The Body Louse as a Vector of Reemerging Human Diseases

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The body louse, Pediculus humanus humanus, is a strict human parasite, living and multiplying in clothing. Louse infestation is associated with cold weather and a lack of hygiene. Three pathogenic bacteria are transmitted by the body louse. Borrelia recurrentis is a spirochete, the agent of relapsing fever, recently cultured on axenic medium. Historically, massive outbreaks have occurred in Eurasia and Africa, but currently the disease is found only in Ethiopia and neighboring countries. Bartonella quintana is now recognized as an agent of bacillary angiomatosis bacteremia, trench fever, endocarditis, and chronic lymphadenopathy among the homeless. Rickettsia prowazekii is the agent of epidemic typhus. The most recent outbreak (and the largest since World War II) was observed in Burundi. A small outbreak was also reported in Russia in 1997. Louse infestation appears to become more prevalent worldwide, associated with a decline in social and hygienic conditions provoked by civil unrest and economic instability.

Lice have been recognized as human parasites for thousands of years [1, 2] and have been identified on Egyptian mummies and on Pompeii’s conserved bodies [2]. Lice are extremely well-adapted insects that are usually host-specific, and they have recently served as a paradigm for host-parasite coevolution [3]. The three species of human lice are transmitted in different ways and behave differently. The head louse [4] is prevalent in all countries, and outbreaks have been described at all levels in society. The pubic (crab) louse is usually a sexually transmitted organism, although atypical locations, such as eyebrows and eyelashes, have been reported [2, 4]. The body louse lives in clothes and multiplies when such conditions as cold weather, lack of hygiene, or war are present. Its prevalence reflects the socioeconomic level of the society [5], as it is increasingly described in the poorest populations of developed, industrialized countries such as France [6], Russia [7], the Netherlands [8], and the United States in Seattle [9–11]. The threat posed by body lice is not the louse itself but three associated bacterial diseases that have recently reemerged (table 1). Relapsing fever caused by Borrelia recurrentis has occurred in large outbreaks in Eritrea, Sudan, Somalia, and Ethiopia [12–14]. Trench fever caused by Bartonella quintana is currently highly prevalent in homeless populations in the United States [9], Burundi [15], France [16], and Russia [7]. After a 12-year absence, epidemic typhus caused by Rickettsia prowazekii infected 100,000 people during the recent civil war in Burundi [15, 17, 18].

This review describes the body louse and the spectrum of louse-associated diseases that are currently reemerging.

Taxonomy and Phylogeny

The superorder Psocodea comprises two orders: Psocoptera and Phthiraptera (lice) [19]. Lice are insects without wings. Three thousand species of lice have been described, and most taxonomists agree that the Phthiraptera comprise four major groups: Anoplura (sucking lice), Rhyncophthirina, Amblycera, and Ischnocera. Anoplura are obligate hematophagous ectoparasites found on nearly all groups of mammals; of the 540 validated species, 20 are parasites of domestic animals or humans [20]. Anoplura are confined to mammals, and it is reasonable to assume that they developed on and coevolved with this group in the late Cretaceous or early Tertiary periods [19]. There is still controversy over the relative importance of coevolution [19, 21, 22]. Fifteen families are recognized [2] among the Anoplura order, two of which are of medical interest (see table 2). The Phthiridae family comprises the species Phthirus pubis (the crab louse) [2], and the Pediculidae family comprises the body louse and the head louse. Classification of these two human parasites into a single or separate species is a matter of controversy. Consistent anatomic differences have been observed between these lice, and it has been suggested [23] that the head louse is the ancestor of both species. In theory, the two lice can interbreed, but as they hardly ever meet in the wild [23, 24], this is unlikely. Today, taxonomic opinion...
considers them to be two subspecies: Pediculus humanus humanus (the body louse) and Pediculus humanus capitis (the head louse) [2].

**Anatomy and Physiology**

The two P. humanus subspecies share many identical anatomic characteristics (figure 1). The head is short and constricted, with two antennae that are each split into five segments. The thorax is compact, and the seven-segment abdomen is long and membranous with lateral paratergal plates [25, 26]. The cuticle may be colored, and the degree of coloration may reflect the skin color of their host. This phenomenon was first observed in a study of head lice, in which it was found that lice infesting dark-skinned people were markedly darker than those recovered from native Scandinavians [4]. The male louse can

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be identified by its large vesicular penis and its stout first tibiotarsus, which is used to grasp the female during mating [2]. Although head and body lice are anatomically very similar, an experienced entomologist can distinguish between them on the basis of clearer abdominal segmentation in the former subspecies, which may also exhibit black pigmented areas on the sides of the thorax [4]. Differences in the length of the first tibia have also been observed.

