

NATIONAL STANDARD METHOD

CHLAMYDIAL ZONOTIC INFECTIONS

QSOP 47

Issued by Standards Unit, Department for Evaluations, Standards and Training
Centre for Infections



Association of Medical Microbiologists
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CHLAMYDIAL ZONOTIC INFECTIONS

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AMENDMENT PROCEDURE

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Each National Standard Method has an individual record of amendments. The current amendments are listed on this page. The amendment history is available from standards@hpa.org.uk.

On issue of revised or new pages each controlled document should be updated by the copyholder in the laboratory.

Amendment Number/ Date	Issue no. Discarded	Insert Issue no.	Page	Section(s) involved	Amendment

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CHLAMYDIAL ZONOTIC INFECTIONS

Types of specimen: Serum
Whole blood
Sputum
Throat swabs
Placental tissue from abortions
Eye swabs

INTRODUCTION

Chlamydial infections from birds are among the longest recognised zoonotic infections but recently there have been several publications that suggest that the spectrum of diseases caused by such chlamydial infections may be much wider than has been realised before. This document will describe the two well established types of zoonotic infection and their diagnosis and briefly review the type of diagnostic tests and surveillance that may be needed in the future.

Understanding and searching the chlamydial literature has been complicated by changes in chlamydial taxonomy. Initially, the family Chlamydiaceae had only one genus - Chlamydia (C.) and two species *C. trachomatis*, found in humans, mice and pigs, and *C. psittaci*, found in birds, ruminants, cats and guinea pigs. Two further species were then added, *C. pneumoniae*, initially found in humans and subsequently in horses, marsupials and amphibians, and *C. pecorum* which infects many species of ruminants. Recently, a revision has occurred based on phylogenetic relationships deduced from the sequences of the ribosomal RNA (rRNA) cistron and supported by analyses of several other genes including the major outer membrane protein gene (MOMP)^{2,3}. The genus Chlamydia now contains only *C. trachomatis* and two new species, *C. muridarum* and *C. suis* for the mouse and pig isolates respectively. All the other species are members of the new genus Chlamydophila (Ch.). Species from birds became *Chlamydophila psittaci* while the species associated with ruminant abortions became *Chlamydophila abortus*, isolates from cats *Chlamydophila felis* and guinea pig isolates *Chlamydophila caviae*. All the non-abortion isolates from ruminants became *Chlamydophila pecorum* while *Chlamydophila pneumoniae* still comprises human and animal isolates. It is very likely that this taxonomy will be revised and expanded further as there is now an extensive effort to derive complete genome sequences for all chlamydial species and *Ch. pecorum* and *Ch. pneumoniae* may well be split into further species. The new classification has been rejected by some groups and some medical papers still use the old, single genus system.

Chlamydiology, as the study of Chlamydia and Chlamydophila is often known, is a field that has benefited greatly from the introduction of molecular techniques, particularly Polymerase Chain Reaction (PCR). These have allowed the detection, identification and quantification of chlamydial infections with relative ease. Molecular characterisation has also expanded the order Chlamydiales and several members of new families have recently been described. These include *Simkania nevegensis* which is associated with human respiratory disease; it was first discovered in Israel but has recently been found in the UK⁴. PCR has also led to the characterization of chlamydia-like microbes found replicating in amoebae, including acanthamoebae which are human pathogens. Classified in a new family called the Parachlamydiaceae, there are already many different species (or possibly genera) in this group. They have been detected by PCR in a wide range of clinical specimens from both human and animal sources. Simkania and some members of the Parachlamydiaceae are therefore considered as emerging pathogens. Their pathogenic potential and diagnosis have recently been reviewed⁵ but, as animal to human transmission has not been described, they are currently outside the scope of this document.

