Emerging or re-emerging bacterial zoonotic diseases: bartonellosis, leptospirosis, Lyme borreliosis, plague

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Summary
There are a whole series of emerging and re-emerging zoonotic diseases present in the Northern Hemisphere and the author describes four of them, namely, bartonellosis, leptospirosis, Lyme borreliosis and plague. Reasons for the emergence or re-emergence of such diseases are not clear, but factors such as human demographics, economic development and land use, international travel and commerce, and microbial adaptation, are thought to be involved. Control of emerging and re-emerging diseases has become a major challenge for the international community and it is important to disseminate information about diagnosis and control capabilities, particularly to people working in public health.

Keywords

Introduction
Once a new pathogen has been introduced into the human population, its ability to spread becomes a critical factor in emergence. The introduction of an agent into a host population can occur separately from its dissemination amongst that population, but it can also happen simultaneously (18). The re-emergence of an ‘old’ agent whose spread has been successfully controlled, is often the result of a failure in public health measures. Such a failure is also listed by the Institute of Medicine of the National Academies of the United States of America (USA) as one of the factors related to the emergence of human pathogens, some of the others are, as follows:
– human demographics and behaviour
– technological and industrial development
– economic development and land use
– international travel and commerce
– microbial adaptation (18).

In addition, one should add environmental changes that may be directly or indirectly related to human behaviour (18).

This article presents four diseases which appear to have emerged or re-emerged as a result of some of the conditions listed above. The first disease, bartonellosis, formerly known only as cat-scratch-disease, is now diagnosed with increasing frequency in acquired immune deficiency syndrome patients and immunosuppressed persons and is associated with a variety of manifestations such as endocarditis, bacillary angiomatosis and peliosis. The second disease, leptospirosis, which is usually caused by exposure to water contaminated with the urine of infected animals, is a re-emerging condition because recreational activities associated with water sports are becoming increasingly popular. The third disease, Lyme borreliosis, has emerged in some parts of the USA, due in large part to reforestation and the proliferation of
deer, which are the preferred host of the adult ticks that spread this disease. The fourth disease, plague, has re-emerged in some countries and is considered as a threat by some authors, even in the 21st Century, mainly because of antibiotic resistance and because of the ease with which the disease could spread as a result of frequent international air travel (18).

Bartonellosis

Introduction

Bartonella spp. are emerging pathogens in humans and animals (6, 33, 55) and knowledge about this genus has evolved considerably over the last decade. There are currently 18 recognised species of Bartonella, all of which are associated with mammalian hosts: B. alactica, B. bacilliformis, B. birtlesii, B. bovis, B. capreoli, B. claridgeiae, B. doshiae, B. elizabethae, B. grahamii, B. henselae, B. koehlerae, B. peromysci, B. quintana, B. schoenbuchensis, B. talpae, B. taylorii, B. tribocorum, B. vinsonii (subsp. vinsonii, arupensis and berkoffii) (16). Another species, ‘B. washoensis’, has been proposed. Most of these facultative intracellular bacterial species have zoonotic potential (25).

Epidemiology

Bartonella spp. are believed to be transmitted by infected vectors such as sand flies (B. bacilliformis), human body lice (B. quintana), cat fleas (B. henselae, B. claridgeiae), vole ear mites (B. vinsonii subsp. vinsonii), and ticks (B. vinsonii subsp. berkoffii and arupensis) (6). Vector species seem to have a preference for specific hosts, therefore, some Bartonella spp. are particularly associated with certain animal species, e.g. B. henselae, B. claridgeiae and B. koehlerae with cats, B. vinsonii subsp. berkoffii with dogs and coyotes, B. alactica with rabbits, and B. quintana with humans (6). Some species have a worldwide distribution (B. henselae and B. quintana); others have been recovered only in the USA (B. elizabethae, B. koehlerae and B. vinsonii subsp. vinsonii and arupensis); others only in Europe (B. alactica, B. birtlesii, B. capreoli, B. doshiae, B. grahamii, B. schoenbuchensis, B. taylorii and B. tribocorum); and some have been found in both Europe and the USA (B. bovis, B. claridgeiae and B. vinsonii subsp. berkoffii). The distribution of these pathogens seems to be related to the distribution of their vectors or their hosts (16). It is not uncommon to find, in cats or rodents, simultaneous infection with more than one Bartonella spp. (6).

The domestic cat has been proposed as a potential vector and reservoir of Bartonella spp., infecting humans either directly through scratches, bites, or licks, or indirectly via an arthropod vector (43). Cat fleas are the vector for B. claridgeiae among cats and the main vector for cat-to-cat transmission of B. henselae. Cat fleas are also the main flea species that infest dogs (10). Ticks are suspected to be responsible for the dog-to-cat transmission of B. vinsonii (10). (Transmission from dogs to humans has been documented, but it is infrequent [6].) The role of ticks in the transmission of Bartonella spp. among animals seems relatively certain, but there is also a possibility that they may be involved in transmitting the disease to humans as well (6, 10). It is speculated that the disease can also be transmitted to humans if they come into contact with the blood of infected animals during the butchering process (6). Transmission from other environmental sources or animal hosts is also possible.

