Major infectious abortion diseases of domestic animals and their zoonotic implications

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Abstract

Convergence of people, animals, and our environment is inevitable in the present world creating a new dynamic. A dynamic in which the health of humans and animals and the wellbeing of the environment are inextricably linked carrying both benefits and risks. One such risk includes the impact of animal abortion diseases on human health. Abortions that occur in animals not only result in severe economic loss but also pose a threat to people if these agents have zoonotic implications. Knowledge of 'nonabortion pathology' of animals is important since these are the major lesions, more than the incidence of abortion, observed in people following infection by these agents. Major infectious abortion diseases of domestic animals that have zoonotic importance are discussed. The list includes brucellosis, leptospirosis, coxiellosis, listeriosis, chlamydophiliosis and waddliosis, toxoplasmosis, and campylobacteriosis. This review summarizes the information on etiological agents, major clinical signs in animals and humans, and available vaccinations for animals. Four key future directives are suggested to address the domestic animal abortion diseases from the perspective of their impact on human health. The directives are establishment of programs in comparative medicine, initiation of further research in the disease process in animals, continuation of spatial and temporal analyses of the diseases for a region, and finally completion of epidemiological representation of the disease.

Keywords: Domestic animals; infectious abortion; bacterial agents; protozoan agents; zoonotic importance

Introduction

Human contact with animals has grown in part due to increases in demand for production of food of animal origin and in part due to increases in desire for animal companionship, and finally increases in participation in animal sporting events. Undoubtedly, the importance of animal value in the current global economy forces more people to work with them in intensive animal agriculture programs and thereby increasing the chances of exposure to diseases of animal origin. Zooeyia, the positive benefits on human health resulting from people interacting with pets, is well established. Furthermore, there is a growing body of evidence documenting the improved physical, social, and mental health in people who share their households and environment with pets.[1] These findings have created a mindset in more people to own pets and interact with them regularly. In summary, convergence of people, animals, and our environment is inevitable which creates a new dynamic in which the health of humans and animals and the well-being of the environment are inextricably linked[2] which incidentally carries both benefits and risks.[3]

The above new dynamic brings challenges to human health, specifically, increasing the risk of zoonotic problems. Rudolf Virchow, a 19th century German physician, coined the term zoonosis[4] and indicated that there is no dividing line between animal and human medicine and nor should there be one, although the object is different but the experience obtained constitutes the basis of all medicine. James Law in 1878[4,5] mentioned that physicians are not to be left ignorant of the affection in the beast, and veterinarians of the same in man, they each miss the golden link which would reveal the true nature and dangers of the disease, and enable them to contend with it successfully; both branches of medicine (veterinary and human) suffer from separation; each is necessary to the rapid progress and highest advancement of the other. Furthermore, it has become evident that our increasing interdependence with animals and their products has spurred the medical and veterinary professions to readdress the approach to veterinary medicine and human health.[6] Besides the existing zoonotic diseases there is also a possibility of emerging zoonotic pathogens. Among the infectious agents considered to be emerging, 175 species from 96 genera have been documented, of which 132 (75%) species from 76 genera are zoonotic.

The importance of zoonotic problems is further strengthened by the fact that zoonotic pathogens are twice more likely to be emerging than their non-zoonotic counterparts.[7]

Miscarriage or abortion in people and animals has been with us since the dawn of civilization and one can find it mentioned in the pages of faith; 'no one will suffer miscarriage' (Exodus 23:26) and 'their cows calve without miscarriage' (Job 21:10). Abortions that occur in animals not only result in economic loss but also pose a threat to people if these agents have zoonotic implications. Besides causing abortion these agents also inflict damage to other organs in animals. Knowledge of nonabortion pathology of animals is equally important since these are the major lesions recognized in people due to infection by these agents more than abortion. Hence the purpose of this review is to address specifically the major abortion conditions that occur in domestic animals due to bacterial and protozoal agents of zoonotic importance. First, the organism, clinical signs of the condition, lesions, and preventive and diagnostic measures including the handling of these cases are reviewed. Second, the clinical ramification observed in people due to these specific zoonotic pathogens is considered. Finally, future directions in the study of 'one health' in the area of infectious abortion in animals are proposed.

Brucellosis

Animals

Brucellosis is caused by the microorganisms of the genus Brucella which are gram-negative facultative intracellular bacteria that infect phagocytes. Transmission of these organisms in general occurs via contact with infected fetal membranes, fetuses, fetal fluids, and vaginal discharges, with subsequent bacterial entry via ingestion, through mucous membranes of the oropharynx, upper respiratory tract, and conjunctiva or abraded skin. Although there are many brucella organisms that currently exist, the focus of the discussion will be on four brucella organisms that cause abortion in domestic animals, hence, nonabortion causing brucella organisms in domestic and brucella organisms affecting nondomestic species will not be discussed.

Brucella melitensis contains three biovars, all of which can cause disease in goats and sheep despite their variable geographic distributions. The primary clinical signs in naturally infected sheep and goats include abortions, stillbirths, and birth of weak neonates. The condition significantly reduces production yields and can cause widespread infertility, posing extensive economic loss for producers on account of infected flocks. Sheep and goats become infectious following abortion or parturition and can shed the organism for weeks (sheep) to months (goats) in vaginal discharges, semen, and milk. Lifelong shedding in milk can occur, particularly, in goats. Nursing offspring can become infected and shed organisms in their feces. *In utero* transmission is also possible. Postmortem lesions include granulomatous inflammation of the reproductive tract, udder, supramammary lymph nodes, joints, and synovial membranes. Necrotizing orchitis, epididymitis, seminal vesiculitis, and prostatitis are some of the lesions in males. Aborted fetuses may be normal, autolyzed, or may have excess bloodstained fluids in the body cavities along with splenomegaly and hepatomegaly. Inflammation of fetal membranes with edema and/or cotyledonary necrosis and thickened/leathery intercotyledonary spaces are some of the lesions.