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1 ZONOTIC INFECTION WITH CHLAMYDIAE OF AVIAN ORIGIN

This condition was first described in the 19th century; however the fashion for avian pets particularly from the parrot family in the 1930's led to a pandemic of psittacosis and greatly raised public consciousness of the disease. Chlamydiae are found in the faeces, respiratory secretions and feather dust of infected birds and therefore direct contact with an infected bird is not necessary for infection. Disease manifests after an incubation period of 5-15 days and, in serious cases, progresses from flu-like symptoms through mild to moderate pneumonia to serious pneumonia and thence to acute respiratory failure and septic shock. Many other symptoms and signs have been reported on an occasional basis⁶. In the pre-antibiotic era, mortality was estimated at 15-20% of infections.

Other bird species, especially turkeys, pigeons, ducks, and wild birds can also be responsible for outbreaks of the disease^{7,8}. Where birds other than parrots are the source of infection, the disease is called ornithosis. *Chlamydophila psittaci* has been isolated from many species of bird. Serology and sequence comparisons have shown a considerable diversity in the isolates^{9,10}. It is often assumed that strains differ in their pathogenicity for man. However, there may also be human genetic and immune status determinants of disease and the infectious dose may also be a factor. The evidence for human to human transmission is largely anecdotal.

Recently, an outbreak of psittacosis occurred in a veterinary school in the Netherlands at which, somewhat fortuitously, a real-time PCR specific for *Chlamydophila psittaci* had just been developed^{11,12}. This has allowed a unique assessment to be made of the diagnostic methods used and of the variability in disease severity. Some 38 staff and students were exposed to diseased parrots during a practical class and 10 were found to be infected. Of these, seven were symptomatic with four patients only having fever and chills but there were two cases of pneumonia and one case of sepsis leading to multi-organ failure that required intensive therapy. PCR on sputum detected the three serious cases and PCR on throat swabs from the other seven detected three further cases. The complement fixation test (CFT) on paired sera taken around 21 days apart also detected six cases. Amplification and sequencing of the MOMP gene showed that the infected birds and patients all had the same strain. This outbreak underlines variability of disease presentation and the problems of diagnosis. The one case out of seven symptomatic patients with multi-organ failure suggests that the former estimate of mortality is of the right order. That seven patients had unapparent infections or only mild symptoms makes it likely that, as has often been suggested before, the infection is more prevalent than is reported and this finding is relevant to the recent findings described below.

For those seeking a more in depth introduction to chlamydial infections in animals and zoonotic infections, the field was reviewed in depth by Longbottom and Coulter (2003)¹³.

2 DIAGNOSIS OF PSITTACOSIS/ORNITHOSIS

The diagnosis of psittacosis/ornithosis is problematic. Historically there has been a reliance on serology but a definite diagnosis depends on observing a rising titre, typically equal or greater than a fourfold rise, over 2-4 weeks. This may be possible in an outbreak situation, such as in the veterinary school as described above, but with individual patients it gives only a delayed answer at best and obtaining paired sera can be difficult.

Early diagnosis and treatment may well depend on the clinician dealing with a case of community-acquired pneumonia (CAP) establishing if there has been any contact with birds or an environment contaminated by birds and giving anti-chlamydial antibiotics on grounds of suspicion. However, the evidence for the advisability of establishing bird contact is equivocal. An early review of psittacosis cases in Cambridgeshire from 1975-83 (prior to the identification of *Ch. pneumoniae*) found bird contact in only 17% of cases¹⁴. A later review of cases in the

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same county, in which *Ch. pneumoniae* and *Ch. psittaci* infections were distinguished by the micro-immunofluorescence test (MIF, see below), reported that bird contact could be established in 84% of confirmed cases¹⁵.