Body lice are defenseless, and their only natural enemy is their host [4]. The louse’s life cycle begins as an egg, laid in the folds of clothing (but nowhere else). As the body louse is highly susceptible to cold, the eggs are usually attached to inner clothing, close to the skin. When seeking lice or eggs, the inner belts of underwear, trousers, or skirts are therefore the best places to look. Louse eggs are held in place by an adhesive produced by the mother’s accessory gland [2] (figure 2). When held at a constant temperature (i.e., when clothes are not removed) the eggs will hatch 6–9 days after being laid. The emerging louse immediately moves onto the skin to feed before returning to the clothing, where it remains until feeding again. A louse typically feeds five times a day. The growing louse molts three times, usually at days 3, 5, and 10 after hatching. After the final molt, the mature louse will typically live for another 20 days. Digestion of the blood meal is rapid. Erythrocytes are quickly hemolyzed and remain liquified [27]. The gut is susceptible to rupture, and the louse may turn red as the gut contents diffuse into the hemolymph [2]. This phenomenon is most frequently observed when lice are infected by *R. prowazekii*, because the intracellular multiplication of these bacteria disrupt the gut. The red coloration is easily recognized but is only rarely observed in “healthy” lice. However, among colonies of laboratory lice that have adapted to feeding only once a day, this vermilion red color is apparent but transient. Louse feces are extremely dry and powdery, with a water content of only 2% [2]. Feces contain a large amount of ammonium, which acts as an attractant for other lice. Sensory glands in the antennae of lice identify this stimulant.

At maturity, lice can mate immediately, and during the prolonged mating, both the male and the female will continue to feed throughout the process [4]. Females lay about eight eggs a day, and because they do not have a sperm storage organ, they must mate before laying eggs; thus, frequent mating is critical. Local louse populations vary in size, dynamics, and sex ratio [28–30]. It has recently been shown that among head lice, mating competition favors females that produce more female than male offspring. In natural populations, the ratio of males to females is usually ~1/6 [30]. Population density is variable; usually only a few lice are observed on the same host, although anecdotal reports have mentioned people infested with “thousands of lice.” Theoretically, a pair of mating lice can generate 200 lice during their 1-month life span. Evans and Smith [31] calculated that a population can increase by as much as 11% per day, but this rate is rarely observed. Although merely theoretical, this calculation shows how rapidly an outbreak of louse infestation could develop.

Humidity is a critical factor for lice, which are susceptible to rapid dehydration [2]. The optimal humidity for survival is in the range of 70%–90% [4]; they cannot survive when this value falls below 40%. Conversely, under conditions of extremely high humidity, louse feces become sticky and can fatally adhere lice to clothing. The louse’s only method of rehydration is to feed on blood. The small diameter of the proboscis prevents the rapid uptake of blood; thus, frequent, small meals are necessary [2].

Temperature is also highly influential on the louse’s physiology. Laboratory lice prefer a temperature of between 29 and 32°C [4]. In the wild, lice are able to maintain this temperature range by nestling in clothing. However, if a host becomes too hot because of fever or heavy exercise, infesting lice will leave him. Body lice die at 50°C, and this temperature is critical when washing clothes, as water or soap alone will not kill lice. Although eggs can survive at lower temperatures, their durability is limited to ~16 days.

In conclusion, several points are pertinent as bases for the
control of infestation with body lice: Lice feed only on the blood of human beings and they need to feed every day or they die; they usually live around the waistbands of clothing and are often difficult to find; and their multiplication potential (10% per day) is enormous. Thus, the best way to prevent infestation is to undress completely and put on a new set of clothes. Washing the worn clothes with hot water allows them to be worn again immediately when dry. However, leaving the clothes unwashed but unworn for 7 days also results in the lice and eggs dying. Indeed, Maunder [4] hypothesized that this is the basis for weekly clothes changes and that the religious seventh day cycle is a ritualization of a necessity of hygiene. The Sabbath or Sunday rest associated with this change of clothes could therefore be attributed to the ancient cycle used for delousing.

Epidemiology of the Body Louse

Because lice live in clothing, their prevalence is determined by the weather, humidity, poverty, and lack of hygiene. Consequently, they are more prevalent during the colder months, and louse-transmitted diseases, especially epidemic typhus, are more frequently reported during winter and early spring [32]. The permanent foci of the body louse occur in regions subject to cold weather, where inhabitants need to wear multiple layers of clothes, and in poverty-stricken communities whose inhabitants lack multiple sets of clothes. Such populations are most common in mountainous regions of countries in intertropical zones, including Ethiopia [33], Burundi, and Rwanda in Africa [15], Peru in South America, and Nepal and Tibet in central Asia [34]. In all three regions, the prevalence of body lice increases with altitude, as observed in Ethiopia [35], in Burundi [15], and in Peru [36]. In infested communities, the proportion of people parasitized by lice can be very high. A recent study has shown that two-thirds of Ethiopian students are infested with lice [35]. The louse is transmitted by body contact; thus, sexual promiscuity also favors infestation. Infestation with lice is more frequent during wars, in trenches and in jail, where conditions are cramped, when cold is present, and where hygiene is limited [17]. Trench fever (B. quintana infection), jail fever, and pestis bellica (epidemic typhus) [1, 17] are louse-transmitted diseases. Natural foci of body louse have remained continually extant but have been slowly declining, as witnessed by the fall in the number of reports of louse-associated diseases during the 1980s. Widespread louse infestation is thought to exist only in Ethiopia and Eritrea, perpetuated by continual war and social upheaval [32, 33, 35, 37, 38]. A study of Ethiopian migrants reported that 39% had body lice, 65% had head lice, 10% had scabies mites, and 4.3% had human fleas [33]. Other transmissible skin diseases are also highly prevalent [37]. Men and women appear to be equally prone to infestation [35].