Vaccines (e.g., Rev 1 strain vaccine) are available and have been successfully used in control programs. In general, serological or intra-eyelid allergy testing followed by slaughter protocols are essential to control the disease.

Serological testing is primarily used for a presumptive diagnosis as they are not very specific. The card, rose Bengal plate agglutination, and complement fixation tests are commonly used. Gel diffusion or radial immunodiffusion tests can be used to distinguish vaccination from true infection. Definitive diagnosis is by the isolation of the organism from the animal. Samples from live animals should include milk samples, vaginal swabs, or semen and should be handled with precaution given the high pathogenicity in humans.

Brucella canis displays low mortality rates but high morbidity in breeding kennels or where large numbers of dogs are kept in close quarters. Subclinical infections characterized by lymphadenopathy are very common despite *Brucella canis* being the leading cause of spontaneous late term abortions in dogs. Infection causes decreased fertility, early embryonic death, death of the fetus at virtually any part of gestation followed by abortion, stillbirths, and birth of weak puppies. In male dogs the pathogenesis includes orchitis, epididymitis, and testicular degeneration and atrophy. Less common presentations include diskospondylitis, pyogranulomatous dermatitis, osteomyelitis, and endophthalmitis.

Serological tests used in the dog include 1) rapid-slide agglutination test (RSAT), a highly sensitive test used for screening, 2) mercaptoethanol RSAT, a specific test, 3) tube agglutination test, and 4) agar gel immunodiffusion (AGID). A positive AGID result is considered diagnostic,[8] however, animals are often not positive on this test until approximately 12 weeks postinfection. Two case reports[8,9] described adequately the practical course of action when dealing with the type of tests, implication of test findings, handling of positive cases and kennel, and quarantine measures. The infected dog should be euthanized, other dogs in the kennel should be quarantined, and dogs that had contact with the female dog, contaminated tissues, or fluids (including urine, vaginal discharges, and aborted materials) should be serologically tested by the RSAT.[9] It is imperative that the kennel be quarantined during an outbreak of brucellosis and no dogs should enter or leave the premises until the disease is eradicated. Space will not allow elaboration on the details of the comprehensive information provided in these case-reports and readers are encouraged to go over the excellent discussion points provided in these reports.

Since *Brucella canis* is an intracellular organism it is difficult to eliminate it by administration of antimicrobials.[10-12] Furthermore, the bacteria is shed in large numbers in milk, as well as in post-abortion discharges for up to six weeks following abortion, which provides a continual source of infective material for other dogs.[11] It is recommended that these dogs not be sold or placed in homes as pets.[13] Brucellosis is a reportable disease in some states.[14] Specific regulations can be obtained by contacting the Department of Agriculture and State Veterinarian in the USA or similar regulatory offices in other countries.

Brucella abortus infection in cattle usually results in abortion after five months of pregnancy and occasionally in the birth of weak offspring. Retained fetal membranes and post-abortion metritis are common. Lesions include inflammation of fetal membranes, focal necrosis of thickened cotyledons with or without a yellow exudate. The fetus may show no gross lesions or may be autolyzed and in some cases there may be evidence of bronchopneumonia. Calves vertically infected (or from milk) may remain serologically negative and show no sign of disease but serve to maintain the disease in the herd. Infected cattle also show reduced milk production with or without an increased milk somatic cell count. Other clinical signs include infertility in bulls and cows, and possible systemic illness in bulls characterized by anorexia, fever, depression, and/or orchitis.

Brucella ovis causes abortion in sheep[15,16] albeit to a lesser degree. A yellowish purulent exudate may be seen, particularly, in the intercotyledonary areas. The fetal membrane is edematous, gelatinous, and thickened with the adherence of amnion to chorioallantois. The intercotyledonary areas are thickened with multifocal to coalescent areas of plaque-like thickening resembling yellow-white chamois leather. The cotyledons can be found in various stages of necrosis and detachment.[17] Typically *Brucella ovis* infection in rams results in epididymitis, or orchitis. Immunization of rams with *Brucella melitensis* Rev-1 vaccine has been recommended for control of *Brucella ovis* in some countries.

Diagnosis is via culture and serology although serology cannot distinguish animals exposed to infection or responding to vaccination. Information on maternal serology is most useful from a non-vaccinated animal. The screening tests include the buffered acidified plate antigen test and the milk ring test, both of which are highly sensitive. Important samples to test include fetal membranes, uterine fluid, milk, fetal lung/abomasa fluid of infected/aborted animals. Modified live vaccine of the rough strain RB 51 interfere with serological testing.

