Review Article

The Emergence Potential of *Chlamydia psittaci* and *Chlamydia felis* as Zoonotic Agents Causing Ocular and Respiratory Infections in Humans and Animals

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ABSTRACT

Members of the *Chlamydiaceae* are obligate Gram-negative intracellular pathogens that cause a variety of infectious diseases. As a zoonotic pathogen, *Chlamydia psittaci* (*C. psittaci*) has been associated with a wide range of infections in both wild and domestic animals, particularly birds. In humans, *C. psittaci* causes influenza-like symptoms, pneumonia, endocarditis, fever, chills, myalgia and headache. Similar to other *Chlamydia* species, the virulence factors of *C. psittaci* mainly include type III secretion system, type IV system effectors (TARP), CopN, HctA and HctB, OmcA, OmcB, OmpA, major outer membrane protein (MOMP), PorB and Euo. In particular, *C. psittaci* may predispose patients to other respiratory pathogens. Direct contact and inhalation of contaminated air droplets from birds is a risk factor for transmission of infection. Other risk factors include pregnancy, overcrowding, bird litter, and close contact with cats and dogs. Therefore, greater care should be exercised in close contact with these pet animals. Fortunately, these infections have been treated more effectively thanks to the development of novel drug delivery systems in recent decades. There is no similar review study to assess zoonotic potential of these species. Considering the highly contagious potential of *C. psittaci* and *C. felis*, together with the wide host range and available risk factors, appropriate control strategies are essential to prevent their dissemination.

Keywords: *Chlamydia Psittaci*, *Chlamydia Felis*, Zoonoses, Eye Infections, Respiratory Infections

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1. Background

A variety of infectious agents can cause eye infections. Viruses of the *Adenoviridae* and *Herpesviridae* families and bacterial pathogens such as Str*eptococcus pyogenes, Staphylococcus aureus, Nisseria gonorrhoeae, Clamydia species,* and *Escherichia coli* are prominent examples (1-3). Members of the genus Chlamydia are obligate, gram-negative, intracellular microorganisms that cause a wide range of diseases in humans and many other warm-blooded animals. Animal infections can cause in abortion , infertility, enteritis , encephalomyelitis, swollen joints, and respiratory disease (4,5). In humans, *Chlamydia* is one of the most reported pathogens associated with several diseases, including eye infections, pneumonia, sexually transmitted diseases (6, 7), and cardiovascular diseases. *Chlamydia felis* (*C. felis)* is endemic to all domestic cats worldwide and can cause inflammatory conjunctivitis, nasal mucositis and respiratory complications (8). The pathogen can be retrieved from the instine and reproductive system of infected cats (9,10). The morphological characteristics and life cycle of the bacterium are similar to those of other of *Chlamydia* species. Ocular secretions are a major sources of the infection. Chlamydial infections are evident in an environment where many cats live together, particularly among in purebred cats with an exceptionally high prevalence of disease (11). Cats also serve as a reservoir for certain zoonotic pathogents, including Tox*oplasma gondii*, *Bartonella hensella* , and *Coxiella bornetti* (12, 13). Another species of *Chlamydia* is *C. psittaci*, causes zoonotic infections in a variety of animals, including birds, mammals, and humans which have long been neglected e due to their low incidence rates (14-16). To make matters worse, the majority of infections in animals are asymptomatic. Humans can be infected by inhalation of these pathogens, which are present in feces and secretions from the eyes and nose. The microorganism has the ability to survive in the environment for a long periods of time (17, 18). Psittacosis are present with many clinical manifestations in humans. Direct contact or inhalation of contaminated air droplets from birds, especially those infected with *C. psittaci*, is a major risk factor for transmission of infection (19, 20). In addition, multiple sexual partners, pregnancy, overcrowding, older age (65 years), poor hygiene, immunocompromised conditions, intensive farming, bedding material, close contact with pets such as cats and dogs are other potential risk factors (11,21,22). In addition, risk factors associated with *C. felis* infection mainly include close contact with infected cats, multi-cat households or crowded environments, stress or weakened immune systems and contact with other outdoor cats. Notably, *C. felis* is primarily a cat-to-cat infection and is not known to be transmitted to humans (23). This review study aimed to assess the emergence potential of *C. psittaci* and *C. felis* as zoonotic agents causing eye and respiratory infections in humans and animals. Major limitations of the study include gaps in the economic burden, morbidity and mortality rates behind these infections.