Large outbreaks of lice have been associated with the recent civil wars in Burundi, Rwanda, and Zaire [18, 39]. During those outbreaks, it was estimated that the rate of infestation by lice frequently reached 90%–100%. In a refugee camp in Goma (Zaire), all 800,000 refugees became lice-infested within 1 month, although no case of any louse-transmitted disease was reported [39]. An outbreak of typhus occurred in a jail in Burundi 2 years later [17, 18]; then, catastrophically, in 1997, a huge outbreak of typhus occurred in several refugee camps, in which nearly all inhabitants were louse-infested [15]. These observations show that the emergence and dissemination of body lice can be very rapid when the conditions are appropriate, such as war, cold weather, and lack of control of hygiene.

Infestation with body lice and louse-transmitted diseases are also being increasingly reported among homeless and deprived populations in inner cities of developed countries. Cases of B. quintana infections have been reported in the United States [11], France [16, 40], the Netherlands [8], and Russia [7]. This phenomenon appears to be unprecedented but is now widely observed. Interestingly, in western Europe, a large proportion of homeless migrants come from eastern Europe, the historical source of many louse-transmitted outbreaks [16]. It would seem that social decline underlies all body louse infestations. Thus, the best strategy to fight louse infestation would appear to be an improvement in or resolution of such problems, rather than medical treatment.

The Consequences of Louse Parasitism

The condition caused by body louse parasitism is known as pediculosis. The number of bites made by lice can be astonishingly high at worst; a louse-infested person can be parasitized by several hundreds or thousands of lice, each of which bites five times a day. Like other biting insects, the louse injects the puncture with biologically active proteins, which include an anticoagulant and an anesthetic [2]. These antigens provoke an allergic reaction within 3–4 weeks, which can lead to pruritus, after which the insect bite begins to become detectable. Scratching may result in identifiable lesions, and superinfection by Staphylococcus aureus can occur. Heavily bitten areas, such as the base of the thorax, the groin, and the flanks, may become darker. This characteristic skin staining is often referred to as vagabond’s disease [2].

A more general reaction has also been reported as appearing a few weeks or months after the beginning of the parasitism. This syndrome comprises fever, headaches, a diffuse rash, fatigues, and myalgias. Patients can also develop adenopathies and, when severely parasitized for months, an allergy to the louse feces associated with fever. The diagnosis of louse infestation is based on three factors: an interview, although many patients will deny having lice; physical examination of the patient, seeking evidence of scratching of lesions, specifically on the trunk; and a search for lice and eggs in clothes. If louse infestation is to be confirmed, living lice as well as eggs must be observed. However, many patients will be infested with only
a few insects, and these can be difficult to find. An Ethiopian study found that 36% of infected students had <10 lice on their body, 34% had >25, and only 5% had >200 [35]. As *R. prowazekii* can remain viable in feces for 3 months, louse excrement can also act as a source of typhus. Russian clothes cleaners have been reported to have acquired infection via this route [32]. Similarly, *B. quintana* is able to survive in louse feces for up to 1 year [41]. Although a definite diagnosis of pediculosis can be obtained only by finding lice, itching lesions on the trunk or the presence of eggs in clothes can also suggest lice infestation [2].

A long-term consequence of infestation with lice can be a syndrome characterized by apathy, lethargy, and fatigue [4]. Body louse infestation must be considered a disease in itself as well as a necessary prelude for the bacterial infections the lice transmit. Under natural conditions, only the body louse has been implicated as the vector of these three diseases, despite the fact that the two other human lice, the head louse and the pubic louse, can act as competent vectors under laboratory conditions.

**Laboratory Colonization of the Body Louse**

Since being first recognized as a vector of infectious diseases, the body louse has been used for the laboratory growth of *R. prowazekii* [42], the production of Weigl vaccine [43], the testing of antibiotic susceptibility of *R. prowazekii* [44, 45], and diagnostic testing of *B. quintana* [41].

The Weigl louse intestine vaccine was produced from 1920 to 1930. Lice were inoculated intrarectally with viable *R. prowazekii*. Then Weigl allowed the lice to feed on himself and his coworkers twice a day, permitting the rickettsiae to multiply in the intestinal cells of the arthropods [43]. Many lice were necessary to produce vaccine (100 infected lice for a single dose of vaccine), and in the course of the experiments, several members of Weigl’s staff developed typhus and died [42]. A trench fever outbreak was later observed among volunteer feeders of *B. quintana*–infected lice [41]. For many years, the susceptibility of *R. prowazekii* to antibioccid compounds was tested in Poland [44] and in the former Union of Soviet Socialist Republics [45] by using lice. Lice were inoculated intrarectally with first *R. prowazekii* and then the antibiotic compound. The survival of the louse was used as a marker of susceptibility, as lice usually die of *R. prowazekii* infection. Another approach used was to determine the percentage of “red lice” as a marker for those infected with *R. prowazekii* [45]. Lice were also used for testing efficacy of insecticides, and as the technique was improved, 30,000–40,000 lice were allowed to feed at the same time [46, 47].