Humans

To this day, brucellosis remains a significant zoonosis in the developing world[18-20] and is emerging or reemerging in many parts of the world.[17] Consumption of sheep or goat milk containing *Brucella melitensis* is an important source of human brucellosis worldwide and has caused several outbreaks.[21-24] Human outbreaks related to aerosol transmission in laboratories have also been reported.[25] Although *Brucella melitensis* infection is frequent among people (farmers and veterinarians) in developing countries who have close contact with infected animals, human outbreaks attributed to contact with infected animals have been rarely reported. The majority of human cases, and the more severe ones, are caused by *Brucella melitensis*, although it has a more limited geographical distribution than *Brucella abortus*. Transmission of *Brucella melitensis* from infected animals to humans may be either direct or indirect. The first mechanism involves the respiratory, conjunctival and cutaneous routes, and is more important in people in close contact with infected goats[26] or sheep. Conversely, indirect transmission is made possible in people by the consumption of unpasteurized goat milk or cheese by consumers who are not familiar with this type of infection. Infection may result in encephalitis, spondylitis, endocarditis, and arthritis. An unusually high number of abortions has occurred among goats bred on a farm in Argentina. Shortly afterwards an outbreak of human brucellosis took place among farm workers. It was established that epidemic human infections by *Brucella melitensis* may develop among people in contact with infected goat herds or goat manure and not necessarily consuming goat products such as milk and cheese.[27]

Although still considered uncommon, increasing numbers of reports over the past decade have documented human infection with *Brucella canis* causing endocarditis and peritonitis. The most common routes of transmission to humans are through contact with infected dogs or their secretions, fetal membranes or aborted puppies. Diagnosis of *Brucella canis* infection in humans is likely underdiagnosed due to a low index of suspicion, nonspecific symptoms (e.g., fever and fatigue), and lack of cross-reaction on common serologic tests using smooth Brucella antigens. *Brucella canis* infection in humans appears to be an emerging problem primarily in people of low socioeconomic status living in urban slums where there are high numbers of free-roaming dogs. Epidemiologic investigations of a human *Brucella canis* infection in a slum environment in Argentina revealed 29 of 97 (29.9%) neighborhood dogs and 13 of 69 (18.6%) neighbors of the index case were serologically positive for *Brucella canis*. Likewise, a serologic survey in Turkey documented the highest prevalence (7.8%) in patients from an urban area where stray dogs outnumbered pet dogs. Some reports suggest that there may be a link between *Brucella canis* infection and patients with immunosuppressive, inflammatory, or metabolic disorders, such as endocarditis, Gaucher disease, human immunodeficiency virus, and Guillain-Barre´ syndrome.[17] There is a possibility of clinical brucellosis in workers in vaccine production wherein M-strain of *Brucella canis* is used.[28] Finally, it should be remembered that infected offspring from breeding facilities may result in widespread exposures to humans and other dogs and breeding facilities.[29]

Infection is possible for people working in the plants making vaccine for *Brucella abortus*[30] which may result in prepatellar bursitits.[31] *Brucella ovis* is widespread in its occurrence in sheep but very much limited to this species and its zoonotic implications is limited. It is also possible for people to have meningoencephalitis following *Brucella suis* infection.[32]

The diagnosis is made difficult since literally all the organs and systems are affected. The suspicion of infection by the above organisms, apart from epidemiological history and clinical symptoms, must therefore be supported by laboratory diagnostics that were reviewed recently.[33] As with many classic zoonotic diseases, the role of veterinarians is critical for the detection and continued prevention and control. This role remains vital since there has been difficulty among human health-care professional in recognizing and diagnosing brucellosis in humans in nonendemic areas.[34]

Leptospirosis

Leptospires are gram-negative, highly motile, obligate-aerobic spirochetes; these organisms are tightly coiled with characteristic hooked ends and are 0.2 μm in diameter and 6 to 20 μm in length; their taxonomy has been continually evolving. There are many different serovars associated with the *Leptospira interrogans*, each having one or more maintenance hosts. Pathogenic serovars include hardjo, grippotyphosa, pomona, canicola, and icterohemorrhagiae. These organisms can survive for prolonged periods of time in warm/wet/humid environments, especially in a neutral to alkaline environment like soil. While they are robust in the right kind of environment, they will not replicate outside of a host.

Transmission occurs via direct and indirect routes. Direct transmission occurs through contact of mucous membranes, abraded skin, or even intact skin with infected urine, vaginal discharge, or other tissues from infected animals. However, indirect transmission from contact with contaminated soil, water, food or bedding is likely more common. In direct transmission entry of the organism into the blood stream is followed by rapid replication resulting in bacteremia and hematogenous spread to other organs including kidney, liver, spleen, central nervous system, eyes, and genital tract. Despite positive immune response by the host, the bacteria can persist within the renal tubules, evading host immunity which results in persistent shedding of leptospires in the urine for weeks. In general, acute leptospirosis in animals is associated with fever, hemolytic anemia, hemoglobinuria, icterus, and high mortality.

Animals

In ruminants, particularly in cattle, a range of reproductive disease may result in anything from infertility to abortion or birth of weak calves. Abortion is a manifestation of chronic infection in adult cattle and usually occurs between four months of gestation to term. Serovars hardjo, grippotyphosa, and pomona can cause abortions. Abortion lesions include diffuse inflammation of fetal membranes described as avascular light tan cotyledons with yellowish intercotyledonary spaces and in most instances the fetus is autolyzed. Small ruminants are less susceptible to leptospirosis, however, chronic infection can cause impaired fertility, abortions, neonatal deaths, and decreased production. A good control program can increase the productivity of small ruminants in developing tropical countries.[35]

Leptospirosis is a common disease of swine throughout the world and can be a significant cause of reproductive loss[36] with serovar pomona causing abortion, stillbirth or the birth of infected piglets.[36] Other serovars such as grippotyphosa, pomona, canicola, and icterohemorrhagiae can cause abortion.

