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Chlamydiae as agents of human and animal diseases

J. SCHACHTER,[1] J. STORZ,[2] M. L. TARIZZO,[3] & K. BÖGEL[4]

A brief review is given of the properties, occurrence, and public health significance of chlamydiae in man and animals and of the diagnosis and control of chlamydial infections. Chlamydiae occur naturally in a large number of avian and mammalian species. Man is the primary host of chlamydiae causing trachoma, inclusion conjunctivitis, genito-urinary tract infection, and lymphogranuloma venereum. In animals chlamydial infections have been recognized as a cause of pneumonia, encephalitis, abortion, arthritis, diarrhoea, and conjunctivitis. Chlamydial infections have been recognized in a wide range of avian hosts. Sporadic psittacosis/ornithosis in man is associated with close exposure to birds and may occur as an occupational disease. Transmission studies suggest that mammalian chlamydial strains are not very host-specific and that diseases and even chains of infection may develop in secondary hosts. There are a few well-documented cases of human infection with chlamydiae of mammalian origin. Although various chlamydial isolates have specific antigenic components, no routine test for identifying different serotypes has been generally accepted. Further investigation of the host range of chlamydiae and of their antigenic properties is essential for a more accurate assessment of the potential danger of chlamydia-infected animals to human health. The frequent occurrence of inapparent or latent infections makes it imperative to establish adequate laboratory facilities for the effective surveillance and control of chlamydial infections.

In recent years chlamydiae have come to be recognized as a separate group of microorganisms that have many characteristics in common with bacteria but, like viruses, are obligatory intracellular parasites. The taxonomic position of this group is still somewhat unsettled, but their biological characteristics have led to their study by methods similar to those used for rickettsiae. Chlamydiae are however easily distinguished from rickettsiae by differences in their developmental cycle and in their antigenic structure.

Trachoma is certainly the most widespread and the most important of the human diseases caused by chlamydiae, and a considerable amount of experience has been accumulated concerning the agent and the control of the disease. Chlamydiae are also responsible for a number of other diseases in man and in animals and there is a growing awareness of their public health significance.

Several gaps in present knowledge about chlamydial infections are concerned with (*a*) the epizootiology of mammalian chlamydial infections, particularly the transmission chains within or between species; (*b*) the possible role of chlamydiae of mammalian origin as agents of human disease; (*c*) the definition of effective chemotherapeutic regimens for the eradication of overt and inapparent chlamydial infections; (*d*) the identification of isolates by serologic or other methods; and (*e*) the prevalence and clinical manifestations of chlamydial infections in the human genital tract. It is hoped that the international research efforts that have succeeded in defining the epidemiology and chemoprophylaxis of avian chlamydial infections and the clinical syndromes caused by chlamydiae in birds and lower mammals, and that have led to an awareness of human genital tract infections, will soon contribute to the solution of these and other problems.

This paper is a review of present knowledge on chlamydial diseases other than trachoma. It is not intended to be comprehensive and only a few bibliographical references have been included.

[1] Co-Director, WHO Collaborating Centre for Reference and Research on Trachoma and other Chlamydial Infections, University of California, San Francisco, Calif., USA.

[2] Professor of Microbiology, Department of Microbiology, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, Colo., USA.

[3] Medical Officer, Virus Diseases, WHO, Geneva, Switzerland.

[4] Veterinary Public Health, WHO, Geneva, Switzerland.

PROPERTIES OF CHLAMYDIAE

Host range and pathogenicity

Naturally occurring infections. Chlamydiae naturally infect a large number of avian and mammalian species (2), and a comprehensive review of the subject is included in a recent monograph (5).

Chlamydial infections of man can be subdivided into two groups according to their mode of transmission. Direct person-to-person transmission occurs in trachoma, inclusion conjunctivitis, genito-urinary tract infection, and lymphogranuloma venereum. In the second group, the zoonoses, man is only an accidental host, usually acquiring the infection from birds, although other domestic and wild animals may possibly be involved. Commonly, pneumonia is the main clinically significant infection of this group in man, but signs of systemic infections are also seen, and subclinical infection may be established in man after contact with chlamydia-infected animals.

Chlamydial infections of animals have been recognized as a cause of pneumonia, encephalitis, abortion, arthritis, diarrhoea, and conjunctivitis. Carrier stages of long duration in apparently healthy animals have also frequently been noted.