2. Conjunctivitis

The conjunctiva is a transparent, thin layer of mucous membrane that covers the inner surface of the eyelid and the sclera. Conjunctivitis is an inflammation of the conjunctiva and cornea, in which symptoms of congestion and discharge develop with conjunctival hyperplasia, itching, foreign body sensation in the eye, and eyelid edema (24). In order to properly cure the disease, it is imperative to identify and characterize the etiologic agent. To date, several pathogens and many non-infectious (e.g. trauma, allergy, etc.) causes have been reported in the literature (25, 26).

2.1. Viral and bacterial agents of conjunctivitis

Viral agents of conjunctivitis include members of the *Adenoviridae* and *Herpesviridae* families, enteroviruses (*Picornaviridae*), and vaccinia virus (poxvirus) (27-29). Bacterial pathogens such as Str*eptococcus pyogenes, Staphylococcus aureus, Nisseria gonorrhoeae Chlamydia* species, and *Escherichia coli* may also be involved (30, 31). Atypical *Mycobacteria* species are opportunistic pathogens that usually cause this complication after trauma or surgery. As for *Chlamydia*, three species including *C. trachomatis, C. psittaci, and C. pneumoniae* have been shown to be associated with conjunctivitis. *C. trachomatis* is frequently pathogenic in humans and causes classical trachoma (32). The pathogen causes conjunctivitis thatmanifests itself as follicular conjunctivitis in infants and inclusive conjunctivitis in adults. However, *C. trachomatis* conjunctivitis is usually associated with chlamydial infection of the genital tract. Genital infections, if not diagnosed and treated promptly, can lead to pelvic inflammatory disease, infertility, Reiter's disease, neonatal eye disease, and neonatal pneumonia (33). It may be too difficult to differentiate between the viral and non-viral etiology of keratoconjunctivitis based on the clinical picture, as some of viral cases have been misdiagnosed as bacterial conjunctivitis (26). A number of the *Chlamydia* species have been associated with non-human conjunctivitis, including *C. caviae* (guinea pigs), *C. suis* (pigs), *C. psittaci* (birds), and *C. pecorum* (cattle and sheep) (34, 35). Clamydial infection has also been associated with keratoconjunctivitis in sheep and goats, but molecular studies in sheep have not demonstrated a clear association. Using molecular techniques, *C. felis* and *C. pneumoniae* have been shown to cause infection in cats. *C. psitasi* was isolated from keratoconjunctivitis and respiratory symptoms in a dog breeding center. Human trachoma and conjunctivitis are caused by *C. trachomatis* (35). Bacterial conjunctivitis usually resolves spontaneously, although antibiotic therapy is effective. Viral and chlamydial conjunctivitis are indistinguishable from allergic conjunctivitis in the early stages (36). Commercial laboratory tests are not commonly used to diagnose these infections. In industrialized countries, *C. trachomatis* is the

most common sexually transmitted disease causing conjunctivitis in infants and toddlers. Similar trends are also observed in some developing countries, such as China. In other countries, such as Argentina and Hong Kong, *S. aureus* has been reported as the most common cause of conjunctivitis in infants (37, 38). These differences may be related to the epidemiological diversity of different countries or may reflect sexually transmitted diseases, which are the second most common cause of blindness worldwide after HSV1. It is also a major cause of corneal blindness in developed countries. Viral ocular infections can present in a variety of clinical forms. Acute eyelidconjunctivitis(pink eye) (acute belfaroconjunctivitis) with or without keratitis, recurrent corneal ulcers, and recurrent interstitial corneal inflammation are the most common. Primary ocular infection may present as acute follicular conjunctivitis or keratoconjunctivitis with or without eyelid and corneal ulcers (39). Purulent conjunctivitis is characterised by the formation of vesicle with ulceration and corneal bleeding. It should be distinguished from scleritis, iritis, glaucoma, conjunctivitis, and even herpes zoster. Prompt referral to an ophthalmologist is recommended to prevent progression of the disease (e.g. permanent scarring, secondary bacterial infection, meningoencephalitis, and loss of vision). Infants with Herpes simplex virus (HSV) eye infection may develop systemic or central nervous system (CNS) infection. Adenoviruses can cause follicular conjunctivitis, where there is a pebble or nodule in the conjunctival mucosa of the eyelid and both conjunctiva (eyelid and eyeball) become inflamed. This conjunctivitis may be seen as a single event or as outbreaks with a common source. Conjunctivitis associated with swimming is an example of a common source of adenovirus infection (40, 41).