In companion animals such as cats and dogs,[37] the clinical signs depend on whether the infection is acute, peracute or chronic. Subacute infections are the most common and the animal is present with fever, anorexia, emesis, dehydration, and polyuric renal failure. Reproductive problems are very minimal while the major serovars of *Leptospira interrogans* have been isolated.[38]

The standard serological test used for diagnosis is the microscopic agglutination test and is considered positive when there is a fourfold rise in antibody titer over serial sampling for three weeks or a single high titer, if the animal has not been vaccinated in the last three months. Without elevation of titer the animal may be shedding organisms hence caution is necessary while interpreting serology. In addition the vaccination status of the animal has to be considered.

Treatment involves early and aggressive antimicrobial therapy, particularly with penicillin or alternatively with doxycycline along with supportive care in accordance with the signs present. Annual vaccination can prevent leptospirosis caused by serovars included in the vaccine and is recommended for dogs at risk of infection.[39]

Humans

Leptospirosis is a worldwide zoonotic disease and its transmission is linked through multiple factors in the animal-human-ecosystem interface,[40] chief among them is the local/regional animal demand for production.[41,42] *Leptospira interrogans* serovar canicola has been isolated in people among other serovars.[42] Data emerging from prospective surveillance studies suggest that most human leptospiral infections in endemic areas are mild or asymptomatic. Development of more severe outcomes likely depends on three factors: epidemiological conditions, host susceptibility, and pathogen virulence.[43] A zoonosis outbreak summary[44] provided detailed information on the transmission, epidemiology, clinical signs, control and prevention, and public health implications. Leptospirosis in humans is characterized by a wide variety of symptoms and a biphasic course of illness. The first phase corresponds to the multiplication and spread of the organism throughout the body. The second phase is characterized by the development of circulating antibodies and the detection of leptospires in the urine. The incubation period is typically one to two weeks (range, two to 30 days). Most infections appear to be subclinical or so mild that they are never reported. Among clinical cases, initial influenza-like signs during the first phase include fever, headache, chills, myalgia, and occasionally a maculopapular skin rash and conjunctival suffusion (i.e., redness of the conjunctiva without inflammatory exudates). This phase is followed by a one to three day period of defervescence and symptomatic improvement. Leptospirosis is considered the most widespread zoonosis in the world. It has a global distribution with a higher incidence in the tropics and subtropics, ranging from 10 to 100 human cases per 100,000 individuals.[45] In addition to their involvement in the prevention, diagnosis and treatment of leptospirosis in animals, veterinarians have an important role in public health by providing guidance and information on risk factors, prevention, and control measures.[46]

Coxiellosis

Coxiellosis is caused by the gram-negative, obligate intracellular bacterium *Coxiella burnetii*. The term 'Q fever' has been adapted in veterinary medicine although the 'query fever' or 'Q fever' refers to a febrile illness originally observed in abattoir workers in Australia. This terminology has been maintained but the more appropriate term might be coxiellosis since fever is only one of the clinical signs.[47] The diagnosis is often overlooked due to its non-specific presentation both in animals and humans. As a result the true worldwide incidence is not known. Coxiella appears in three different morphological forms: large cell variants, small cell variants, and small dense cells which can be differentiated by their morphology, physical and chemical resistance, and antigenic and metabolic characteristics. The last two are considered to be the persistent forms in the host and are responsible for the high resistance of the organism to environmental stress. In addition, the organism displays antigenic variation by appearing in two infectious forms, phase I, a highly virulent one with lipopolysaccharide and phase II, a less virulent form with atrophied lipopolysaccharide.

Animals

Coxiella burnetii infection is reported worldwide with the apparent prevalence higher in cattle than in small ruminants.[48] However, the presence of the organism in dairy herds has not been clearly demonstrated to negatively affect reproductive performance.[49] It should be noted that cattle can be one of the important reservoirs for this organism in some parts of the world.[50] The problems in small ruminants have been reviewed[51] and it is established that infections in goats and sheep are usually asymptomatic during the non-breeding period. The most common clinical manifestations appear during late pregnancy until lambing, i.e., abortion, stillbirth, and the delivery of weak offspring. Other symptoms such as pneumonia, conjunctivitis, and hepatitis occur rarely in infected animals. Infected female animals shed large quantities of bacteria into the environment in the course of abortion or normal delivery, not only through the allantoic and amniotic membranes and their fluids but also through urine and feces. Shedding occurs via vaginal mucus and milk.[52] In contrast to ewes, goats may experience reproductive failure and they shed the organism in two successive parturitions after an infection. Goats remain chronically infected. Diagnosis is generally undertaken only if abortions are observed. The detection of *Coxiella burnetii* DNA in the placenta and vaginal mucus by PCR has radically changed the diagnosis of coxiellosis. Several PCR kits are available and provide a specific, sensitive, and rapid tool for the detection of the organism in various clinical samples. Real-time PCR kits are available for quantification and identifying animals shedding the organism.[53] The phase 1 vaccination has potential for the vaccination of not only infected flocks, but also nearby flocks, to reduce the risk of disease dissemination; prevent abortion and greatly decrease the shedding of the organism in milk.[53] Recombinant vaccines have been developed in experimental conditions and have great potential for the future.[54]

Humans

The organism posed a considerable risk to people because of its environmental stability, aerosol transmission possibility, and its capacity to use animal reservoirs. It has become a major health problem in certain parts of the world[55-59] and a relatively minor problem in other parts. Inhaling aerosols, which have been contaminated with the organisms, is the most important route of human infection. It is also transmitted, less commonly, through the consumption of raw milk and dairy products. Clinical signs include fever,[60] pneumonia, headache, and weakness. Chronic infection can result in severe valvular endocarditis, granulomatous hepatitis, and rarely in osteomyelitits. Human-to-human transmission (following child birth/autopsy) has been reported, as has infection following tick bites. Studies confirmed the association between coxiellosis and spontaneous abortion.[61,62] Although seropositivity is observed and the condition has accounted for a notable proportion of undifferentiated febrile episodes and infective endocarditis in humans in Africa, further studies are needed to determine the exact incidence and its impact in animals and humans.[63] Recently coxiellosis has become a threat to USA military personnel who are deployed in the Middle East[64] due to possible exposure to livestock. The signs include flu-like illness that responds to antibiotic therapy. There is a potential for infection among farm workers dealing with dairy cattle and individuals working in the milk processing industry with dairy products.