Since Bartonella spp. are intracellular organisms, the prevalence of bacteraemia within animal populations does not directly correlate with the seroprevalence. Bacteraemia can persist despite the presence of high antibody titres (24). Similarly, despite the high prevalence of bacteraemia, most infected rodents have low or undetectable levels of serum antibodies (6). The rate of bacteraemia in cats has been shown to vary from almost 90% in some parts of the USA, to less than 10% in Japan (6). The maximum period of persistence in most animal species is unknown, but it has been shown to reach at least 14 to 15 months in cats and dogs (6). In humans, infection can persist for several weeks and it has been documented that B. bacilliformis has been transmitted via blood transfusion (6). In the United Kingdom, rodents, with a prevalence of infection of 40%, are likely to be the natural reservoir of B. grahamii and B. taylorii (2). Finally, some Bartonella spp. have only been isolated on a few occasions and it is too early to discuss their epidemiological characteristics.

Clinical features

Humans are the only host in which infection by Bartonella spp. leads to severe clinical disease (43). About nine species or subspecies of Bartonella are known to be pathogenic for humans, as follows (the first two pathogens only affect humans; the remainder also affect other species; common clinical features are included in brackets):

- B. bacilliformis: B. bacilliformis infection is also known as Carrion’s disease, Oroya fever or Verruga peruana
- B. Quintana: B. quintana infection is also known as trench fever (common manifestations include endocarditis,
chronic lymphadenopathy, bacillary angiomatosis and bacillary peliosis
– **B. henselae** (can cause cat-scratch disease [CSD], fever with bacteraemia, endocarditis, neuroretinitis, bacillary angiomatosis and bacillary peliosis hepatitis)
– **B. clarridgeiae** (also causes CSD)
– **B. elizabethae** (endocarditis)
– **B. washoensis** (myocarditis)
– **B. grahamii** (uveitis)
– **B. vinsonii** subsp. **berkhoffii** (endocarditis)
– **B. vinsonii** subsp. **arupensis** (fever) (10, 16, 37, 43, 49).

As is the case in humans, the health status of animals prior to becoming infected will determine the outcome of the infection. Infected cats appear to remain asymptomatic and bacteraemic for many months if they are left untreated (24). Ocular involvement, such as uveitis and choroiditis, has been reported in cats and dogs (6, 48). Endocarditis in dogs has been associated with **B. clarridgeiae**, **B. vinsonii** subsp. **berkhoffii** and **B. washoensis** (10, 11). Endocarditis due to **B. henselae** has also recently been reported in a domestic cat (12). Apart from cardiac lesions, other abnormalities observed in cats infected with **B. henselae** or **B. clarridgeiae** are fever, anemia, eosinophilia, lymphadenomegaly, cataracts, cholangitis, reproductive failure, renal lesions and neurologic dysfunction (38). In dogs, **B. vinsonii** subsp. **berkhoffii** has also been shown to cause arrhythmia, myocarditis, granulomatous lymphadenitis and granulomatous rhinitis, whereas **B. henselae** has been associated with peliosis hepatitis (10).

**Diagnosis**

Cat-scratch disease and other bartonellosis cases can be diagnosed by observing clinical and epidemiological features (19), but the diagnosis can be confirmed using microbiological (57) and/or histological methods. **Bartonella** spp. are very fastidious organisms. Primary isolation of these bacteria is rather difficult and only successful if the interval between collection and culturing is as short as possible. Although very difficult in many cases, isolation of the organisms is highly important, not only for aetiological diagnosis, but also for genetic investigations on the isolates which will provide the basis for further studies on the epidemiology and pathogenicity of these agents (57).

Serology should be used with caution in the diagnosis of the cause of endocarditis in humans since cross-reactions between **Bartonella** spp. and **Chlamydia** spp. are well-established and because other studies have also suggested that there may be a cross-reaction with **Coxiella burnetii**. It appears that some cases of endocarditis previously associated with **Chlamydia** were in fact due to **Bartonella** spp. (44). Consequently, molecular testing methods are becoming more and more important in the diagnosis of bartonellosis, as they have the opportunity to compensate for the difficulty of culturing **Bartonella** spp. and for the problem of cross-reactions in serodiagnosis (23).

**Control**

In humans, the treatment of **Bartonella** spp. infections has not been standardised, mainly because of the variety of manifestations (16). For CSD, antimicrobial treatment is not generally indicated, as most typical cases do not respond to antimicrobial agents. Moreover, symptoms are generally self-limiting over time. Antimicrobial treatment is indicated for patients with bacillary angiomatosis, bacillary peliosis or relapsing bacteraemia (9). Most antibiotics, except the aminoglycosides, do not display any bactericidal activity against bartonellae and the bactericidal activity that does exist may be more important in vivo, especially in immunocompromised patients or patients with chronic infections or endocarditis (45). In animals, attempts to clear **Bartonella** bacteraemia using antibiotics have had mixed results, most of which were disappointing, particularly in cats (9).