2.2. Keratitis

Keratitis, or purulent infection of the eye cornea, is one of the leading causes of blurred vision and even blindness if not properly diagnosed and treated. Blindness is now a serious health problem, especially in developing countries (42). Symptoms include eye pain, photosensitivity, watering and runny eyes. Climate, geography, and risk factors all play a role . Adenoviruses are the most common etiologic agents of keratitis, accounting for between 10% and 75% of cases (43). The treatment of herpetic keratitis can be a serious challenge for the ophthalmologist (44). The ocular manifestations of HSV infection are diverse . Herpetic keratitis occurs in two main forms, involving the superficial layer of the cornea or epithelial keratitis and involving the deep layer of the cornea or stromal keratitis. Epithelial keratitis accounts for 63% of cases and is characterized by a dentate ulcer (45). The other one is less common and accounts for 6% of primary infections and 17% of recurrences. Stromal disease occurs when the viral antigen enters the stroma and triggers an immunological response that manifestsas an edematous disc lesion. Severe cases may develop to necrotic stromal keratitis. Herpetic keratitis is almost always confined to one eye. In herpetic keratitis, the virus infects all layers of the cornea directly or by stimulating the immune response (46). Necrotizing stromal keratitis is a rare manifestation of herpes virus. In this type of keratitis, destruction of the corneal stroma occurs as a result of direct viral invasion and is usually refractory to anti-inflammatory and antiviral therapies. This type of keratitis can eventually lead to perforation and thinning of the cornea in a short period of time. Therefore, proper treatment and prompt management are essential to preserve the cornea and prevent early and late complications such as lesional or corneal opacity, desmatocellular perforation, corneal inflammation, or intraocular inflammation. Optimal management (evidence-based and appropriate treatment algorithms) of the herpes keratitis is a significant issue (47). Primary herpes simplex infection occurs in individuals without prior exposure. The disease is usually subclinical in childhood and adulthood without imapcts on eye. Recurrence of the ocular infection has high rates following the activation of a latent virus in the trigeminal neuralgia (48). Over the past three decades, the prevalence of fungal keratitis has increased, particularly in tropical and subtropical climates, with the highest rates in Asia and Africa (49). Fungal microorganisms are responsible for 1.2% to 62% of keratitis infections. *Fusarium* spp. are the most common causes of fungal mycocarditis and are frequently isolated from the eye in the tropics and subtropics. Some of these species are plant pathogens and others are saprophytes in the environment. The most common species in the genus is *Fusarium solani* (50). There are many clinical manifestations of fungal keratitis. In the early stages, the lesions appear as granular lesions in the cornea that closely resemble the granular lesions associated with the herpes simplex virus. In severe cases or when there is no response to the treatment, surgical treatment such as corneal transplantation is recommended. Corneal transplantation in these conditions can lead to various complications and recurrence of the infection (51, 52).

2.3. Keratoconjunctivitis

Worldwide, keratoconjunctivitis is the most common multifaceted eye disease. Dry keratoconjunctivitis (SICCA) has the same dry eye symptoms observed in ceratin rheumatic diseases. The development of keratoconjunctivitis is especially important in children, and various bacteria have been shown to be implicated (53, 54). Although antibiotics are usually effective in treating bacterial eye infections, their misuse in recent years has led to the emergence of drug-resistant bacterial species, limiting the treatment options for patients with bacterial ocular infections. Among the isolated bacterial species, *S. aureus* is acknowledged as the most common bacterial agent involved in ocular infections (55). Other bacterial species contributing to the development of the disease, based on the prevalence of the pathogen, include coagulase negative *staphylococci*, *Bacillus* spp, *Pseudomonas aeruginosa*, *Enterobacter species*, *Klebsiella pneumoniae*, and group D *streptococci* (56, 57). Vernal Keratoconjunctivitis (VKC)