Early colonies of lice required two feeds each day on human volunteers, but subsequently the lice became adapted to taking only a single daily feed [47] and then to feeding on rabbits [46, 48]. The Orlando colony, named after the city in Florida where it was bred, has formed the basis of many other colonies in other laboratories and is now considered as the reference [49–51]. These lice are adapted to rabbits and maintained by feeding on their shaved abdomens five times a week. Lice are kept at 30 ± 1°C and 70%–80% humidity. The possibility of feeding lice through artificial membranes has been raised [52].

**Susceptibilities to Insecticides**

Field samples of head lice have been tested for susceptibility to insecticides [53]. Such procedures are often difficult and have resulted in allergic side effects for volunteer hosts [25] when wild lice were tested. An alternative to such methods has been to use a laboratory colony of body lice [25, 30, 46, 54, 55]. In many tests, the insecticide is dissolved in a solvent and deposited on filter paper, onto which the insects to be tested are placed. Mortality is assessed after 24 hours [56, 57].

Boucherinc et al. [58] tested laboratory body lice and eggs on a cloth substrate against various insecticide concentrations. Their results suggested that to kill at least 50% of insects or eggs, for nearly all insecticides tested, lower doses were required than those determined by other studies. This method is currently used as a reference and closely resembles that described by Meinking et al. [53].

Lice have been shown to develop resistance to insecticides. Resistance of lice to DDT was first detected in Korea [59] and Japan [60]. Body lice resistant to lindane have also been reported in Europe, Africa, and Asia [61]. The first reports of resistance of body lice to malathion were made in Burundi [62] and Ethiopia [63]. However, selection trials failed to induce resistance to malathion in a laboratory colony of lice [54]. No evidence of any resistance to carbamates has, thus far, been demonstrated in any of the lice, although Clark and Cole [55] found it relatively easy to induce carbaryl resistance in a laboratory colony of body lice.

**Control and Eradication**

Eradication is the only management strategy for lice. In the long term, control of lice has largely been a failure. In the short term, it has shown itself to be greatly beneficial, especially when louse-borne diseases are prevalent. In such cases, efforts to control louse infestations among the majority of those at risk can stop an outbreak, even with limited resources and sometimes inappropriate measures [38, 64]. However, since the body louse is a symptom of chronic poverty, its eradication will be attained only when the general level of hygiene of the population rises significantly [4]. The treatment of body lice on the individual is not based on the use of insecticides. The simplest method for delousing is a complete change of clothing. However, since this is not always either practical or even acceptable, other simple measures, such as washing, can be effective. Chemical dry cleaning can also be effective, but its benefits are usually outweighed by its cost. Steam sterilization
Detection of Bacterial Pathogens in the Body Louse

Detection of bacteria in blood-sucking arthropods, such as ticks, lice, mites, fleas, and mosquitoes, has been possible for a long time by association of staining, immunodetection, and cell culture methodologies. Staining and cell culture approaches were previously difficult because of the presence of a complex microbial flora in arthropods, and serological reactions required species-specific antisera that were not always available. More recently, the association of amplification of specific fragments and analysis of the PCR products has been shown to be effective to obtain rapid and specific identification of the suspected bacterial agent in arthropods [72–76]. Different methods have been described for the extraction of bacterial DNA from arthropods: boiling triturated arthropods in saline buffer or in PCR extraction buffer [77], boiling hemolymph [78], phenol-chloroform extraction [79], or other recent extraction techniques [80, 81]. In our laboratory, we have used columns (QIAamp Tissue Kit; QIAGEN, Hilden, Germany) to extract DNA from different arthropods, including lice, ticks, fleas, and ladybugs. The validity of the extraction was tested by the positivity of PCR incorporation of 18S rRNA primers 18sai and 18sbi5.0 [76]. We tested ~600 lice. To validate PCR results, we included in each run several negative controls consisting of the DNA of lice, *P. humanus humanus* rested on pathogen-free laboratory rabbits, extracted at the same time as the DNA of the lice being studied. If laboratory lice are not available, we recommend the use of DNA from insects (e.g., ants) as negative controls.

To perform PCR amplification, genus-specific primers can be used. In our laboratory, we have used the primers CS-877/CS-1273 (*gltA*) and 120.333/120.900 (*rOmpB*) (obtained from the genes coding for *Rickettsia* citrate synthase and RompB protein), the primers CSBAR.240/CSBAR.720 and QHVE1/QHVE3 (which amplified a part of the *Bartonella* *gltA* gene and the ITS1), and the primers Bf1/Br1 (which amplify the *Borrelia* 16S rRNA–encoding gene) (figure 2). All of these primers have an excellent sensitivity and specificity.

In countries where no medical and biological facilities are available, lice are a convenient tool in epidemiological studies of body lice-transmitted diseases in place of collecting blood samples onto blotting paper by fingertip punctures. When outbreaks are suspected or during a routine survey, lice collected in plastic tubes can be easily transported or shipped to laboratories equipped for analysis; the bacterial DNA is preserved even after the death of the insect. In this laboratory, we have been able to show the usefulness of the detection of bacterial DNA in lice by PCR in several cases over the last few years. Sporadic cases of typhus had been reported in Africa [82], but in 1995, *R. prowazekii* was characterized by sequencing the PCR product amplified from lice collected from patients in a jail in Burundi [15]. This observation predated a massive outbreak of epidemic typhus in 1997 in refugee camps after the civil war: Among the lice collected, 33% were found to be infected with *R. prowazekii* [15]. Infection of lice with the bacterium leads to rapid death of the arthropod, so detection of rickettsial DNA in lice is as good a marker for the spreading of