Humans can reduce their risk of contracting bartonellosis by choosing an appropriate companion animal (adult cats should be preferred to kittens) (26) and by being particularly rigorous about implementing flea-control measures. Commonsense, hygiene and, possibly, teaching cat owners how to avoid being scratched when handling their cats, are other important means of control. People should wash their hands after handling pets, and clean any cuts, bites or scratches promptly with soap and water (9). No vaccines are commercially available to prevent **Bartonella** infection in animals.

Considering the extensive animal reservoirs and the large number of insects that have been implicated in the transmission of **Bartonella** spp., both animal and human exposure to these organisms may be more substantial than is currently believed (6). The list of **Bartonella** spp. is far from complete and it is likely that new species will be described in the near future (16). Research is needed to develop better tools for the diagnosis and surveillance of these infections, as well as for their control and prevention.

**Leptospirosis**

**Introduction**

Leptospirosis is an infectious disease caused by a flexible and helicoidal bacterium belonging to the genus **Leptospira**, which comprises twelve species and five genomospecies (7). Leptospires are categorised according to their serovars,
and this method of classification does not strictly equate with their speciation classifications. Leptospires are widespread among feral and domestic mammals as well as reptiles and amphibians, all of which serve as maintenance hosts for the over 250 known serovars (53).

Formerly considered to be primarily an occupational disease associated with activities such as mining, sewer maintenance, livestock farming and butchering, veterinary medicine and military manoeuvres (1), leptospirosis is now increasingly related to recreational activities, and several authors now refer to this infection as a re-emerging infectious disease, involving both rural and urban cases (8, 27, 46, 58). Leptospirosis is thought to be the most widespread zoonotic disease in the world (1, 46, 53).

Epidemiology

The central point in the epidemiology of leptospirosis is the host animal which sheds the bacteria in its urine. The renal tubules of these animals are lined with leptospires that adhere to the tubular epithelial cell border. Leptospires remain viable in the renal tubules despite the humoral or cellular immune responses mounted by the host (17). Some serovars may also be present in the genital tract tissues of chronically infected animals. Maintenance hosts (reservoir hosts) are those in which the cycle of infection is perpetuated within the species of animal, usually by direct transmission (17). Infected animals contaminate pasture, yards, drains, soil and surface waters with leptospires from their urine. Leptospires can survive for long periods in water or soil (17). Although the evidence is indirect, it seems that pathogenic leptospires may grow and multiply under suitable conditions in the environment. Very large numbers have been encountered in fast-flowing rivers and soil (17). Leptospirosis has a higher prevalence in tropical regions (e.g. most reported cases in the USA occur in Hawaii [36]), especially following periods of heavy rainfall (27).

Surface waters contaminated with leptospires from the urine of infected animals are major sources of infection for humans. Transmission frequently occurs via skin abrasions or exposed mucous membranes, especially the oropharyngeal mucous membranes, which seem to be the principal portal of entry for the infection (27). Contact can occur in floods and during military activities, especially in tropical environments. Fish farming in fresh water is a recognised hazardous occupation as the ponds can be contaminated by urine from rodents or large farm animals. Rice and sugarcane workers are also a high risk group. Water sports (swimming, boating, sailing, windsurfing, waterskiing, kayaking or canoeing, rafting and fishing) which involve immersing part or all of the body in water, are especially hazardous (17).

Adventures travel is now the largest growing sector of the leisure travel industry (58) and infection can occur as a result of this type of activity. The participation of 304 athletes from 26 countries in the Eco-Challenge-Sabah multisport endurance race, held in Malaysian Borneo in August and September 2000, resulted in an international leptospirosis outbreak. At least 68 cases of leptospirosis were diagnosed. Moreover, the illness was severe, and a number of young, otherwise exceptionally healthy endurance athletes were hospitalised (58). All surveyed athletes reported cuts and abrasions that may have facilitated the entry of leptospires (52). A leptospirosis outbreak was also reported in the Philippines during an iron man contest (62). The largest recorded outbreak in continental USA occurred in June and July 1998 in Wisconsin and Illinois, where there were 110 cases in a group of 775 athletes who were participating in triathlons (8). In California, leptospirosis is considered to be a re-emerging infection, with most cases appearing after recreational freshwater exposure (46). Such a re-emergence could occur anywhere in the Western Hemisphere where there are similar environmental conditions. Significant increases in incidence have also been reported from several countries following heavy rainfall and flooding (8), e.g. the cases that occurred in the wake of Hurricane Mitch in Nicaragua in 1995.

In North America, leptospirosis has also re-emerged in the dog population over the last ten years. Serovars grippotyphosa and pomona are responsible for the majority of cases of acute renal deficiency syndrome in dogs (4, 35, 54). Serovars icterohaemorrhagiae and, to a lesser extent, canicola, are now rarely found in the dog population, probably due to vaccination (17). Vaccines against the ‘new’ serovars have been available since 2000 and the number of canine leptospirosis cases is already decreasing. There is evidence that leptospiral infection is being spread by raccoons in some parts of the USA and Canada (54). Skunks and other wildlife reservoirs may also contribute to maintaining the infection in both rural and urban environments (54). The urine of infected dogs, vaccinated or not, represents a risk for dog owners and their families. The changing epidemiology of canine leptospirosis in North America, with changing serovar patterns and clinical signs, reflects the variable nature of leptospirosis within animal populations (17).