is an inflammation that can develop due to seasonal, bilateral, and antimetric allergies. Males are usually 2-3 times more likely to be affected before puberty than females. At the age of 13-19 years, the severity of the disease decreases and finally disappears in the early 20_s The disease is more common in hot and dry climates such as the Middle East, the Mediterranean and Central America. Spring keratoconjunctivitis appears with the onset of spring and its severity decreases in the fall. Itching is a prominent sign of the disease at the early stages and the photophobia is also often evident. Other symptoms include inflammation, tearing, and a foreign body sensation in the eye. Bovine infectious keratoconjunctivitis is an infectious and contagious disease of the bovine eye characterized by swelling of the conjunctival and cornea. The only microorganism isolated from clinical cases capable of causing the disease is a gram-negative coccobacillus *Moraxella bovis*. The disease is transmitted by direct contact with aerosols and objects. Insects also serve as mechanical vectors. The disease is globally distributed and occurs at the time when insects are most active. Clinical features include photophobia, blepharospasm, and ocular secretion together with conjunctival and corneal swelling. Several studies have highlighted the economic impact of the disease (58, 59). Different pathophysiological mechanisms are associated with the development of infectious keratoconjunctivitis. Among the various forms of viral keratoconjunctivitis associated with adenovirus epidemics, adenoviral keratoconjunctivitis is of importance. Regarding the epidemiology of the disease, different strains of adenovirus have been isolated in different parts of the world. The most prevalent strains include serotypes 3, 4, 8, 11, 17, 19, and 37. Two forms of conjunctivitis syndromes related to adenoviruses have been mentioned; fever due to laryngitis-conjunctivitis ,which usually occurs in children and is caused by adenovirus serotypes 3, 7, and 8, and epidemic keratoconjunctivitis, which usually occurs in adults and is caused by serotypes 8, 19, and 37 (60, 61). Primary acute blepharitis and chronic keratitis have been shown to be associated with HSV infection. Acute follicular keratoconjunctivitis without eyelid or corneal ulcers ulceration is less common. Ocular herpes simplex virus infection is common and accounts for 25% of follicular keratoconjunctivitis cases and outpatients. This type of eye infection typically develops early in life and is associated with herpes lesions on the face, eyelids and cornea. HSV is usually isolated from follicular conjunctivitis with keratitis similar to adenoviral keratoconjunctivitis (62).

2.4. The genus *Chlamydia*

Members of the genus ***Chlamydia*** are obligate, gram-negative intracellular pathogens that cause a wide range of diseases in humans and other warm-blooded animals (63-67). Infections in animals can result in abortion, infertility, enteritis, encephalomyelitis, swollen joints, and respiratory disease. In humans, *Chlamydia* spp cause preventable blindness, respiratory, cardiovascular and sexually transmitted diseases (68, 69). The growth cycle of *Chlamydia* sp is characterized by two completely distinct morphological forms, including small infectious intracellular elementary bodies (EB) and non-infectious reticular bodies (RB) as metabolically active forms (70, 71). The growth cycle begins with endocytosis of EB bodies by cells. Each EB consistes of a bacterial cytoplasmic membrane with a periplasmic space and an outer membrane containing lipopolysaccharide. EB forms are intracellular cytoplasmic aggregates that grow into larger bodies called RBs and multiply by division. Depending on the species, the RBs transform into metabolically inactive EB bodies after about 24 hours, which are released after the lysis of the host cell and attack the adjacent cells. The major part of the cycle proliferation is probably similar to that of organotrophic bacteria, although they multiply as obligate intracellular parasites. These microorganisms are stable outside the cell by reducing metabolic activity. They also become resistant to unfavorable environmental and chemical substances, which is as a result of cell wall stiffness and impermeability of EB forms. The surface area of these bodies is smaller than that of the RB forms; therefore, EB forms have the ability to survive outside the cell for a long time (an average of months). Human zoonotic eye infections have been caused by C. *trachomatis*, *C. psittaci*, *C. pneumoniae* and *C. felis* (72-74). Psittacosiss was first diagnosed by Ritter in 1879 during a domestic epidemic in seven poultry-associated patients in Switzerland who developed an unusual pneumonia. With the outbreak of the disease in Paris, it was named after the Greek word for parrot, psittakos, as the source of infection (75).