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**Figure 3.** Recommendations of the World Health Organization for large-scale use of insecticides.

is no longer an appropriate method in most countries, but boiling is effective when more sophisticated methods are not possible (e.g., this method was efficient in the control of an epidemic of relapsing fever in Ethiopia) [64]. However, a more rapid method, which has some lasting benefit in reducing the risk of reinfection, is powder dusting of the entire clothing with 10% DDT, 1% malathion, or 1% permethrin dust [65] (figure 3). Since body lice visit the human skin only to feed and otherwise spend their time in clothing, where they also lay their eggs, there is no need to take any delousing action on the patient. Neither shaving nor bathing is necessary to rid the patient of lice [26]. In addition, there is no need to disinfect other belongings, with the exception of recently used blankets or clothes. Recently, the therapeutic efficacy of compounds taken orally to eradicate lice has been reported. Ivermectin, a macrocyclic lactone, causes paralysis in many nematodes and arthropods [66]. It is mainly used for treatment of onchocerciasis. It has been used for the treatment of lice-infected swine [67] and cattle [68]. It has also been used successfully in the treatment of human head lice. In this study, the authors suggested a two-phase treatment of a single 200-mg/kg oral dose repeated for 10 days to avoid relapses [69, 70]. Cotrimoxazole has also been reported as efficient in the treatment of head lice [71]. However, these compounds are not currently recommended for body lice.

When large-scale use of insecticides is necessary, the protocol proposed by the World Health Organization [39] (figure 3) should be used.

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**Box 1.**

- Permethrin 1% dusting powder is the insecticide of choice. This powder should be applied in a dose of 30-50 g per adult (125-250 mg per m² of clothing) and approximately half that amount for children, by means of a motor-driven air compressor with multiple duster heads. Socks, head coverings, the inner surface of garments, and bedding should also be treated where possible.

- Those treated should remain fully clothed so that skin and clothing can be treated simultaneously. The recommended method of treatment is as follows: apply dust or powder by blower nozzle into the openings of clothing of persons standing or sitting. Blow powder for a few seconds through neck openings and sleeves, and treat the seams and hems of trousers and skirts. Those treated should be free of lice within a few hours. Treatment should be repeated every 6 weeks. Clothing may be rinsed, but only in cold water, and soap should not be used.

- The quantity of permethrin required should be calculated at the rate of 30-50 g per person, on average; i.e., 3.5 million g, or 3 to 5 tons of powder will be needed for 100,000 people. To treat 1 million people, 30 to 50 tons will be needed.
the illness as is the presence of “red lice.” B. quintana was detected in body lice collected from deprived inhabitants from different countries in Africa (Zimbabwe and Burundi), South America (Peru) [36], and Europe (France and Russia) [76, 83]. Apparently, a reservoir of the bacteria exists, at least in the arthropods, highlighting the potential for an outbreak if auspicious conditions are combined. We did not determine the presence of B. recurrentis DNA in lice, because arthropods from Ethiopia, where the bacterium is prevalent, were not tested [64].

Origin and Future of Lice

Lice have been recognized for thousands of years as human parasites [1, 2]. Ancient lice and eggs have been recognized on 5,000-year-old mumified Egyptians [2] and pre-Columbian Incas [1]. Thus, speciation of the louse predates the human colonization of America 10,000 years ago, which makes it one of the first-ever human pathogens. It seems that the body louse diverged from the head louse, its ancestor, when humans started wearing clothes, as the new subspecies specifically adapted to life in clothing. Differentiation is probably recent, as the two subspecies, despite the virtual impossibility of meeting, are capable of interbreeding [4]. It has been speculated that the louse originated in Asia and has since spread throughout the world [4].

It was expected that lice would slowly disappear as civilization progressed and standards of hygiene improved [84]. However, this has not been the case. The head louse has proliferated in all countries [2, 4] and the body louse is re-emerging. In fact, wars and social changes are rapidly promoting an increase in the numbers of body lice [84]. The number of refugees and displaced persons is rapidly increasing [85]. In Africa, refugees from Liberia, Somalia, Sudan, Ethiopia, Zaire, Congo, Rwanda, Burundi, Mali, Mozambique, Sierra Leone, Guinea, and Togo have reached several million [18, 39, 85] and have been associated with outbreaks of lice where investigated. In Europe, countries of former Yugoslavia have generated 2 million refugees [85], and the former Union of Soviet Socialist Republics has been associated with several wars, including those in Georgia, Armenia, Azerbaijan, Tajikistan, and Chechnya. In Asia, Afghanistan is still at war and Iraq, Bhutan, and Myanmar have been at war for the last decade. These events are associated with a recrudescence in body louse infestation. Even more surprisingly, an increase in body lice has been noted in developed countries [8, 76]. For decades, body lice had disappeared in hospitals in Marseille but have been reappearing for 8 years in association with the new homeless population currently being observed [86]. As with many other infectious diseases, we believed too early that the fight against lice was over. In fact, it is still a major threat to humanity [87].