In the USA, it has been shown that many inner-city residents have antibodies against leptospires. In the absence of recognised occupational, recreational, or epidemic risk factors, the manner in which these people acquire the bacterium is not well established. However, since rats are well known carriers of leptospires, it could be that residents become infected after being exposed to rat urine (64).
Clinical features

In humans, leptospirosis is frequently misdiagnosed as a result of its protean and non-specific presentation (36). Fever, headache and myalgia are the most common symptoms of leptospirosis, but the clinical presentation of the disease can be highly variable and may be related to different infecting serovars, the amount of inoculum, host factors, or a combination of all these. Two classic forms have been described: a mild influenza-like anicteric febrile illness, and the more serious icteric leptospirosis, also known as Weil’s disease, which can cause severe renal and hepatic failure, myocarditis, haemorrhages and death (17). The incubation period for leptospirosis may be as short as two days, or as long as 30 days; the usual range is five to fourteen days (17). All types of the disease start the same way: sudden onset of headache, muscle pain, tenderness and fever, sometimes accompanied by rigors, nausea (with or without vomiting), conjunctival suffusion, a transient skin and mucosal rash, photophobia and other signs of meningism. Pulmonary involvement has increasingly become recognised as an important manifestation of the disease and ocular manifestations are also encountered (1, 50).

In domestic animals (ruminants, swine), abortion, stillbirth, or the birth of weak animals, are often the first and only signs of leptospirosis. In cattle, a transient fever with a precipitous drop in milk production lasting for two to ten days may also be seen (17). In horses, abortion is also a clinical feature, but some of them may develop periodic ophthalmia, with recurrent iridocyclitis, or uveitis (17). Leptospirosis has been found in almost every warm-blooded animal, including sea-lions, while birds are not known to acquire the infection in nature (17).

Diagnosis

The clinical diagnosis of leptospirosis is not straightforward, because the signs of the disease, i.e. fever, fatigue, stiff neck, headache, nausea, vomiting and myalgia, are also symptomatic of many other illnesses, such as mononucleosis, hepatitis B and C, meningitis, and the zoonotic infections brucellosis, tularemia, hantavirus, dengue, Colorado tick fever, plague, rickettsiosis, ehrlichiosis and Q fever (46). If the patient has a history of rural freshwater exposure, additional infections worth considering include hepatitis A, salmonellosis, toxoplasmosis and Naegleria meningitis (46). If other signs are also present, such as pulmonary involvement, thrombocytopenia and abdominal pain, the list of possible causes must be expanded to include yet more diseases and differential diagnosis becomes more complicated (46, 50).

For several decades, laboratory diagnosis of leptospirosis has been based on the isolation of the organism and/or on the detection of specific antibodies. However, polymerase chain reaction (PCR) and immunohistochemical assays, both very sensitive methods of detecting leptospirosis, are now available in some laboratories. Isolation of the organisms is difficult and requires several weeks of incubation. Leptospires can be isolated from blood and cerebrospinal fluid samples during the first seven to ten days of illness and from urine during the second and third week of illness (1). The microscopic agglutination test, which is the reference standard test, is the principal serological diagnostic method used. However, it requires significant expertise from its users and interlaboratory variation in results is high (1). Rapid genus-specific tests have also been described. Those in contemporary use are primarily IgM-detection assays (1, 41).

Control

The majority of cases of leptospirosis are self-limiting and the best treatment for the disease continues to be supportive management and use of appropriate antibiotics (1). Doxycycline, ampicillin and amoxycillin are recommended in mild disease, whereas penicillin G and ampicillin are indicated for severe disease (1, 27). Chemoprophylaxis is effective for people at risk of exposure. Oral doxycycline is highly effective, but is not recommended for long-term use (27, 58). Finally, vaccination for humans exists in some countries, but a universally effective vaccine has not been developed (58). Problems such as side effects, short-term and incomplete protection and a considerable variation in the serovars that are involved, have still to be resolved (1). For domestic animals, other than horses, vaccination is a very useful tool for preventing clinical manifestations of the disease.

Travellers should be taught how to minimise exposure to potentially contaminated soil and water. Protective clothing, especially footwear, should be worn and other measures to prevent dermal cuts and abrasions should be followed. Travellers to the tropics should avoid submersion in, and drinking of, surface water (27).

Further research into the epidemiology of leptospirosis should be encouraged. Research would also help to develop rapid and effective diagnostic methods, establish preventive measures for the general public, and help in the development of educational materials that would increase awareness and assist doctors and other professionals to recognise the disease.

Lyme borreliosis

Introduction

Lyme borreliosis, the most common vector-borne disease in the Northern Hemisphere, is caused by a spirochete belonging to the *Borrelia burgdorferi* (*sensu lato*) complex.
About 60,000 cases are reported each year in Europe and about 15,000 in the USA (29, 60). In some European countries, the incidence of the disease has been estimated to be as high as 155 cases per 100,000 inhabitants, with marked regional variability and differences in the risk of infection even within the same geographical area (59).