2.5. Chlamydia felis

C. felis is a gram-negative, spherical bacterium endemic to all domestic cats worldwide and can cause inflammatory conjunctivitis, nasal mucositis and respiratory complications. This bacterial pathogen can be isolated from the gut and reproductive system of infected cats (76, 77). The morphological characteristics and life cycle of this bacterium are similar to other *Clamydia* species. Ocular secretions are the most important source of the infection. Diseases caused by this bacterium are prevalent in environments where cat populations exist, especially in purebred cats with a significantly high prevalence (11, 78, 79). The majority of cases are found in cats less than one year of age (over 30% of cats with the disease or even in carriers). Serological studies have shown that 10% of vaccinated domestic cats have antibodies against the pathogen (80, 81). In some studies, 12-20% of cats with symptoms of eye diseases and upper respiratory tract infections had this bacterial agent, and this rate was reported to be 3% in cats without symptoms. In other prevalence survey of *C. felis* in European countries, the prevalence of the pathogen in domestic cats and stray cats without clinical signs reached 3% (11, 82). The prevalence of this pathogen in the United States and European countries is reported to be 0-10%, whereas it is 59.1%,

20%, and 11.5% in Australia, Italy, and Japan, respectively (81, 83, 84). The primary target of *C. felis* is the epithelial cells of conjunctival tissue of the eye. Transmission of the microorganism among cats occurs by direct contact with ocular secretions or equipment infected with these pathogens, as well as by sexual contact. The incubation period is approximately three to five days. *Chlamydia* infections are usually chronic and unexplained, often progressing without obvious symptoms. These infections may be caused by *Chlamydia* spp remaining in the tissue. *C. felis* can be recovered from tissue over 200 days after experimental infection (76, 85). In a study conducted in Iran in 2020, of 100 patients with keratoconjunctivitis, one sample was positive for *C. psittaci*, but none were positive for *C. felis* (21). In many cats, ocular discharge from the conjunctiva ceases 60 days after infection, although they remain as reservoirs and can transmit the infection (86). Long-term discharge from the rectum and vagina of infected cats is observed in the intestine and reproductive system. In one case, *chlamydial* infection with peritonitis was observed in cubic cells and macrophages of peritoneal fluid (45). These pathogens are also found in the mucous layer of the gastrointestinal tract and upper respiratory tract, causing mild gastritis and pneumonia, respectively (87). *Chlamydia* spp. infections can be associated with reproductive disease, especially in humans and sheep. *C. felis* appears to be a cause of miscarriage, fetal mortality, and infertility in cats. In one study, 8% of cats were co-infected with *Chlamydia* and one of the most common diseases caused by feline virus (FCV), or F-1 (FHV) (88, 89). In another survey, 64% of cats were infected with *C. felis* (90). FCV- infected cats present with symptoms such as oral ulcers and conjunctivitis with discharge. *Chlamydia* spp are susceptible to tetracyclines, erythromycin, rifampin, and fluoroquinolones (91, 92). As expected, sulfonamides and chloramphenicol are ineffective against *C. felis*. Doxycycline is used as the drug of choice for the treatment of *Chlamydia* infections, especially due to its synergistic effect with azithromycin. *C. felis* has unique hosts including cats and dogs (causing conjunctivitis and mild pneumonia) which are in close contact with humans. The prevalence of infection in animals is reported to be high (3-10%) in some countries such as Japan, Italy, Slovakia, and China (12, 72). Seropositive human cases have also been reported in Japan. In case reports of human conjunctivitis, *C. felis*-positive kittens have been reported (12). Various hosts, clinical signs, and virulence factors related to *C. felis* and *C. psittaci* are listed in Tables 1 and 2.