Chlamydial agents parasitize and multiply in cells of the host's reticuloendothelial system, in epithelial cells of the conjunctiva or the genital and intestinal tract, in synoviocytes, and in cells of the placenta. This process can elicit lesions in one or more organ systems depending on the invasiveness and virulence of the causative agent.

While chlamydial agents may differ in other respects, they all share the ability to infect the placenta and the fetus *in utero*. Different degrees of this pathogenic capacity have often been observed when pregnant animals were inoculated with different chlamydial isolates.

The intestinal tract appears to be a natural habitat for chlamydiae. In ruminants and most avian species at least, inapparent infections of the intestinal tract are common. Faecal shedding of the agent may be the most important mode of transmission. It is, however, not known whether there are intestinal infections in all chlamydia-induced diseases of ruminants such as those that lead to abortion, encephalitis, polyarthritis, or pneumonia. The different diseases of ruminants caused by chlamydial agents have never been observed simultaneously in an affected herd.

Host specificity. This appears to be rather uncommon for avian and mammalian chlamydial strains. A highly virulent chlamydial strain from turkeys was found to affect man and many animals including sheep and calves; the sheep so infected transmitted the infection again to turkeys.

Little is known of the behaviour of mammalian chlamydial agents in birds. A chlamydial strain that caused polyarthritis in lambs proved to be pathogenic for turkeys, causing air-sacculitis and arthritis. Another chlamydial strain causing ovine abortion was infectious for pigeons and lethal for sparrows. This ovine chlamydial agent induced abortion in cattle, and caused mastitis in cows after intracisternal inoculation. Pneumonic lesions in pigs and goats were caused by a chlamydial strain isolated from cattle with sporadic bovine encephalomyelitis, and a goat pneumonia strain caused lung lesions in cattle, sheep, swine, and a horse.

Chlamydial agents isolated from cases of ovine pneumonia, abortion, or latent intestinal infection, all induced pneumonia in sheep after intratracheal inoculation. Faecal chlamydial strains caused experimental abortions in some instances. Antigenic and pathogenic differences have been detected in neutralization and complement fixation tests between chlamydial strains isolated from specimens of aborted fetuses and from polyarthritic sheep and cattle. It would be desirable to compare not only chlamydial strains isolated from one disease entity with those from another, but also chlamydial strains from the same type of infection in animals from different localities.

Many laboratory animals, such as Swiss mice, guinea-pigs, ferrets, and hamsters, have been used as indicator hosts for the isolation of chlamydiae. Experimental animals must be screened carefully, because naturally occurring chlamydial infections in these animal species have also been detected.

Inapparent and latent infections, Although chlamydial agents may produce severe and often fatal diseases in man and many animal species, this is the exception rather than the rule. A well-balanced host–parasite relationship in which persistence of the chlamydial agent causes no obvious harm to the host is more common. The chlamydial agents may be excreted by the apparently healthy carrier and thus can be transmitted to new hosts under appropriate conditions. Chlamydial agents may also persist in the latently infected host in a non-infectious stage.

Inapparent chlamydial infections were first demonstrated in parakeets and in experimentally and naturally infected mice. Meyer and Eddie (3) proved that

man may remain a silent carrier for several years after contracting the infection from parakeets. Inapparent chlamydial infections occur under natural conditions in birds, cattle, guinea-pigs, and sheep.

Chlamydiae and arthropods. The isolation of microorganisms of the psittacosis group (also called " neorickettsiae ") has been reported from a variety of ticks in central and western Africa and in France (1). The evidence furnished, however, is insufficient to allow definite conclusions on the nature of these microorganisms and on their role as agents of diseases in mammals.

Similar findings were obtained in investigations carried out in California. Chlamydiae were isolated from three species of ticks, two hard ticks (*Ixodes pacificus* and *Dermatocentor occidentalis*), and one soft tick (*Ornithodoros coriaceus*). Preliminary observations indicated that external contamination of the ticks had occurred. The chlamydial agent was eliminated rapidly from the bodies of the ticks. Evidence for ticks being vectors could not be found (2).

Chlamydiae have been isolated from ectoparasitic biting lice of poultry and from free-living mites. There is no evidence that chlamydiae multiply in these arthropods, and it is believed that their bodies are merely contaminated with these infectious agents. It remains an open question whether arthropods participate in perpetuating or spreading the chlamydial infection among poultry or other birds.