In the last few years, the complete genome of the spirochete has been sequenced, animal models have been developed for studies of pathogenesis, guidelines and treatment have been established and vaccines have been developed (60). However, the control of the disease is difficult because of the lack of epidemiological data and the large number of the *Borrelia* species and tick species involved, and because of the wide variety of host species and various different geographical locations in which the disease is found.

**Epidemiology**

Lyme borreliosis is the most common vector-borne disease in the USA (60). Although cases have been reported in 45 states, three distinct foci have been identified: Northeast (from Maine to Maryland), Midwest (in Wisconsin and Minnesota), and West (in northern California and Oregon). However, the highest reported frequencies of the disease are in central Europe (Germany, Austria and Slovenia) and Scandinavia (Sweden). Cases are also found in Russia, the People’s Republic of China and Japan (60). In Canada, the disease is endemic in southern Ontario only.

The causal agents of Lyme borreliosis are *B. burgdorferi* (*sensu stricto*) in the USA and *B. burgdorferi* (*sensu stricto*), *B. afzelii* and *B. garinii* in Europe (29, 60). The spirochete is transmitted by ticks that have a blood meal during each of their three life stages: larval, nymphal and adult. The risk of infection in a given area depends largely on the density of these ticks as well as their feeding habits and animal hosts, which have evolved differently in different locations (60). The black-legged tick or deer tick (*Ixodes scapularis*) is responsible for cases in the Northeast and Midwest of the USA, while the western black-legged tick (*I. pacificus*) is associated with cases in northern California and Oregon (60). The proliferation of deer, the preferred host of the adult tick, was a major factor in the emergence of epidemic Lyme borreliosis in the northeastern USA at the end of the 20th Century. In Europe, the principal vector is the sheep tick (*I. ricinus*) and in Asia, it is the taiga tick (*I. persulcatus*) (60). There is no evidence of natural transmission from person to person. Recent data have shown, for example, that male and female ticks are not equivalently infected by *B. burgdorferi* (*sensu stricto*), that *B. afzelii* affects tick migration capabilities and that adult female *I. ricinus* feed mostly on large mammals (13). These data could help to better understand the epidemiology of vector-borne diseases.

*Borrelia* spp. can survive and multiply in vertebrate reservoirs and ticks become infected when feeding on the blood of these animals. In Europe, small mammals such as mice and voles provide reservoirs for the bacterium, while in North America, rodents and birds are the principal reservoirs (22).

**Clinical features**

In humans, the clinical manifestations of Lyme borreliosis may vary according to the infecting strain (28). In the early stages of infection (stage 1) there is a localized ‘bull’s eye’ rash (*erythema migrans* [EM]) at the site of the tick bite. Within days or weeks, the bacteria spread via the bloodstream and infect the nervous system, heart, or joints (stage 2). If the condition persists over the following weeks and months the patient enters stage 3 of the disease (60). Contrary to cases in Europe where the stage 1 lesion is indolent, cases in North America are generally associated with more intense inflammation (60). However, classification of this disease by stages can present problems, as symptoms may overlap and all stages do not necessarily occur in every patient. Moreover, differences in clinical manifestations and severity occur throughout the world, with a wider range of disease presentations in Europe than in North America. This probably reflects the wider variety of *B. burgdorferi* genotypes found in Europe (22).

In Europe, in contrast to North America, a special type of late-stage borreliosis, in which there is inflammation of the extremities and then advanced atrophy of the skin, sometimes occurs years after a tick bite. Contrary to *erythema migrans*, this manifestation, called *acrodematitis chronica atrophicans*, does not heal without treatment. It is almost exclusively reported in Europe as a result of infection with *B. afzelii* transmitted by *I. ricinus* (28).

In Europe, *B. garinii* may cause chronic encephalomyelitis, characterised by spastic paraparesis, cranial neuropathy, or cognitive impairment. In the USA, a mild, late neurological syndrome has been reported, called Lyme encephalopathy, manifested primarily by subtle cognitive disturbances (60). In Europe, *B. burgdorferi* has been isolated from endomyocardial-biopsy samples from several patients with chronic dilated cardiomyopathy. However, this complication has not been observed in North America (60). Months after the onset of the illness, about 60% of untreated patients in the USA begin to have intermittent attacks of joint swelling and pain, primarily in large joints, especially the knee (60, 61).

Lyme borreliosis has been reported in a wide range of domestic animals, including dogs, cats, horses, cattle, and other ungulates, but is best described clinically in dogs. The manifestations most often described are lameness,
sometimes with signs of migratory arthritis of the large joints, fever, lethargy and anorexia. There are also reports of hepatic, renal and ocular involvement. In horses, sporadic lameness, weight loss, laminitis, low-grade fever, swollen joints, anterior uveitis and neurological abnormalities have been reported. Finally, cattle may exhibit fever, stiffness, swollen joints and decreased milk production (14). A paper by Manion et al. reported that viable B. burgdorferi had been found in the urine of clinically healthy horses in an endemic region in the USA. Although the number of organisms shed in the urine was low, it was suggested that urine/mucosal transmission of the infection in horses could have clinical importance in the spreading of the disease (42). The same authors indicated that zoonotic spread of the disease in this manner is a possibility that deserves further investigation (42).