Listeriosis

Listeriosis is caused by *Listeria monocytogenes*, a saprophytic gram-positive facultative anaerobic and intracellular rod-shaped bacterium. The bacterium can be classified into four genetic lineages (I-IV) and 13 serotypes and is ubiquitous in the environment. *Listeria monocytogenes* is among the most versatile, adaptive, and widely distributed pathogenic bacteria.[65]

Animals

In general listeriosis causes abortion in animals. Bovine listeriosis is usually acquired by ingestion of poorly fermented silage or by ingestion of organisms from aborted tissues. Infection can also arise from ingestion of contaminated soil, milk, silage, feces and the organism can survive in the proper environment for years. The lineage of the organism may determine whether it can cause abortion since certain lineages are associated with the encephalitis while other lineages can cause major forms of listeriosis in cattle including abortion.[66] Clinical presentation involves abortion, usually, occurring in the third trimester. Abortions are sporadic but abortion storms may be noticed in some herds. Aborting cattle may or may not show non-specific signs of systemic illness, however, retained fetal membranes are common. Fetuses are autolyzed and display a fibrinous polyserositis and white necrotic foci in liver and/or the cotyledons.

Similar to cattle, listeriosis infections in small ruminants occur mostly due to contaminated feed. Acidified silage provides an excellent survival medium and a substrate for multiplication of the organism. Feeding of contaminated grass silage in sheep resulted in abortive, encephalitic, and septicemic forms of listeriosis.[67]

Listeriosis is rarely identified in cats and dogs, however, it can infect these species. Clinical disease is characterized by nonspecific signs such as vomiting, diarrhea, and fever with neurologic and dermatologic signs in rare instances. Abortion has been reported in a dog.[68]

Humans

In people, it is recognized as a life-threatening pathogen, poses severe risk during pregnancy causing abortion, fetal death or neonatal morbidity as a result of septicemia and meningitis. Nearly all (99%) cases of listeriosis in humans in the USA are thought to result from the consumption of contaminated foods.[69,70] The chance of humans contacting infection via the biological materials of an aborted animal is very minimal. The most common route of infection for people is via ingestion of contaminated ready-to-eat food products, soft cheeses, and deli meats. These observations may be true for all over the world. Clinical listeriosis is associated with high mortality, especially in immunocompromised patients, pregnant women, neonates, and the elderly. A recent review summarized listeriosis in humans and domestic animals during pregnancy and described the animal models used to study the pathogenesis and immune response to *Listeria monocytogenes* infection.[71] The health concern of listeriosis during pregnancy has been reviewed.[72] The organism has been isolated from cervical and vaginal discharges of women with a history of abortions, miscarriages, stillbirths or neonatal deaths. The organism has the ability to induce its own entry into host cells such as macrophages, epithelial cells, and endothelial cells of the gastrointestinal tract.[73] Cells surviving the low pH of the stomach, pass through the small intestine and once the organisms arrive at the mesenteric lymph nodes they disseminate to the spleen and liver. From these organs the organism can reach the brain or the placenta, causing, respectively, infections of the central nervous system (CNS), mostly in immunocompromised patients, and intrauterine/cervical infections in pregnant women.[74] Encephalitis, ataxia, septicemia, and meningitis are other clinical signs. Diagnosis of listeriosis abortion both in animals and in humans is based on the isolation of the organism and with PCR. Currently, the real-time PCR diagnosis has become much easier further strategies for vaccine development and novel therapies for control of listeriosis have been proposed.[75]

Chlamydophilosis and Waddliosis

As per the recent taxonomy,[76] organisms belonging to the order Chlamydiales are responsible for causing abortion in domestic animals and these agents have zoonotic implications. The first organism, *Chlamydophila abortus,* belongs to the family chlamydiaceae and genus chlamydophila and causes abortion in cattle,[76] sheep,[77] goats, horses, and pigs. *Chlamydophila abortus* is a major cause of abortion in small ruminant-rearing regions of the world, with the exception of Australia and New Zealand.[78] The second organism is *Waddlia chondrophila* that belongs to the family Waddliaceae and genus Waddlia causes abortion in cattle.

Animals

Usually, abortion in small ruminants is associated primarily with *Chlamydophila abortus* and rarely with *Chlamydophila pecorum.*[79] Lesions caused by the latter organism to the fetus included moderate fetal anasarca, intermuscular edema in the hindquarters, brachygnathia, and palatoschisis. Placental lesions included fibrinosuppurative exudate that covered the cotyledons and extended to the inter cotyledonary areas.[79] Early investigations into the pathogenesis of this disease in sheep revealed that sheep typically aborted late in gestation or gave birth to weak or stillborn lambs.[80,81] Progression of the disease follows placental colonization with subsequent inflammation and necrosis of the maternal-fetal junctions.[82] In both natural and experimental infections, ewes that experienced abortion or the birth of weak lambs were shown to be protected against further pregnancy failure due to this organism[81,83] Although apparently protected, such ewes continued to excrete the organism during the peri-ovulatory stage of subsequent estrous cycles[84] and venereal transmission is possible.[84] The most noticeable lesions included placentitis with a variable number of necrotic cotyledons.[80-85] One report documented that the pathologic changes in the placenta were evident after 90 days gestation.[82] These changes seldom affected the entire placenta and the peripheral regions were delineated by zones of hyperemia and hemorrhage. It has been suggested that infection may precipitate premature labor by altering placental steroid and prostaglandin release.[86]