Origin of Louse-Associated Bacterial Pathogens

Because the body louse itself is probably 5,000–10,000 years old, the pathogens strictly associated with it represent a recent evolution, as indicated by the fact that they appear to be strictly confined to humans [88]. The three pathogens associated with lice, R. prowazekii, B. quintana, and B. recurrentis, have recently diverged from their respective genus (figure 4). They belong to different clades and were therefore independently associated with the louse; two bacteria (Rickettsia and Bartonella) belong to the α subgroup of Proteobacteria and Borrelia is a spirochete [89]. R. prowazekii is in a clade with Rickettsia typhi, another insect-transmitted rickettsial disease—causing organism [89, 90]. These two bacteria differ from other rickettsiae because of antigenicity, based on lipopolysaccharide and membrane protein, growth temperature, guanine plus cytosine percentage (29%–30%), and the fact that they are unable to move intracellularly by using actin polymerization [91–93]. However, whereas R. typhi keeps a part of its intracellular motility, R. prowazekii does not. This fact could explain why R. prowazekii does not spread in its vector and is the only Rickettsia species unable to be transmitted transovarially to its progeny in its arthropod host. A number of studies have been performed regarding infection of lice by Rickettsia species. When inoculated with R. typhi or R. prowazekii, the body louse becomes infected and sick. Therefore, the potential for R. typhi to become a louse-transmitted pathogen is high. However, this relies on the period of bacteremia in humans, which is probably spontaneously shorter than for epidemic typhus [94, 95]. On the other hand, R. prowazekii is unable to infect the tissue of ticks [88].

There are conflicting theories regarding the origin of R. prowazekii, but one of the most consistent is that it is a recent pathogen that first appeared in America, where the only nonhuman reservoir was found to be flying squirrels. The fact that it could use the louse as a vector meant that it was very successful. Some authors have suggested that the Spanish imported the body louse, which led to epidemic typhus sometime in the 16th century [88]. The fact that R. prowazekii is so aggressive to the louse is also in favor of its recent apparition as a louse/human pathogen. It could be speculated that after infection of a louse-infested human, contaminated by the flying squirrel reservoir, the disease spread from Mexico, where it was described by the Aztec [88].

B. recurrentis emerged phylogenetically from a group of African tick-borne Borrelia species. Because several reports [96] have shown that its closest species, Borrelia duttonii, could be louse-transmitted, it could be speculated that B. recurrentis originates in Africa. This is also suggested by the fact that the most recently identified focus of B. recurrentis was in Ethiopia and its surrounding countries. However, this contradicts recent events, as it appears that it was imported into Africa sometime in the 20th Century (see below).

B. quintana is phylogenetically situated within a cluster of
bacteria that are extremely well-adapted to mammals. In fact, *Bartonella* species constitute a unique group of bacteria determining chronic and/or asymptomatic bacteremia. *Bartonella henselae* can be recovered from the blood of asymptomatic cats [79, 97, 98], many *Bartonella* species are found in asymptomatic wild rats [99], and *B. quintana*, as well as *Bartonella bacilliformis*, were isolated from apparently healthy patients [41, 100]. This genus of bacteria is unique in that it is the only genus to be recovered on systematic culture of blood from mammals. It is transmitted from mammals to mammals by all kinds of arthropod vectors, including sand flies for *B. bacilliformis*, cat fleas for *B. henselae*, and lice for *B. quintana*. We suspect that in this group of bacteria, the vector is probably unspecific, as we have epidemiological evidence that *B. quintana* can be transmitted by fleas [101].

**Reservoir of Louse-Associated Bacterial Pathogens**

The body louse is the only established vector for the three diseases discussed herein. To contaminate lice and allow transmission, bacteremia may occur and be prolonged. *R. prowazekii* is not eradicated at the apparent end of the disease. Nicolle [102] reported that chronic asymptomatic bacteremia could be observed. However, the bacterium remains present, leading immune-depressed patients to relapse, known as Brill-Zinsser disease, which is associated with bacteremia. Consequently, until all hu-
mans who have had typhus are dead, typhus can constitute a threat. This fact has been highlighted recently in Burundi, where after 20 years without any reported cases, a huge outbreak of typhus followed an outbreak of lice in refugee camps [15]. Moreover, we predicted the same risk in Russia [90], which was observed 2 years later when an outbreak of body lice was observed in a psychiatric institution [103].

*B. quintana* is also a cause of relapsing fever and is associated with chronic asymptomatic bacteremia. It is the most efficient reservoir and, to the best of our knowledge, the most prevalent louse-associated pathogen worldwide.

*B. recurrentis*, as is obvious by its name, causes a relapsing fever. This relapsing character enhances its bacteremic duration and favors louse infestation. All three pathogens are only (or mainly) associated with relapses and bacteremia and have a unique human reservoir (except for *R. prowazekii*, which also has the reservoir of flying squirrels). Several pathogens can infect the same louse, a fact that has been observed for *B. quintana* and *R. prowazekii* in laboratory colonies [41] and in the wild [15]. Therefore, any outbreak of typhus may also be investigated for the prevalence of trench fever [15].