**Diagnosis**

Diagnosis of Lyme borreliosis in endemic areas is based largely on clinical presentations, and relies heavily on the recognition of EM or, less commonly, a ‘flu-like’ illness during the summer months. However, diagnosis can be more difficult in the absence of recognised EM lesions or in the case of later-stage infection. In such cases, appropriate laboratory tests are necessary (22).

Microbiological or serological confirmation of infection is needed for all manifestations of Lyme borreliosis except for typical early skin lesions (59). Culture of the organism on Barbour-Stoenner-Kelly medium permits a definitive diagnosis (60). However, except in the case of a few patients with acrodermatitis, positive cultures have only been obtained in the early stages of the illness, primarily from biopsy samples of EM lesions, less often from plasma samples and only occasionally from cerebrospinal fluid samples in patients with meningitis (60). During later stages of infection, PCR testing is greatly superior to culture for detecting B. burgdorferi in joint fluid (59, 60).

Since culture tests and PCR can only be done satisfactorily in specialised laboratories, antibody detection is currently the most widely used method of microbiological diagnosis of Lyme borreliosis (59). However, serological testing has some limitations: its reliability is problematic in early infections; an IgM response can be induced by several conditions, including ehrlichial infection, leading to false-positive results; borrelial antibodies can remain detectable for years after infection, so that testing might not reliably distinguish between active or past infection; and finally, a substantial degree of interlaboratory discrepancy has been recorded (59). Borrelial antibodies can be measured in blood, cerebrospinal fluid, or synovial fluid. In the USA, the recommended serological testing is a two-step process: a positive or equivocal result to enzyme-linked immunosorbent assay (ELISA) is followed by an immunoblot on the same sample, which can detect IgM and IgG antibodies against individual B. burgdorferi antigens that have been separated by electrophoresis. If the immunoblot is positive, the diagnosis of Lyme borreliosis is confirmed (22). In Europe, where it seems that the seropositivity rate is relatively low, no single set of criteria for the interpretation of immunoblots results in high levels of sensitivity and specificity in all countries (60). Thus, European researchers are evaluating strategies for the use of serology to assist in the diagnosis of this disease (33).

**Control**

In about 20% of patients with early-stage Lyme borreliosis and recognisable EM, the localised infection will resolve without any treatment and 90% of patients treated at this stage have an excellent response to antibiotic therapy (29). The most effective antibiotics seem to be amoxycillin and doxycillin (29, 60, 61).

An effective and apparently safe vaccine against Lyme borreliosis was withdrawn from the market in 2002 because of low sales (29). Since Lyme borreliosis is not contagious and is rarely, if ever, fatal, there was concern that vaccinated people might abandon other precautions against tick-borne illnesses. Also, there was a theoretical concern that the vaccine might cause autoimmune arthritis, although this concern was not supported by available data on outcomes (29). A commercial vaccine is nonetheless available for the prevention of the disease in dogs.

To prevent Lyme borreliosis at community level, it is not necessary that all residents adopt the same strategy, but it is necessary that most people adopt at least one strategy (29). If health education programmes were to focus on a single personal-protection strategy for community residents, performance of daily tick checks would be the most likely to be accepted and the most likely to be effective. Use of repellents and protective clothing can be recommended as supplementary strategies (29). Prompt removal of attached ticks may be less effective in Europe than in North America, since I. ricinus is capable of transmitting B. afzelii within 24 h of attachment (30). Prophylactic treatment of B. burgdorferi generally requires at least 36 h of tick attachment (29). Prophylactic treatment after tick bites still needs to be evaluated. Clinicians must consider the time of attachment of the tick and the type of tick before treating the bite. Finally, strategies leading to the control of tick populations in areas where Lyme borreliosis is endemic must be considered (29). It should be noted that tick control is likely to reduce the risk of other infections transmitted by ticks, such as babesiosis and granulocytic ehrlichiosis in eastern USA and tick-borne encephalitis in Europe and Asia (transmitted by I. ricinus in Europe and by I. persiculatus in Asia) (29, 32). In the USA, as the annual incidence of Lyme borreliosis is
closely correlated with the abundance of nymphal *I. scapularis* in an area, chemical control efforts should target ticks in the nymphal stage (22).

The strategies most likely to be effective in any given area should be selected on the basis of the local ecology and the preferences of community residents and they should be evaluated for effectiveness as they are implemented. The cooperative engagement of public health officials, clinicians and residents of the affected communities will make it possible to reduce the incidence of Lyme borreliosis (29).

### Plague

#### Introduction

Up to the present time, three major plague pandemics have been recorded worldwide: the Justinian plague in the 6th Century, the Black Death in the 14th Century (about 25 million people died) and the recent 20th Century pandemic which started in the 1880s and lasted until the 1950s (40). At the present time, in view of the recent increase in the number of cases in humans and the re-appearance of epidemics in several countries, the disease is categorised as a re-emerging disease by the World Health Organization (WHO) (47).

