydophila felis*

410 Doxycycline is generally recommended for the treatment of conjunctivitis in cats. Oral
411 treatment with 10 mg/kg is more efficacious than antibiotic eye ointment, but several weeks
412 of treatment (at least 4 weeks) are needed to avoid relapse (Dean et al., 2005). Infected cats
413 should be kept indoors to prevent the spread of the infection. In the case of outbreaks in a
414 cattery, all cats must be treated and infected cats must be separated from the others to
415 minimize exposure.

416

417 **8. Vaccines**

418 *8.1 Chlamydophila psittaci*

419 No commercial vaccine is available for avian chlamydiosis despite work on vaccines
420 for turkeys and, the good protection obtained in turkeys by plasmid DNA vaccines expressing
421 the MOMP of *C. psittaci* serovar A (Vanrompay et al., 2001; Vanrompay et al., 1999), and

422 the demonstration of the MOMP expression for at least ten weeks after vaccination with such
423 vaccine (Loots et al., 2006).

424 8.2 *Chlamydophila abortus*

425 Both live and inactivated vaccines for *C. abortus* have been developed. The live
426 thermosensitive vaccine (Ovilis Enzoowax® or Cevac® Chlamydia) is more efficient and
427 induces the same immunity as the natural disease (Rocchi et al., 2008), which reduces the
428 clinical signs and prevents infection in challenged ewes and goats (Rodolakis and Souriau,
429 1983, 1986). This live vaccine may be combined with other live vaccines against brucellosis,
430 salmonellosis (Souriau et al., 1988), and toxoplasmosis (Chalmers et al., 1997). It could be
431 compatible with the Q fever phase 1 vaccine (Coxevac CEVA) at two different injection sites
432 as demonstrated in mice (Rekiki et al., 2004b). It is effective against all *C. abortus* strains
433 tested and *C. pecorum* (Rekiki et al., 2004a), but not against *C. psittaci*. However, vaccination
434 induces the production of antibodies that cannot be differentiated from those of naturally
435 infected animals (Borel et al., 2005). Until now, no subunit or recombinant vaccines are as
436 effective as the live vaccine (Longbottom and Livingstone, 2006). In contrast to *C. psittaci*,
437 plasmid DNA vaccines expressing the MOMP of *C. abortus* either did not protect mice
438 against a virulent challenge (Hechard et al., 2003) or less effectively than the live vaccine
439 (Zhang et al., 2008).

440 No boosters are needed for about five years, but young animals and those newly
441 introduced to the flock must be vaccinated during those five years. Indeed, abortion may
442 persist during three to five years after the vaccination due to the infected females that give
443 birth to infected young susceptible to abortions. The live vaccine is very safe. Thousands of
444 ewes and goats have been vaccinated without problems, but pregnant females should not be
445 vaccinated.

446 8.3 *Chlamydophila felis*

447 Both live and inactivated vaccines for *C. felis* have been used in Europe, the US, and
448 Japan. The live attenuated vaccine is more efficient and reduces clinical signs, but does not
449 completely prevent infection (Shewen et al., 1980). This live vaccine may be combined with a
450 trivalent live vaccine against herpesvirus, calicivirus, and panleukopenia virus (Starr, 1993).
451 In addition, a new specific antigen should distinguish between infected and vaccinated cats, as
452 high levels of antibodies against this antigen are detected only in the sera of infected cats
453 (Ohya et al., 2008). Vaccination of cats living in close contact (cattery, pet shops, or pet
454 keepers) is recommended.

455 **9. Conclusion**

456 The prevalence of chlamydial infections in humans, including the psittacosis, is likely
457 underestimated in many countries, including the US, Australia, and several European
458 countries, such as Belgium, Germany, and Switzerland, where it is a notifiable disease.

459 A cheap and efficacious vaccine against *C. psittaci* is needed to prevent infection in
460 poultry and avoid contamination of workers in turkey and duck processing plants. Genetic
461 vaccines are too expensive and probably not acceptable to consumers but could be considered
462 for pets birds to reduce the use of systematic antibiotic treatments, or perhaps for at risk
463 humans.

464 Everyone in contact with birds should be informed about the clinical signs of
465 chlamydial infection and quickly seek medical attention for themselves and their pets if they
466 have any suspicion of contamination. In addition, routine hygienic precautions are
467 recommended when handling and feeding birds and cats. Children must be advised to avoid
468 close face-to-face contact with cats and guinea pigs with conjunctivitis. Pregnant women,
469 especially those who live in rural areas, should be made aware of the risks of zoonotic
470 diseases and how to avoid them.

471
472

473 **Conflict of Interest Statement**

474

475 The authors certify that they have no financial or personal relationship with other people or
476 organizations that could inappropriately influence or bias the paper entitled “Zoonotic
477 Potential of *Chlamydophila*”.

478

479

480 **References**

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Table 2 Clinical signs induced by *C. pecorum* according to host species

Clinical signs	Ewes and goats	Cattle	Swine	Koalas
encephalomyelitis	-	+	-	-
pneumonia	+	+	+	+

arthritis	+	+	+	-
conjunctivitis	+	+	+	+
abortion	<u>±</u>	<u>±</u>	+	-
metritis and infertility	-	+	+	+
enteritis	-	+	+	+
urinary tract disease	-	-	+	+

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Table 1 Zoonotic potential of the *Chlamydophila* species and routes of transmission from animals to humans

<i>Chlamydophila</i> species	Host		Pathology in animals		Route for human transmission	Pathology in humans	
	Principal host	Occasional host	Clinical signs	Severe disease		Usual disease	Severe disease
<i>C psittaci</i>	Bird	Dog, horse, pig	Hyperthermia, anorexia, lethargy, diarrhoea	Conjunctivitis pneumonia, pericarditis, death	Inhalation	Influenza-like illness	Endocarditis, encephalitis, pneumonia, death
<i>C abortus</i>	Sheep, goat cattle	Pigs, deer, horse	Abortion, stillbirth, epididymitis ¹	Metritis	Inhalation	Influenza-like illness	Pneumonia, abortion, renal failure, respiratory distress, death
<i>C felis</i>	Cat	- ²	Conjunctivitis	Pneumonia, chronic salpingitis	Contact	Conjunctivitis	Endocarditis, severe liver breakdown
<i>C caviae</i>	Guinea-pig	-	Conjunctivitis, genital tract infection	-	Contact	Conjunctivitis	-
<i>C pneumoniae</i>	Human koala, horse	Reptiles, amphibians	Respiratory diseases	-	Inhalation	Pneumonia, bronchitis, asthma ³	Atherosclerosis ³

			Intestinal				
	Ruminant,		infection,	Encephalomyelitis,			
<i>C pecorum</i>	swine,	Wild	conjunctivitis,	pneumonia,	Contact	-	-
	koala	animal	urinary tract	arthritis			
			disease				

- 1- clinical sign in infected male
- 2- (-) Not reported
- 3- Clinical signs by human *C pneumonia* isolates