Antigenic structure and other properties

The known chlamydial agents comprise a large number of antigenically related and culturally, morphologically, and tinctorially similar microorganisms. They possess a limiting membrane of complex chemical composition (apparently containing traces of muramic acid) similar to the cell walls of Gram-negative bacteria. Chlamydiae are obligate intracytoplasmic parasites and have limited metabolic activities independent of those of the host cells. They have both ribonucleic acid (RNA) and deoxyribonucleic acid (DNA). They are sensitive to the inhibitory action of some specific antibiotics that affect bacterial multiplication and some of them are sensitive to sulfa drugs.

The principal antigenic component of all chlamydiae is a group-specific antigen apparently consisting of a glycolipid complex that is readily dissolved by a variety of chemical or physical treatments. The reactive component is ether soluble, heat stable, and sensitive to periodate, and it is probably a carbohydrate. This is the antigen used in the complement fixation test; the haemagglutinin appears to have the same reactive group.

Specific antigens appear to reside in the cell walls. They are heat-labile in crude form (in the intact elementary body) and heat-stable when purified. These antigens are in part probably protein since they are sensitive to treatment with proteolytic enzymes. The specific antigens probably stimulate the production of neutralizing antibodies (when they are demonstrable) and of the antibodies that protect mice against toxicity and death.

The unique characteristic of the chlamydiae that distinguishes them from all other known microorganisms is their developmental cycle. Early in the cycle these obligatory intracellular parasites undergo a period of reorganization in which the infective particle (elementary body) changes from a dense-centred particle 250–400 nm in diameter to a less dense, RNA-rich, reticulate body (initial body), approximately 1 μm in diameter, and apparently non-infective. During this reorganization the particle retains its integrity. The initial bodies divide by a process similar to binary fission but apparently without cross-wall formation. Approximately 20 hours after infection of the cell, the dividing initial bodies begin to " condense ", reforming the elementary bodies.

The chlamydiae, unlike the rickettsiae, are cytochrome-free, do not produce ATP in their limited metabolic processes, and do not exhibit preferential metabolism of glutamate (4).

The elementary bodies are readily stained and appear in a characteristic colouring and distribution with a variety of specific stains (e.g. Giemsa, Machiavello, Giménez).

Although some chlamydiae are relatively unstable in the laboratory (being easily inactivated by heat and under routine conditions of storage), they may be extraordinarily stable under natural conditions. For example, the agents excreted in the faeces of turkeys have been recovered from litter and dried feathers as long as six months after the last turkeys had been removed from the premises.

METHODS AND CRITERIA FOR STRAIN OR TYPE IDENTIFICATION

The chlamydiae are separated into two groups for which binomial specific names have been proposed: *C. trachomatis* for one group including all those that produce iodine-staining inclusions and are sensitive to sulfonamides (i.e., the agents causing tra-

choma, inclusion conjunctivitis, lymphogranuloma venereum, and some rodent pneumonias); and *C. psittaci* for another group including the strains that produce iodine-negative inclusions and are usually resistant to sulfonamides (i.e., the agents causing psittacosis, ornithosis, and a variety of infections of domestic and other mammals).

Iodine-staining inclusions may be demonstrated by growing the agents in susceptible cells and then staining the inclusions at the optimum time (usually around 48 hours, although this may vary with different systems). The cells may be fixed in methanol and stained with either Lugol's solution or a more concentrated iodine solution. Agents that do not grow spontaneously in cells may be centrifuged into the cells to force infections that will allow the development of inclusions. A cell system that has been proven to produce iodine-staining inclusions when infected with known members of this group should be used.

Sulfonamide sensitivity can be determined by titrating the chlamydial agent in the yolk sac of embryonate eggs in the presence and absence of the drug (1 mg per egg immediately after the infective inoculum). At least a 10^2 difference in egg LD_{50} is required for a strain to be considered sulfonamide sensitive. However, sulfadiazine sensitivity alone is not sufficient to differentiate between the two groups; a number of psittacosis isolates, producing glycogen-negative inclusions, are sensitive to sulfadiazine.