In September 1994, India reported cases of plague for the first time in 28 years. By 24 September, more than 300 unconfirmed cases of pneumonic plague and 36 deaths had been reported from the city of Surat (20). After these reports, hundreds of thousands of Surat’s two million residents fled, some to the major cities of Bombay, Calcutta and New Delhi. Unconfirmed pneumonic plague cases and plague-related deaths were subsequently reported from several areas throughout India (20). Several countries closed their borders to Indian travellers and cargo and discontinued all flights to and from India. Because of its epidemic potential, plague is listed as a Class 1 internationally quarantinable disease in the International Health Regulations of the WHO (20). The considerable destructive potential of the pathogen and the occurrence of antibiotic resistance, coupled with rapid international air travel, means that plague presents a real danger to public health even in the 21st Century (18).

#### Epidemiology

*Yersinia pestis* is primarily a parasite of wild rodents that persists in permanent, discrete enzootic foci throughout the world (31). The bacterium is transmitted from mammal to mammal by the bites of infected fleas. Maintenance of plague is absolutely dependent upon cyclic transmission between fleas and mammals (51). More than 200 species of rodents, such as rats, marmots, hares, ground squirrels, hamsters and chipmunks and at least 80 species of fleas have been implicated in maintaining cycles of plague throughout the world (31). The worldwide rodent plague foci constitute a vast enzootic reservoir that is an ever present threat to human health, as history has demonstrated (31).

The infesting flea often determines the potential of an epizootic to cause human disease (51). In the USA, prairie dogs, although prominently affected, are not a common source of human plague since their fleas are not prone to feed on humans even in the absence of their normal hosts. Squirrels carrying *Ornithodoros montanus*, which will bite humans, constitute the most common source of human plague (51). While cat and dog fleas will also feed on humans, they are poor vectors and do not cause significant human disease (51). Isolated cases of plague also occur as a result of direct contact with infected rodents, their predators and other animals, including exceedingly rare cases of transmission from goats and camels. In the USA, domestic cats have become significant sources of plague for cat owners and veterinarians (21, 39, 51). The disease may also be transmitted to humans (particularly those working in the leather and fur industries) who come into contact with the skin of infected animals; they can become infected if any cuts or abrasions come into contact with the animal skin or if they inhale infected skin particles. Occasionally, but rarely, consumption of meat from infected animals may lead to human infection. Human-to-human transmission of pneumonic plague is possible (39).

Enzootic North American foci, the largest in the world, are primarily found in the western and southwestern USA (New Mexico, Arizona, California, Colorado, Nevada and Wyoming), with plague-infected animals detected as far north as Alberta and British Columbia in Canada, and as far south as the state of Coahuila in Mexico. Multiple stable foci occur in Africa (East Central Africa, Uganda, Tanzania, Zambia, the Democratic Republic of the Congo, Libya and Madagascar), Asia (Vietnam, China, Mongolia, Kazakhstan, India and Burma) and South America (Brazil, Bolivia, Peru and Ecuador). Europe and Australia are free of plague at present (39, 51, 56).

#### Clinical features

In humans, individuals at risk are hunters, shepherds, farmers and tourists who stay in endemic areas. Cat owners and veterinarians may also be at risk (21, 39). Three clinical forms of plague are recognised in humans: bubonic, septicaemic and pneumonic. The septicaemic and pneumonic forms are usually secondary to the bubonic form and the bubonic form is the most common in the Americas (56). It is characterised by swelling of the cervical, axillary and inguinal lymph nodes, depending on the location of the portal of entry of the bacteria. The
incubation period is from three to six days. Haematogenous dissemination of the bacteria to other organs and tissues may cause intravascular coagulation and endotoxic shock, producing dark discoloration in the extremities (so-called black death) (56).

Fulminant septicaemic plague may occur even without recognisable lymphadenopathy. Patients often present with gastrointestinal symptoms, hypotension, organ failure, intravascular coagulation and shock, and death occurs in approximately 50% of cases (39). Symptoms of primary pneumonic plague appear after an incubation period of a few hours to one to two days, with sudden fever, headache, myalgia and pulmonary signs. The mortality rate is about 20% (39).

In the animal population, rodents manifest a variable response to infection. Some rodent species are highly sensitive, e.g. prairie dogs, but most are at least moderately resistant. Carnivores such as domestic dogs, domestic ferrets, black bears, badgers, coyotes and skunks appear to be highly resistant to plague. In most of these animals, ingestion of plague-infected rodents causes inapparent to mild disease and seroconversion (51). However, in contrast to other carnivores, cats are susceptible to septicaemic plague and present with fever, lethargy, anorexia and an enlarged lymph node or bubo (frequently submandibular). The mortality rate in cats can reach 38% (15, 21). Pneumonic plague has also been reported in cats (15).

**Diagnosis**

In endemic areas, plague should be suspected when a patient presents with fever and chills, myalgia, arthralgia, headache, or prostration. There is even more reason to suspect plague if septicaemia or pneumonia are identified, or if there is inguinal, femoral, axillary, or cervical lymphadenopathy. Persons who acquire plague as a result of handling infected cats are most likely to develop axillary or cervical lymphadenopathy, while those infected through flea bites typically develop inguinal or femoral lymphadenopathy (21).