2.6. Chlamydia psittaci

C. psittaci causes zoonotic infections in a wide range of animals and humans which has been neglected due to its low prevalence (64, 96-98). In addition, most of infections in animals are asymptomatic and result in production losses (14). Humans are infected by inhalation of this microorganism, which is present in ocular and nasal secretions and survives for long periodsin the environment. The clinical manifestations of psittacosis in humans can be highly variable and are caused by human contact with infected birds, especially eye, nose and fecal secretions of these birds. Healthy birds can also carry the microorganism and transmit it to humans or other birds (15). In birds, hypersensitivity to the disease occurs under stressful conditions such as starvation, transport, increased density, and spawning. Human-to-human transmission of the pathogen is rare; however, evidence of this type of transmission has been observed in some cases of the outbreaks of this microorganism. For example, in the *C. psittaci* epidemic during 1929-1930, the transport of infected birds from Argentina to other parts of the world caused an outbreak of the infection with a mortality rate of over 40% worldwide and since *C.psittaci* was isolated from 130 species of birds, all species of domestic and wild birds serve as sources of this microorganism (99, 100). Using monoclonal antibody serotyping, six avian (A-F) and two mammalian (WC and M56) serotypes have been identified (101, 102). Genotyping of the *ompA* gene has revealed additional E/B, I and J genotypes (18). The incubation period of these infections lasts 6-19 days. Transmission from ruminants to humans is rare, but uterine infections, diffuse vascular coagulation, and sudden abortion have been observed in women who exposed to infected sheep during childbirth (103). Conjunctivitis, glomerulonephritis, and endocarditis associated with *C.psittaci* have been reported to be transmitted from infected animals (104) to humans (19). *C.psittaci* can interfere with macrophage activity and hence promote the progression of influenza virus infection (105).

Table1. Susceptible hosts, clinical symptoms, and virulence factors of *C. felis* (93-95).

C. felis	Host	Clinical signs	Virulence factor
1	Cat, dog	Ocular, respiratory, reproductive	Type III secretion system, Type IV system effectors (TARP), CopN, HctA and HctB, OmcA, OmcB, OmpA, MOMP, PorB, Euo,
2	Human	Ocular, respiratory	
3	Birds	Ocular, Respiratory	
4	Horse, pigs	Ocular, Respiratory	

Table 2. Susceptible hosts, clinical symptoms, and virulence factors of *C. psittaci* (95, 106).

C. psittaci	Host	Serotype/genotype	Clinical signs	Virulence factor
	Birds	A-F	Respiratory, Ornithiosis, Psittacosis, Blepharitis, Conjunctivitis	Type III secretion system, type IV system effectors (TARP), CopN, HctA and HctB, OmcA, OmcB, OmpA, MOMP, PorB, Euo
	Cattle	WC	Respiratory	
	Rodents	M56	Respiratory	
	Human	All	Influenza-like, Pneumonia, Endocarditis, Fever, Chills, Myalgia, Headache	

2.7. Risk Factors

Exposure/direct proximity and inhalation of contaminated air droplets from bird populations, especially for the *C. psittaci* is a risk factor of infection transmission. In addition, multiple sexual partners, pregnancy, overcrowding, older age (65 years), poor hygiene, immunocompromised conditions, intensive farming, bedding material, close contact with pets such as cats and dogs are other potential risk factors (11, 21, 22). In addition, risk factors associated with *C. felis* infection mainly include close contact with infected cats, multi-cat households or crowded environments, stress or weakened immune systems and contact with other outdoor cats. Notably, *C. felis* is primarily a cat-to-cat infection and is not known to be transmitted to humans (23). Antibiotic resistance is another crisis in the spread of bacteria that requires proper adoption of accurate options (107).

2.8. Bacterial immune evasion mechanisms

Persistent intracellular residence (up to nine months) plays a pivotal role in chronic *Chlamydia*disease. It has been shown that exposure to IFN-γ, amoxicillin or azithromycin can induce persistent infection that forms abnormal bodies via the expression of different genes. The altered expression of various proteins such as those involved in metabolism, cell division, virulence, and transcriptional regulators lead to immune evasion and also resistance of Chlamydia spp to harsh conditions. In addition,,*Chlamydia* spp can increase the levels of the indoleamine 2, 3-dioxygenase (IDO) which aids in immune evasion (108-110). Additionally, *C. psittaci* intervenes in the apoptosis of neutrophils and macrophages via various CPSIT protein-mediated mechanisms such as MAPK-ERK, INF-γ, toll-like receptors signaling pathways (111, 112). Additionally, CTL0225 is a member of the SnatA family of neutral amino acid transporters involved in immune evasion (113).