All current laboratory tests have drawbacks and the need for better means of diagnosis has been recognized for many years¹⁶. For this reason early diagnosis and treatment based on history and clinical signs rather than waiting for laboratory results is recommended. The traditional test is the CFT but, because it detects antibodies to epitopes on the chlamydial Lipopolysaccharides which are present in all members of the Chlamydiaceae, antibodies may be due to infection with *Ch. pneumoniae* or *C. trachomatis*. The other widely used assay is the MIF test originally developed by Wang and Grayston to type *C. trachomatis*¹⁷. This test uses elementary bodies (EBs) of the three human chlamydial pathogens fixed on a slide as antigen and can be used for both total immunoglobulin and specific IgM or IgA detection. Since EBs are at the limits of light microscope resolution, endpoint detection can be difficult and the test suffers from considerable inter-operator variability¹⁸. The main antigen presented in the MIF test is MOMP and this is known to be highly variable in avian isolates with 8 serovars currently described¹⁰. Therefore the infecting strain may well be different from that used to produce the elementary bodies for the test. Although some of the commercial tests treat the EBs to reduce LPS, antibodies against this antigen may still interfere with test specificity. Chlamydiae are highly complex antigens and the species share many B and T cell antigenic epitopes; thus serology may be complicated by cross reactions and by 'original antigenic sin' effects¹⁹⁻²².

An alternative to the MIF test is the whole inclusion immunofluorescence test (WIF) that uses infected cells as antigen and tests sera against slides bearing *C. trachomatis*, *Ch. pneumoniae* and *Ch. abortus* infected cells²². *Ch. abortus* is used in preference to *Ch. psittaci* since it is known to be very closely antigenically related to *Ch. psittaci* and this avoids the biohazard problems involved in growing *Ch. psittaci* which is a Category 3 pathogen. (In addition, see below under *Ch. abortus*). The main advantage of the WIF is that it is much easier to read than MIF. It is the only test that presents all the chlamydial antigens including the 'non-structural' antigens present in the inclusion membranes. This is both an advantage and a disadvantage. It increases sensitivity but decreases specificity due to cross reactions, especially those due to anti-LPS antibodies that react with all three species²³. Because of these cross reactions, sera that show equivalent titres to *Ch. pneumoniae* and *Ch. psittaci* in the WIF test are considered to be infections with the latter, largely on grounds of clinical prudence.

Serological diagnosis of *Ch. psittaci* and *Ch. abortus* infections would be greatly simplified and accelerated if an immunodominant specific antigen or antigens for these species could be found. A publication from Helmut Brade's group²⁴ suggests that two novel forms of LPS oligosaccharide that were only found in *Ch. psittaci/abortus/felis/caviae* may well provide such antigens. A monoclonal antibody against this novel LPS was found to be specific.

There are several reports in the literature of more timely diagnosis being achieved by pathogen detection in sputum, throat swabs or aspirates. The direct immunofluorescence (DIF) test with an anti-LPS, genus-specific, conjugate, has been used^{25,26} but this is a technique that requires experience and this may not be available in many laboratories given the change to molecular diagnosis for *C. trachomatis*. Antigen detection using an enzyme-linked immunosorbent assay for LPS has also been used²⁵⁻²⁷ but, similarly, may no longer be available. PCR has also been reported to be successful^{11,26} and, given the stability of primers and positive control DNA, is the most practical choice of laboratory test for this disease, where demand for testing is likely to be very infrequent.

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3 DIAGNOSIS OF CHLAMYDIAL ABORTION

Diagnosis of these infections has been performed after the abortion and has been important to establish the nature of the infection quickly in order to start aggressive anti-chlamydial therapy as soon as possible. Since the WIF test (see above) uses *Ch. abortus* antigen, it is particularly suitable for serological diagnosis although historically the CFT has been used in most cases. Direct detection of the pathogen in aborted placenta and/or foetus is the quickest method of making a diagnosis. However, the most rapid technique, the DIF test with an anti-LPS, genus-specific, conjugate, may not now be available as mentioned above. Similarly, isolation in cell culture is restricted to very few laboratories. In most reported cases, help has been sought from veterinary colleagues. The PCR used by the VLA to detect *Ch. psittaci* infection in birds will also detect *Ch. abortus* and the Moredun Research Institute in Edinburgh maintains an active research group on this disease.