Chlamydophilal infections in cattle cause abortion, polyarthritis, encephalomyelitis, keratoconjuctivits, pneumonia, fever, depression, nasal secretion, coughing, dyspnea, enteritis, hepatitis, vaginitis, endometritis, infertility, and chronic mastitis.[87] Organisms responsible are *Chlamydophila abortus*, *C. pecorum, and C. psitacci*. Data published in the last two decades suggest a high seroprevalance of chlamydial infection (primarily for *C. abortus* and *C. pecorum*) in herds worldwide with seropositivity at a herd level ranging from 45% to 100%.[87] *C. abortus* is primarily associated with the genital tract and mammary tissue; *C. pecorum* with pulmonary, joint, intestinal, ocular, and central nervous system disease and *C. psittaci* has been identified in samples from the respiratory and genital tracts. A key advance in the laboratory diagnosis of chlamydophilal infections has been the development of tests that do not require the agent to be viable,[87] the detection of chlamydophilal non-replicating spore-like elementary bodies of approximately 0.3 μm diameter. The standard method for detecting antibodies is the complement fixation test using crude or partially purified preparations of the organism-specific lipopolysaccharide. Numerous ELISA methods have been used but due to cross-reactivity between species no commercially available test is able to differentiate antibodies at the species level. For example, the direct fluorescent antibody test cannot distinguish between *C. pecorum* and *C. abortus* because of the antigenic cross reactivity.[79]

Humans

Infection with Chlamydophila abortus can result in acute and sometimes life-threatening illness.[87] Similar to ewes, persistent infection leading to infertility in women has been recognized.[88] It is recognized as an occupational hazard. Women who work with sheep have suffered sporadic, documented cases of abortion[76] and the presence of antibody has been characterized.[89] Although there is anecdotal evidence linking atypical respiratory disorders or asthma-like symptoms in farmers working with chlamydia-infected herds, proof of cause and effect remains elusive. Based on the current evidence, the zoonotic potential of chlamydophilal found in cattle would appear minimal.[87]

Toxoplasmosis

Toxoplasma gondii is an extremely successful obligate intracellular protozoan parasite that infects almost all species of mammals and birds on all continents. Historical facts have been reviewed.[90] A key factor to understand the biology and clinical relevance of this organism is to know its parasitic life cycle. *Toxoplasma gondii* exists in different stages: oocysts are the parasite's sexual cycle in the intestine of its definitive host, the felidae (cat family). Oocysts are excreted in cat feces and following sporulation in the environment, sporozoites become infective. Upon oral uptake of sporulated oocysts by new hosts, sporozoites transform to the invasive tachyzoites. Tachyzoites actively penetrate all nucleated cells and replicate rapidly in an intracytoplasmic vacuole. Following repeated intravacuolar replication, host cells are disrupted and tachyzoites invade neighboring cells. The tachyzoites cause tissue destruction and are therefore responsible for clinical manifestations of the disease including abortion. The ensuing immune response is accompanied by the transformation of tachyzoites into slowly replicating intracellular bradyzoites that form persisting cysts. Tissue cysts become infective to intermediate and definitive hosts via their consumption in meat and tissue. So, entry of sporulated cysts from the environment and tissue cysts from the consumption of tissue of animals enable the parasite to maintain its sexual cycle and incidentally be responsible for the clinical disease including abortion.

Animals

Toxoplasma gondii causes abortion in cats and small ruminants, and particularly, in immune compromised animals. Severe disease may be seen in transplacentally or lactationally infected kittens. General clinical manifestations include fever, lethargy, anorexia, pneumonia, hepatitis, stiff gait, lameness, or CNS signs from encephalitis. *Toxoplasma gondii has* caused considerable reproductive wastage in small ruminants in many parts of the world, particularly, in developing countries.[91,92] Its importance became known when it was found to cause abortion storms in sheep in 1957.[93] Most sheep and goats acquire infections via ingestion of forage contaminated with cat feces (sporulated oocysts). While these animals' fetuses can be infected transplacentally, transmission via this route is much less common. Under most circumstances, clinical disease in infected/exposed dams is rare with the only observable manifestation being abortion. These animals are typically asymptomatic before and after abortion. Abortion can be sporadic among a few animals to a herd-wide abortion storm characterized by mummification, stillbirths, and birth of weak progeny in those dams infected later in gestation. Small white necrotic foci are noticed in the cotyledons and typical fetal brain lesions (gliosis of cerebral white matter) are recognized. In small ruminants, control can be instituted through prophylactic feeding of medications like monensin during gestation or through use of the modified live vaccine Toxovax (S48 strain). Its use results in reduction of tissue cyst development.

Humans

Toxoplasma gondii's human importance remained unknown until 1939 when the organism was identified in tissues of a congenitally infected infant.[93] Animals are key to human toxoplasmosis.[94] Its ubiquitous distribution and its high prevalence makes it an important zoonotic agent. Approximately 25-30% of the human population is infected with *Toxoplasma gondii.* Humans get infected by consumption of undercooked cyst-contaminated meat products or by sporulated cysts. Relatively high seroprevalences in animals meant for human consumption suggests the potential risk factor posed by food animals.