**Louse-Associated Pathogens**

*B. recurrentis*

*B. recurrentis* causes louse-borne relapsing fever. As the disease frequently causes jaundice, it has probably been reported as the yellow plague, which ravaged Europe in A.D. 550 [104]. Apparently, Rutty [105] was the first to distinguish typhus (spotted fever) and relapsing fever (yellow fever) among the famine fevers of the eighteenth century in Ireland. It was then associated with body lice by Mackie in 1907 [106], and the name “relapsing fever” was first used in Scotland by Craigie in 1843 [107]. Since then, there have been reports of huge outbreaks that usually grossly underestimate the number of cases. During World War I, half a million cases (one-sixth of the population) had relapsing fever in Serbia. In Russia and eastern Europe during the civil wars between 1919 and 1923, 13 million cases were reported, leading to 5 million deaths [104]. Hundreds of thousands of cases were reported in West Africa between the two world wars of this century, where it killed large numbers of people. In this case, it was probably imported by soldiers from the Middle East [104]. During World War II, 1 million cases were observed in North Africa (Algeria, Tunisia, Morocco, and Libya), with a fatality rate of 10%, and a large outbreak was also reported in Egypt [96] with more than 1 million cases. Since then, no major outbreak has been reported outside the endemic foci. Cases are currently being reported frequently in Ethiopia (it is estimated that there are probably 10,000 cases per year [104]) and in neighboring countries involved in war, including Sudan, Eritrea, and Somalia [12, 14, 104, 107–109]. It is also suspected of persisting in the Peruvian Andes and the Himalayas.

The bacterium. The spirochete was identified in blood smears by Oberweier in 1867 [104] and was cultured in axenic medium for the first time by Cutler et al. [110] in 1994. *B. recurrentis* is a typical *Borrelia* species. This genus belongs to the Treponemataceae family, which also includes the genera *Leptospira* and *Treponema* (figure 4). Borreliae are helical, are 8–30 μm long and 0.2–0.5 μm in diameter, have 3–10 spirales, are motile, and have 8–30 flagella [111]. *B. recurrentis*, like other *Borrelia* species, has a linear chromosome of 1 Mb [112] and five or six plasmids that vary in size from 11 to 192 kb [113, 114]. The sequences of the 16S rRNA and flagellin genes [111, 115] allow the classification of the borreliae into three groups (figure 5). *Borrelia burgdorferi* complex, which is tick-transmitted, is clustered in one group, and another group involves American species and a Japanese species causing tick-borne relapsing fevers. The third cluster groups *B. recurrentis* with Spanish and African isolates from tick-transmitted relapsing fever. It has been shown that *B. recurrentis* is very closely related to *B. duttonii* by sequence comparison of genes coding for 16S rRNA and flagellin. It can be speculated that the ancestor of *B. recurrentis* was an African tick-associated spirochete that diverged after its association with lice. Further data...
in support of this hypothesis suggest that *B. duttonii*, a tick-transmitted *Borrelia* species, could be transmitted to humans by body lice. This could be the initiation of a new clade when this event will appear in a louse-infected population [116].

**Infection in lice** [117–119]. *B. recurrentis* was first observed in lice in 1907 [104]. When lice feed on infected blood, *B. recurrentis* passes from the gut to the coelomic cavity and multiplies in the hemolymph. Tissues are not invaded, and *B. recurrentis* cannot be found in the saliva or the feces. The bacterium remains infected throughout its life but cannot transmit borreliae to its progeny, as the spirochete is not transmitted transovarially. As *B. recurrentis* cannot be excreted, the only possibility of contamination for human beings is louse crushing, which releases and spreads *B. recurrentis*. This bacterium is highly infective and capable of penetrating intact mucosa and skin. In the recent years, *B. recurrentis* has been identified only in Africa and has not been reported in America, Asia, or Europe. Ethiopia and those countries that immediately surround it are known to have this disease [129].

Pathophysiology [121]. Humans are the only host of *B. recurrentis*. The disease it causes is characterized by relapse, but no chronic infection has been documented. After a primary febrile episode and crisis, which are the more severe and often fatal phases of the disease, the patient apparently recovers after an abrupt defervescence, frequently associated with shock. Seven to 10 days later, the patient relapses. This phase is less severe, lasts for a few days, and can be followed by a few further relapses. During febrile phases, *B. recurrentis* are easily observed in blood smears, as they can multiply to $10^5$ organisms/mm$^3$ of blood. Between febrile periods, blood smears are usually negative, because the bacteria are being sequestered into internal organs. The periodicity results from a cyclic antigenic process. The genetic mechanism has been studied in the *Borrelia* genus [111, 122] and it has been suggested that there is a mini-chromosome shuttle mechanism that allows gene rearrangement and consequently a change in protein composition. When a new serotype is expressed, following expression of the new protein, a relapse occurs. As the number of rearrangements are limited, the disease is controlled by bactericidal antibodies after several relapses.

Antigenic variation as a mechanism for evading the mamalian immune response has been widely described for *Borrelia hermsii*, a tick-borne relapsing fever spirochete [123]. A single bacterium produces as many as 40 antigenically distinct serotypes [124], which can appear at a rate of $10^{-3}$ to $10^{-4}$ per generation. The linear plasmids of *B. hermsii* contain genes encoding the outer membrane, called variable major protein. These genes are silent except when they are adjacent to one of the plasmid telomeres. The translocation of variable membrane protein genes, from silent sites to active, results in antigenic variation. This mechanism of antigenic variation most closely resembles that of the African trypanosome, the causative agent of sleeping sickness [123].