4 ZOO NOTIC INFECTION WITH CHLAMYDIAE OF RUMINANT ORIGIN

Infections with *Ch. abortus* are the main cause of infectious abortion in sheep and goats in the UK and also cause occasional abortions in cattle. In sheep, the main pathology is found in the placenta but the foetus is also infected¹³. Recent evidence from the USA has suggested that low grade infection in cattle is widespread and may be responsible for fertility problems²⁸. When sheep abort, there is usually massive excretion of chlamydiae in the infected placenta and on the aborted lamb which serves as a source of infection for other sheep and for shepherds exposed at lambing time. The infection in men and non-pregnant women is not well documented but an outbreak among workers preparing vaccine in 1981 suggests that it causes a relatively mild upper respiratory tract infection with influenza-like symptoms²⁹. If pregnant women become infected, the infection can spread to the placenta following the respiratory symptoms and this can result in abortion or stillbirth according to the stage of the pregnancy. However, prior to and just following the loss of the foetus, severe symptoms are observed. Typically these are renal failure, hepatic dysfunction and disseminated intravascular coagulation that can lead, in extreme cases, to the death of the mother^{13,30}. This is therefore a rare but serious infection. That *Ch. abortus* is indeed the chlamydial species involved was established by whole genome restriction enzyme profiling (WGREP)³¹.

In cases seen in Europe, there has normally been contact with infected sheep or goats during the pregnancy but in one case a farmer's wife deliberately avoided contact during her pregnancy but was still infected. Therefore transmission by fomites or from her husband, who did tend the sheep, were both possible routes of infection³².

While cases from Europe have been sheep associated, in the USA cases of 'gestational psittacosis' with abortion have been reported following bird contact³³. This is interesting since, when WGREP was introduced as the first practical and universal method of strain typing, one avian isolate, Daruma parakeet, was found to have the same profile as all the ruminant abortion isolates. The most likely explanation for this single observation was a mislabeled strain, a common occurrence at that time³⁴. Subsequently, gene sequences from several avian strains from diverse sources have been reported that have closer homology to *Ch. abortus* than to the majority of *Ch. psittaci* isolates³⁵. It has been speculated that *Ch. abortus* has evolved recently from these abortus-like avian strains. Currently, whole genome sequencing of several avian *Ch. psittaci* strains is ongoing and should help to clarify this issue. However, it should be noted that bird contact in pregnancy may also be a risk and that flocks of sheep thought to be free of the disease may be vulnerable to infection from an avian source.

Clearly for this infection prevention is the best policy. Following the realization of the problem during the 80s and 90s, the dangers received considerable publicity in the farming and general press and, most effectively, in the agricultural soap operas. Currently, detailed advice

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for women who might be at risk is available on the HPA (www.hpa.org.uk) and Scottish Office (www.hps.scot.nhs.uk) websites, and from the HSE (www.hse.gov.uk).

5 SUMMARY

On a practical level, some service developments warrant consideration. The provision of real-time PCR tests to detect *Ch. psittaci* in sputum, throat swab specimens and *Ch. abortus* in aborted placenta and foetus would considerably accelerate diagnosis and such tests have been described^{12,28}. Given the recent findings described above, it is clear that, in suspected cases of infection of avian or ruminant origin, whole blood and/or buffy coat cells would now be sensible additional specimens to investigate by PCR.

It is notable that, for all four of the new species that used to make up *Chlamydia psittaci*, the distinct tissue tropisms seen in the natural hosts are also observed in zoonotic infections. Understanding the cellular and molecular bases of these tropisms constitutes a major challenge for future research.

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6 ACKNOWLEDGEMENTS AND CONTACTS

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CHLAMYDIAL ZONOTIC INFECTIONS

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