Immunity to *Toxoplasma gondii,* congenital toxoplasmosis, ocular toxoplasmosis, and the impact of the strain on the course of human toxoplasmosis have been adequately described.[94] Latent toxoplasmosis is characterized by the life-long presence of cysts in different host tissues, including the nervous system, and by the presence of anamnestic *Toxoplasma* IgG antibodies in the serum. Latent toxoplasmosis is believed to increase the risk of conditions such as schizophrenia and Parkinson's disease.[95] The prevalence of latent toxoplasmosis is found to be higher in female (23.7%) than in male (10.9%) patients in a study conducted in Prague[96] and this difference was speculated to be due to the difference in the gender specific hormones. Accidental ingestion of *Toxoplasma gondii* infected meat products from the domestic animals by women during pregnancy can cause abortion and congenital defects.[97] The risk of ingestion is higher from uncontrolled water supplies from the wells and springs[98] and from the soil contamination.[99] There is a possibility of sexual transmission.[100] The incidence in pregnant women may be influenced by factors such as the trimester of pregnancy.[101] High prevalence is noticed in women who had a repeated history of abortion.[102-104] Estimation of serorprevalence of anti-*Toxoplasma gondii* antibodies and DNA of women with spontaneous abortion may be a way to determine the impact of this disease on abortion.[105]

Only 10-15% of human cases are associated with clinical signs. Immunocompetent individuals are usually asymptomatic but may present with clinical signs such as lymphadenomegaly, fever, or malaise. More severe forms of disease include encephalitis, myocarditis, hepatitis, and reticulocarditis and these are typically manifested in immunocompromised individuals as latent infections. Transplacental transmission results in severe neurological or ocular disease in the developing fetus that may not be apparent at birth. As the infant matures clinical signs develop and may involve blindness, retinochorditis, deafness, mental retardation, learning disabilities, and psychomotor deficiencies. Abortions[106,107] and neonatal deaths occur in 10% of the cases in pregnant women. Toxoplasmosis continues to be a significant public health problem all over the world including the USA.[108] What was said earlier is also true today - the major ways to reduce the transmission of *Toxoplasma gondii* in people is to reduce fecal shedding by cats and by killing tissue cysts in meat.[109] The new trend in the production of free-range organically raised meat may increase the risk of *Toxoplasma gondii* contamination of meat. Foodborne transmission can be prevented by production practices that reduce *Toxoplasma gondii* in meat,[110] adequate cooking of meat, washing of raw fruits and vegetables, prevention of cross contamination in the kitchen, and measures that decrease spread of viable oocysts into the environment.[111]

Diagnostic tests include the Sabin-Feldman dye test, IgM antibody detection by ELISA test, direct agglutination test, and detection of *Toxoplasma gondii* DNA test.[93]

Campylobacteriosis

Campylobacter organisms are gram-negative, curved, slender, comma or spiral shaped rods which appear as 'seagull wings' in silhouette. Ultrastructurally, this bacterium has a double layered outer membrane with loosely packed hexagonal subunits and a three-layered cell wall compromising an outer lipoprotein, a middle lipopolysaccharide and an inner mucopeptide layer. *Campylobacter fetus* compromises two subspecies, *Campylobacter fetus* subspecies *venerealis and Campylobacter fetus* subspecies *fetus.* These two subspecies mainly differ in epidemiological, phenotypic, and molecular characteristics including molecular mechanisms.[112] These two campylobacters along with *Campylobacter jejuni* are responsible for causing abortion in domestic animals.

Animals

In cattle, the organism *Campylobacter fetus* subspecies *venerealis* is highly adapted to the genital tract and is transmitted venereally by carrier bulls. The cattle industry refers to this venereal disease caused by this organism as 'vibrio'.[113] The other subspecies of *Campylobacter fetus (Campylobacter fetus* subspecies *fetus)* and *Campylobacter jejuni* are also responsible for causing abortion. In addition to causing abortion these agents are associated with lowered fertility, embryo mortality, repeated return to service, reduced pregnancy rates, and extended calving intervals. The incidence is highest in developing countries where natural breeding of cattle is widely practiced.[114] Although vaccine against *Campylobacter fetus* subspecies *venerealis* is available[115,116] the major focus is to provide pathogen-free semen for the AI industry. Successful diagnosis and mitigation are dependent on isolation of infected animals and consistent reporting activity and diagnostic tests include culture and PCR.[116]

Humans

Campylobacter fetus subspecies *venerealis* has caused abortion in people[117] and *Campylobacter fetus* has caused bacterial meningitis.[118] Apart from causing abortion in animals and rarely in people, the intestinal campylobacter species are relevant from the aspect of public health since they cause gastroenteritis in people. Discussion of all the campylobacters is beyond the scope of this review. However, it has to be pointed out that there is a greater need for a 'one health' approach[119] to combat campylobacteriosis in general and it will continue to challenge the global heath in the years to come.[120]

Conclusions

Zoonotic infectious diseases are an important concern to humankind due to the ever increasing contact between animals and humans. Today, approximately 75% of newly emerging infectious diseases (EIDs) are zoonoses that result from various anthropogenic, genetic, ecologic, socioeconomic, and climatic factors. These interrelated driving forces make it difficult to predict and to prevent zoonotic EIDs. Although significant improvements in environmental and medical surveillance, clinical diagnostic methods and medical practices have been achieved in recent years, zoonotic EIDs remain a major global concern, and such threats are expanding, especially in less developed regions.[121]

Five decades ago infectious causes of abortion common in animals and humans were reviewed.[122] However, currently, most of the agents that cause abortion in domestic animals cause systemic diseases in humans and abortion only in some instances. The bacterial and protozoan agents that cause abortion in domestic animals were identified and immunization methods were developed for some of them. The table summarizes the salient points of these agents and their clinical impacts on animals and people. As new information emerge this table may have to be updated. Research has clearly and convincingly established that most of the abortion agents of animals are capable of establishing the disease process in immunocompromised people; a plausible reason for higher incidence of these animal illnesses in people in the developing world. Improvement of global health depends on addressing and remedying this very important factor.