Standard bacteriological practices of biosafety level 2 are usually sufficient for clinical laboratories handling Y. pestis, but special precautions must be used if aerosols are produced or deceased animals are handled. Such activities, as well as procedures with cultures of this bacterium, can be performed in a biological safety cabinet with biosafety level 3 practices (3). In humans, Y. pestis can be isolated from blood, by bubo aspiration, from sputum, from throat swabs or throat washings, from skin swabs or scrapings and from cerebrospinal fluid in patients with meningitis (3). In animals, the diagnosis is made by culturing material from the carcass, such as heart blood, spleen, liver, or lymph node tissue; aspirates; or bone marrow (39).

A multiplex-PCR technique has been developed for the detection and characterisation of Y. pestis even when the bacteria are no longer viable and when culture diagnosis has been hampered by the growth of contaminants (47). The use of paired sera taken during the acute and convalescent phases of the disease is preferable for serological testing. Different tests can be used, namely ELISA and passive haemagglutination assay. Test kits are also commercially available (3).

**Control**

Antimicrobial therapy should start immediately after possible exposure or when plague is suspected. The antibiotics of choice are streptomycin, gentamicin, doxycycline, or chloramphenicol (39, 51). In a recent study, it has been shown that gentamicin alone or in combination with a tetracycline was as effective as streptomycin for treating human plague (5). Antimicrobial prophylaxis may also be used under proper conditions. Vaccines are available in some countries, but not in the USA. Rat and insect control is important in urban areas (39, 51). Routine flea control programmes are recommended for cats and dogs in areas where plague is endemic. Serodiagnostic tools have yet to be validated for plague, but they are of great potential value in the surveillance of the disease. A test for the rapid detection of IgG antibodies to fraction 1 (F1) has been designed for diagnosis in both humans and animals (63).

Public education programmes (symptoms, methods of transmission, prevention strategies) are recommended in endemic areas. In 1994, in response to the possibility of an epidemic of pneumonic plague in India (unconfirmed cases), the Centers for Disease Control and Prevention (CDC) developed and implemented an enhanced surveillance system to supplement the existing regulations concerning imported plague. This protocol could serve as a model for the detection and control of any emerging disease imported into a given country (20). A quantitative PCR method to assess the prevalence of plague-infective (blocked) fleas in a population has also been developed. This method could provide a means of monitoring plague epizootics and the associated risks of flea-borne transmission to humans and is also applicable to the study of other vector-borne diseases (31). Finally, the use of Y. pestis as a biological weapon remains a major concern for public health officials (34).

**Conclusion**

The emergence or re-emergence of zoonotic infections may be the result of the exceptional convergence of different predisposing factors, i.e. causal agents, reservoirs, vectors,
geographical distribution, environmental changes, human activities and human interventions. Humans are not in a position to eliminate all the reservoirs and/or vectors of infectious agents, but neither will they cease their activities that contribute to the occurrence of genetic mutations, increased antimicrobial resistance and the emergence of disease, e.g. international travel and commerce, residential development in geographical areas where some infectious agents are endemic, and industrial development known to deteriorate the environment.

Conditions for the convergence of predisposing factors leading to the emergence or re-emergence of zoonotic diseases are more present than ever before. The four diseases described in this article are only examples among an important series of diseases that have emerged or re-emerged. According to the CDC, more than 50 new or newly identified human pathogens have been reported in the past 30 years. Interestingly, many of these agents are of zoonotic nature. Many of these are also seen as potential risk organisms for bioterrorism (18). Control of emerging or re-emerging diseases has become a major challenge for humanity.

L’émergence ou la réémergence des maladies bactériennes zoonotiques : la bartonellose, la leptospirose, la borréliose de Lyme et la peste

R. Higgins

Résumé
L’hémisphère nord est confronté à l’émergence ou à la réémergence de toute une série de maladies zoonotiques ; l’auteur décrit quatre d’entre elles, à savoir la Bartonelle, la leptospirese, la borréliose de Lyme et la peste. Si leurs causes n’ont pas été clairement éclairées, de fortes présomptions pèsent sur divers facteurs tels que la démographie humaine, le développement économique, l’exploitation des terres, les déplacements et les échanges internationaux, ainsi que l’adaptation des agents microbien. Dans la mesure où l’émergence ou la réémergence des maladies est devenue un défi majeur pour la communauté internationale, il importe de diffuser les informations concernant les possibilités de diagnostic et de prophylaxie, notamment aux acteurs de la santé publique.

Mots-clés
Enfermedades bacterianas zoonóticas emergentes o reemergentes: bartonelosis, leptospirosis, borreliosis de Lyme y peste

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Resumen
En el Hemisferio Norte se ha descrito la presencia de un buen número de enfermedades emergentes y reemergentes, de las que el autor describe cuatro: la bartonelosis, la leptospirosis, la borreliosis de Lyme y la peste. No están claras las razones por las que tales enfermedades han surgido o resurgido, aunque se sospecha la intervención de factores tales como el crecimiento demográfico y desarrollo económico de las sociedades humanas, los usos del suelo, los viajes y el comercio internacionales o la adaptación de los propios microorganismos. La lucha contra las enfermedades emergentes y reemergentes se ha convertido en un grave problema para la comunidad internacional, por lo que es importante difundir información acerca de las posibilidades de diagnóstico y control, sobre todo entre quienes trabajan en el terreno de la salud pública.

Palabras clave

References