Most useful in comparing a series of isolates are the so-called pathogenicity tests that are performed often in mice, sometimes in guinea-pigs (particularly useful for isolates from domestic animals), and occasionally in birds. Mice are inoculated intracerebrally and intraperitoneally. In general, the chlamydiae restricted to man (causing genital-tract disease, for example) are not lethal to mice by the intraperitoneal route, although some strains may be lethal by the intranasal and intracerebral routes. Rigorous testing is needed to exclude latent chlamydial infections in any mouse colony to be used. Mice have genetic differences in their susceptibility to chlamydial infection.

Although various chlamydial isolates have specific antigenic components, no routine test for identifying serotypes has been generally accepted. Fluorescent antibody tests, which give results parallel to those of mouse toxicity prevention tests, can be used to serotype chlamydial isolates obtained from patients with inclusion conjunctivitis and lymphogranuloma venereum. Isolates from diseases of the genital tract, such as non-gonococcal urethritis and cervicitis, usually fall into the inclusion conjunctivitis groups. Specific complement fixation tests have been described using either purified elementary body suspensions or the cell walls from elementary bodies, but the antigens are ordinarily of low potency and the results cannot easily be reproduced.

Infectivity neutralization tests are not generally practicable with serum from infected people or animals but can be performed in the laboratory when antiserum is produced in appropriate avian species (usually roosters). Neutralization tests can be performed by mixing the agent and antiserum and then inoculating them into a suitable indicator, such as mice, yolk sacs, or cell cultures.

DIAGNOSTIC PROCEDURES FOR CHLAMYDIAL INFECTIONS

Infections caused by strains of animal origin

The isolation of psittacosis strains should not be attempted in general pathology laboratories or in field laboratories. In laboratories not equipped with appropriate isolation facilities, the diagnosis of chlamydial infections is best restricted to serologic and cytologic methods because of the very high risk of laboratory infections.

The most efficient serologic method of diagnosing chlamydial infection in most mammals, including man, is the complement fixation (CF) test. The test is group-specific and utilizes antigens that can be prepared from virtually any chlamydial strain. The antigens are treated by heat, phenol, ether, or otherwise to render them free of strain-specific activity. Appropriate control antigens should always be employed. Except in prevalence studies it is usually necessary to test paired (acute and convalescent) sera to establish a diagnosis of current chlamydial infection. This may not be possible with relatively chronic infections such as lymphogranuloma venereum.

The direct CF test may also be used with parrot and some pigeon sera. Certain avian species (particularly chickens and turkeys) do not fix guinea-pig complement, and specific tests have been developed to measure antibodies by modifying the CF test. The most commonly used modification is the indirect complement fixation test, although tests using supplementation with normal rooster serum are also in use.

A fluorescent antibody test for determining antibodies to chlamydiae appears to be the most sensitive method for testing sera from patients with

genital-tract infections. However, experience with this test is still inadequate to allow recommendation of its routine use.

The agglutination reaction with purified elementary body suspensions has also been employed and has been found useful with certain avian species. The elementary body suspensions may be stained to facilitate reading of the tests in capillary tubes. Slide agglutination tests are used in some laboratories.

Skin tests of the delayed hypersensitivity type have been employed for the diagnosis of avian or mammalian chlamydial infection. In general, these have not received wide acceptance because of the difficulties in preparing potent antigens or in performing the tests, or because of the danger to personnel in handling infected animals.

In general, the isolation of chlamydia is carried out in embryonate hens' eggs, in mice, or in guinea-pigs. When rodents are used, latent chlamydial infection must always be ruled out. The yolk sac is usually preferred because it supports the growth of all known chlamydial strains. Tissue culture methods are available. Antibiotics not inhibiting the growth of chlamydiae are usually employed to reduce the risk of bacterial contamination of the cultures. The criteria for isolation include the demonstration of elementary bodies and of the group antigen in the indicator system. The isolate should be free of contaminating bacteria and viruses and be capable of serial passage with a measurable endpoint.

The organ systems to be tested for chlamydial infection vary with the host and disease being studied. Often the agent can be recovered from sites other than those obviously affected.

Certain chlamydial diseases produce pathognomonic changes. It is recommended, however, that microbiological confirmation be obtained in at least some of the animals. In some cases it may be possible to demonstrate the inclusions directly from diseased tissue but this method is relatively insensitive. The usual materials to be studied for demonstration of inclusions are exudates (generally peritoneal) or impression smears from the affected organs. Appropriate stains are numerous and include Giménez, Macchiavello, Giemsa, and Castaneda. Fluorescent antibody methods are routinely used for identifying some human infections and may prove practical for diagnosing other chlamydial infections.