2.9. Drug Delivery Systems

Echogenic immunoliposomes (ELIPs) were initially developed by Tiukinhoy et al to incorporate azithromycin to combat *Chlamydia*-infected endothelial cells *in vitro* (114). Mishra et al, used generation-4 neutral polyamidoamine (PAMAM) for intracellular delivery of azithromycin against *C. trachomatis* in HEp-2 cells (115). Inhaled antibiotic-loaded polymeric nanoparticles such as chitosan plus isoniazid, levofloxacin, ciprofloxacin, rifampicin, liposomes, ethambutol dihydrochloride, dapsone, ofloxacin, moxifluxacin, rifabutin, gentamicin, vancomycin, and even combinations of alginate with paclitaxel, tobramycin, isoniazid, rifampicin, pyrazinamide, amikacin, ciprofloxacin, polymixyn, insulin, and poloxamers have been used for lower respiratory tract complications. Notably, poly (lactic-co-glycolic acid) or PLGA, fucoidan, and xanthan gum has also been added to formulations for improved or prolonged drug delivery (116). Mucoadhesive chitosan nanoparticles and bacterial ghosts (BGs), as empty bacterial envelopes, have also been used to reduce respiratory complications by *C. psittaci* (117).

2.10. Future directions for the control of *Chlamydia* spp infections

Control of *Chlamydia* spp can be achieved through education and awareness, safe sexual practices, screening and testing, vaccination, surveillance and reporting, environmental hygiene and animal control measures (118, 119). For *Chlamydia* spp. infections in animals, such as *C. psittaci* in birds or *C. felis* in cats, control measures involve proper hygiene and management practices. These include regular cleaning of cages, proper disposal of waste, isolation of infected animals, and adherence to biosecurity protocols in animal facilities. The establishment of surveillance systems to monitor the incidence and prevalence of *Chlamydia* spp. infections is critical. Timely reporting of cases can help to identify outbreaks, track trends, and inform control measures. It is worth mentioning that specific control strategies may vary depending on the species of *Chlamydia* and the target population. Implementing a combination of these strategies, tailored to the specific context, may help to effectively control and prevent the spread of *Chlamydia* spp. infections (120). For *C. psittaci*, personal protective equipment, quarantine and isolation of birds, and occupational safety measures are needed (120). Moreover, a One Health approach that considers both animal and human health is crucial for effective control and prevention. Noticeably, *C. felis* is primarily a cat-to-cat infection and does not pose a significant risk to humans. However, practicing proper hygiene and following control strategies can help prevent the spread of *C. felis* among cats. Consult with a veterinarian for specific guidance on control and prevention measures based on the individual cat's health status and living environment (65, 121-122).

3. Conclusion

C. psittaci and *C. felis* infections have the potential to emerge or re-emerge in humans from a wide variety of animals and birds. Therefore, the global research community should consider the control and management of these versatile pathogenic species in the field of veterinary medicine because of their significant health and economic impact. *Chlamydia* species employ various immune evasion mechanisms to persist and evade host responses. Undoubtedly, the application of novel drug delivery systems is promising to enhance the efficacy of antibiotics.

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As a review study, all listed authors have made significant scientific contributions to the research in the manuscript, approved its claims, and agreed to be an author. No support was provided for this study by non-author parties.

Authors' Contribution

The manuscript was written by Abdolmajid Ghasemian. Babak Pezeshki, Mojtaba Memariani, Elham Zarenezhad and Hassan Rajabi-Vardanjani edited and approved the content. All listed authors have made significant scientific contributions to the research in the manuscript, approved its claims, and agreed to be an author.

Ethics

Not applicable

Conflict of Interest

Not applicable

Availability of data and material

Not applicable

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