Further efforts are needed to translate our knowledge on abortion causing agents in animals to improve the health management of animals and people. In this regard, certain steps are suggested. First, the concept of 'one health' has to move further by breaking down the historical separation of humans and animals and embrace the development of comparative medicine when it comes to pathology[123] of abortion diseases. Second, the government agencies must continue to provide financial support for the colleges of veterinary medicine and other agencies for studies to be continued in animal abortion diseases. This is one of the ways to realize the far-reaching benefits of the investments made in veterinary medical education and research. Such benefits include the well-being of people, families, and society as well as the economy.[124] Third, a spatial and temporal analyses of a particular zoonotic abortion disease for a region can help to fill in the current gaps in knowledge for public health practitioners to provide vaccination strategies.[125] Fourth, the most complete epidemiological representation of any reemerging threat to animals and people by the agents that cause abortion in animals is necessary to combat any disaster that may be on the horizon.[126] In this context creation of a 'global signaling surveillance system' is worthy of consideration.[127] Furthermore, bringing together the policy makers and the scholars who have identified the 'local spatial heterogeneity' in the distribution of zoonotic diseases is paramount in[128] one health initiatives.

Conflict of interest

The author declares that he has no conflict of interest nor he should be perceived as prejudicing the impartiality of research literature in not citing all publications in this review. This article does not contain any studies with human participants or animals performed by the author.

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Table. Summary of major infectious abortion diseases of domestic animals: etiological agents, major clinical signs in animals and humans, and available vaccinations for animals.

Name of the disease	Organism(s) responsible	Major clinical signs in animals	Major clinical signs in humans	Animal vaccinations
Brucellosis	*Brucella melitensis*	Small Ruminants Abortion, stillbirths, birth of weak neonates. Epididymitis, orchitis, prostatitis, and seminal vesiculitis	Encephalitis, spondylitis, endocarditis, and arthritis	Rev 1 strain
	Brucella canis	Dogs Decreased fertility, early embryonic death, abortion, stillbirth, birth of weak puppies. Orchitis, epididymitis, testicular degeneration and atrophy.	Fever, fatigue, endocarditis, peritonitis	
	Brucella abortus	Cattle Abortion, retained fetal membranes, and metritis. Infertility, systemic illness, and orchitis.	Prepatellar bursitis	Modified live vaccine of the rough strain RB 51
	Brucella ovis	Abortion. Epididymitis and orchitis.	Meningoencephalitis	Rev 1 strain
Leptospirosis	*Leptospira hardjo, L. grippotyphosa, L. pomona, L. canicola,* L. *icterohemorrhagiae*	Cattle Infertility, abortion, birth of weak calves Sheep and goat Impaired fertility, abortion, neonatal death, decreased production Dogs and cats Fever, anorexia, emesis, dehydration, and polyuric renal failure	Fever, headache, chills, myalgia, conjunctivitis, flu-like symptoms, liver or kidney failure	Food animals (cattle, swine, small ruminants) are vaccinated and annual vaccination is recommended for at-risk dogs. Commercial vaccines are available and the serotypes in the vaccine differ between species.
Coxiellosis	*Coxiella burnetii*	Sheep Abortion, stillbirth, weak offspring, pneumonia, conjunctivitis, hepatitis Goat Reproductive failure	Fever, pneumonia, headache, weakness, endocarditis, hepatitis.	
Listeriosis	*Listeria monocytogenes*	Cattle Abortion, retained fetal membranes Dogs Vomiting, diarrhea, fever, abortion	Abortion, intrauterine/cervical infections, encephalitis, ataxia, septicemia, meningitis	
Chlamydophilosis and Waddliosis	Small Ruminants *Chlamydophila abortus* *Waddlia chondrophila*	Small Ruminants Late term abortion, weak or stillborn lambs	Acute, some-times life-threatening illness, respiratory disorders, and	Commercial vaccines are available

	Cattle *Chlamydophila abortus*, *C. pecorum, C. psitacci*, and *Chlamydia suis*.	Cattle Abortion, polyarthritis, encephalomyelitis, keratoconjunctivitis, pneumonia, fever, depression, nasal secretion, coughing and dyspnea, enteritis, hepatitis, vaginitis and endometritis, and infertility and chronic mastitis	abortion	
Toxoplasmosis	*Toxoplasma gondii*	General clinical manifestations include fever, lethargy, anorexia, pneumonia, hepatitis, stiff gait, lameness, or CNS signs from encephalitis. Abortion storms in small ruminants	Lymphadenomegaly, fever, or malaise, encephalitis, myocarditis, hepatitis, and reticulocarditis, neurological or ocular disease in the developing fetus, abortions	Small Ruminants Modified live vaccine Toxovax (S48 strain)
Campylobacteriosis	*Campylobacter fetus* subspecies *venerealis, Campylobacter fetus* subspecies *fetus, Campylobacter jejuni*	Cattle Abortion, lowered fertility, embryo mortality, repeated return to service, reduced pregnancy rate, extended calving intervals.	Gastroenteritis	