Infections caused by strains of essentially human origin

The human diseases to be considered, apart from trachoma, are lymphogranuloma venereum (LGV), inclusion conjunctivitis, and the genital tract infections caused by chlamydiae. In patients with inguinal lymphadenopathy who are systemically ill (fever, chills, etc.), laboratory studies confirm approximately 75% of infections diagnosed as LGV by the clinician, after exclusion of other causes such as bacterial infections. Most commonly used for diagnosis is the Frei test, a delayed hypersensitivity skin test that is often negative in proven LGV cases. The most practical diagnostic test appears to be the CF test, but it is almost impossible to demonstrate rising titres since patients seldom seek medical attention until three to four weeks after the initial infection. The agent may be isolated in the yolk sac or in irradiated tissue cultures. Inoculation into mice has been used in the past, but it is apparently less sensitive. Cytologic methods are of no value for the routine diagnosis of LGV.

The agent of inclusion conjunctivitis may be found most commonly in the epithelium of the conjunctiva, the male urethra, or the uterine cervix. The diagnostic methods are essentially all the same but the sensitivity varies with the site of infection. They include the standard Giemsa staining of epithelial cell scrapings. Characteristic inclusions can be demonstrated in approximately half the patients with acute ocular disease or uterocervical infections and in a somewhat lower proportion in material from urethral infections. Fluorescent antibody methods appear to be more sensitive.

No satisfactory serologic method is available for diagnosing infections caused by the agent of inclusion conjunctivitis. The complement fixation test is relatively insensitive with, at best, positive results in only 50% of proven infections. Rising titres are seldom observed. The newly developed microimmunofluorescence (micro-IF) test is considerably more sensitive and, since the antibodies measured differ from those measured in the CF test, may be more useful (6). Another advantage of the micro-IF test is that it may be possible to demonstrate the antigenic type of the infecting strain. However, more information is required, for instance, about the baseline rates and the effects of previous infections on the serologic results, before this promising test can be recommended for routine use.

PUBLIC HEALTH SIGNIFICANCE

Chlamydial infections of man other than trachoma

The present and future public health significance and the long-term sequelae of chlamydial urethritis

and cervicitis are not known. The results of recent research suggest that infections with this group of agents may be the second most commonly transmitted venereal infection. The most serious overt disease is lymphogranuloma venereum. It is likely that the number of cases and the public health importance of all these diseases will increase through the combined effect of greater awareness and rising veneral disease rates.

Avian chlamydial infections and human health

While psittacine birds continue to be responsible for human chlamydial infections in sporadic and familial cases, other sources for human infections (apart from cage birds of pleasure and show) have become better known and their importance appreciated during recent years. The recognition of chlamydial infections in a wide range of avian hosts altered the pattern of this anthropozoonosis to an occupational disease among persons working in contact with poultry. Thus, human infections contracted from fulmars were recognized in the Faeroe Islands; chickens have been identified as the source of sporadic cases of human infections, and human diseases of pigeon origin have been found in pigeon breeders and fanciers; the pigeons in parks and streets occasionally constitute a health hazard to people who come in contact with the dust from dried droppings; and human infections are known to have been contracted by hunters from game birds.

Some recent epidemics have corresponded with the expansion of poultry industries in several countries and with the creation of large poultry farms, while ducks, geese, and turkeys have also been identified as a source of human infections. Explosive outbreaks have occurred among poultry processing plant employees. Meyer (2) tabulated from the world literature 5 390 cases of human infections resulting from contact with chlamydia-infected ducks, pigeons, chickens, turkeys, and other poultry, and stressed that the reported cases represent only a small proportion of the actual number of infections among persons in contact with poultry.

Respiratory infections are usually acquired by the inhalation of contaminated dust, but little is known about other routes of infection.

Human infections originating from chlamydia-infected mammals

There are a few well-documented cases of human infection with chlamydia of mammalian origin. Several serologic studies on persons in close contact with chlamydia-infected mammals also suggest that these animals may be a source of human infection. However, the potential danger of chlamydia-infected animals to human health has not been adequately assessed as yet and it deserves further study.

CONTROL MEASURES

The tetracyclines are the drugs of choice in the treatment of chlamydial infections in animals as well as in man. Adequate dosage and duration of treatment are important, but clinical cure does not necessarily reflect clearance of chlamydiae.

No generally accepted vaccine for chlamydial diseases is available, and the role of immune mechanisms in chlamydial infection is not clear.

Chemotherapy and quarantine are the main measures for the control of chlamydial infections in imported birds.

The frequent occurrence of inapparent or latent infections makes it imperative to establish adequate laboratory facilities for the effective surveillance and control of chlamydial infections.

RÉSUMÉ

LES *CHLAMYDIA* EN TANT QU'AGENTS DE MALADIES HUMAINES ET ANIMALES

Les *Chlamydia* sont caractérisées par leur cycle de développement intracellulaire qui comporte une période de réorganisation, au cours de laquelle la particule infectante (corps élémentaire) se transforme en un « corps initial » non infectant, suivie d'une phase de multiplication par division binaire. Les *Chlamydia*, contrairement aux rickettsies, sont dépourvues de cytochrome et ne produisent pas d'acide adénosine triphosphorique. On les classe en deux groupes: *C. trachomatis*, souches sensibles aux sulfamides et produisant des inclusions colorables par l'iode (agents responsables du trachome, de la conjonctivite à inclusions, du lymphogranulome vénérien, et de pneumonies chez les rongeurs) et *C. psittaci*, souches produisant des inclusions non colorables par l'iode et généralement résistantes aux sulfamides (comprenant de nombreuses espèces de *Chlamydia* d'origine aviaire ou mammalienne).

On décèle la présence de *Chlamydia* chez beaucoup d'espèces d'oiseaux et de mammifères. L'homme est l'unique hôte naturel connu des *Chlamydia* provoquant le

trachome, la conjonctivite à inclusions et des infections de l'appareil génito-urinaire, y compris le lymphogranulome vénérien. On peut entrevoir que l'importance en santé publique des infections à *Chlamydia* de l'appareil génito-urinaire ira en s'accentuant par suite d'une meilleure connaissance de ces infections et de la recrudescence des maladies vénériennes. Chez l'animal, les infections à *Chlamydia* sont à l'origine de pneumonies, d'encéphalites, d'avortements, d'arthrites, de diarrhées et de conjonctivites. Le tractus intestinal est un habitat naturel des *Chlamydia*; chez les ruminants et chez la plupart des espèces aviaires tout au moins, les infections inapparentes du tractus intestinal sont fréquentes. Des infections inapparentes sont aussi observées chez les oiseaux, les bovins, les cobayes et les moutons. L'homme peut devenir un porteur asymptomatique après avoir été contaminé par des *Chlamydia* d'origine aviaire.

Des infections à *Chlamydia* ont été observées chez un grand nombre d'hôtes aviaires. Chez l'homme, des cas sporadiques de psittacose/ornithose ont été enregistrés chez des personnes en contact avec des oiseaux. Des études de transmission suggèrent que la spécificité d'hôte des *Chlamydia* de mammifères est limitée et que des maladies et même des infections en chaîne peuvent se développer chez des hôtes secondaires. On a isolé des *Chlamydia* chez des arthropodes, mais on n'a aucune preuve décisive du rôle de ces derniers en tant que vecteurs de l'infection.

La meilleure méthode sérologique de diagnostic des infections à *Chlamydia* est l'épreuve de fixation du complément à l'aide d'antigènes spécifiques de groupe. La réaction d'agglutination utilisant des corps élémentaires purifiés est utile chez certaines espèces aviaires. On a employé les tests cutanés du type « hypersensibilité retardée », mais leur pratique requiert des antigènes très actifs difficiles à préparer. En raison du risque d'infection, il est déconseillé de tenter l'isolement des agents de la psittacose dans les laboratoires non spécialisés. Bien que divers isolats de *Chlamydia* renferment des composants antigéniques spécifiques, il n'existe aucune épreuve de routine généralement acceptée pour l'identification des différents sérotypes.

La fréquence des infections inapparentes ou latentes impose de créer des installations de laboratoire appropriées dans le cadre d'une surveillance et d'une lutte efficace contre les infections à *Chlamydia*.

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