**Clinical manifestations** [125–129]. Tables 3 and 4 show symptoms and biological findings in louse-borne relapsing fever. The illness begins abruptly with chills, headache, and fever. Most of these symptoms, which are associated with myalgias, arthralgias, abdominal pains, anorexia, dry cough, and fatigue, are mild for the first few days. Fever ranges between 39.5 and 40°C, and the pulse rate increases. The blood pressure is lowered. A cough is frequently prominent and could be associated with both epistasis and hemoptysis. Neurological involvement is usual [108]. The most commonly reported neurological symptom is meningismus, which is not generally severe unless associated with subarachnoid hemorrhage. Encephalitis and encephalopathy occur occasionally, manifesting

<table>
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<th>Finding</th>
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<td>Leukocytosis</td>
<td>1/3</td>
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<tr>
<td>Anemia</td>
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<td>Thrombocytosis</td>
<td>4/5</td>
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<td>Increased erythrocyte sedimentation rate</td>
<td>4/5</td>
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<tr>
<td>Increased serum aspartate aminotransferase level</td>
<td>2/3</td>
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<tr>
<td>Increased serum alanine aminotransferase level</td>
<td>3/4</td>
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<tr>
<td>Increased bilirubin level</td>
<td>2/3</td>
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<tr>
<td>Prolonged prothrombin time</td>
<td>1/2</td>
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<tr>
<td>Increased blood urea nitrogen level</td>
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<td>Hematuria</td>
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<td>Proteinuria</td>
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NOTE. Data are from [104].
as seizures, somnolence, and sometimes focal involvements. Physical signs may be observed, such as conjunctival injection or conjunctivitis, petechial skin rash on the trunk, splenomegaly that is often tender, and hepatomegaly. Jaundice is possible and is a diagnostic clue in louse-associated diseases. One of the complications of louse-borne relapsing fever is bleeding, purpura and epistaxis being the more common findings [128]. Other hemorrhagic phenomena include hemoptysis, hemaemesis, hematuria, cerebral hemorrhages, bloody diarrhea, retinal hemorrhage, and splenic rupture. Hemorrhages are associated with blood abnormalities, including thrombocytopenia, prolonged prothrombin time, and a decrease in coagulation factors. Laboratory data usually show that the WBC count is normal. Liver function tests frequently yield abnormal results, with elevations in serum alanine and aspartate aminotransferases and bilirubin. Renal function tests often show mild abnormalities of the serum urea nitrogen and creatinine values, and patients may have proteinuria and microscopic hematuria.

Clinical characteristics of relapsing fever are an initial febrile episode terminating in the crisis phenomenon, followed by an apyrexial interval of variable length, which is followed by relapse, with return of fever and other clinical manifestations [127]. Periods of relapse are less severe and shorter than the first febrile attack, with each relapse being less severe. Occasionally, no relapses are observed. The duration of the primary febrile attack averages 5.5 days. The duration of afebrile intervals averages 9.25 days (range, 3–27 days). Most patients have only one relapse, although a few have two. The duration of relapse averages 1.9 days. Peak temperatures are lower during relapses. Herpes labialis is relatively common during each episode. The phenomenon of the crisis is an important distinctive feature of relapsing fever. It is abrupt and is marked by rapid defervescence accompanied by sweats and thirst. Bradycardia is common, whereas hypotension and shock are rare. Occasionally, clinical features are severe and prolonged. Women who develop relapsing fever during pregnancy have a high incidence of abortion [104]. Finally, without treatment, the death rate varies from 10% to 40%; antibiotic therapy decreases it to 2%–4% [127].

Diagnosis. Diagnosis of relapsing fever is mainly based on demonstration of spirochetes in blood. Blood from the patient is examined by direct observation of unstained wet preparations by light- or darkfield microscopy or by examining thick blood films stained by light microscopy. Spirochetes are readily detected under low power because of the organism’s characteristic locomotion [130]. The Giemsa stain is most commonly used for demonstration of spirochetes in thick and thin film preparations (figure 6). This can be easily replaced by Diff-Quik (Baxter Dade, Düdingen, Germany) staining, which is more helpful in field situations [131]. Detection of spirochetes in the patient’s blood is considered to be evidence of relapsing fever, although failure to detect spirochetes microscopically should not exclude the diagnosis. PCR followed by sequencing can be useful for diagnosis [111, 131].

No specific or standard procedure has been developed for serodiagnosis of relapsing fever, because spirochetes undergo one or several antigenic phases. Burgdorfer [130] expects that the immunofluorescence tests will emerge as the method of choice in the serodiagnosis of relapsing fever, as in Lyme disease. Suckling Swiss mice have long been used for the culture of relapsing fever spirochetes [130]. Spirochetes are first detected in smears of tail blood 3–6 days after inoculation. Culture of B. recurrentis has recently been possible in axenic medium [110, 111, 115]. Recently, Cutler et al. [110] were able to obtain 18 strains from patients who tested positive on blood smears. All isolates were cultured in BSK II medium [132]. Strains should be maintained by twice-weekly subculturing [111]. In our laboratory, we used this first isolate from Cutler et al. [110] to start an indirect immunofluorescent assay with interesting preliminary results (unpublished data).

Treatment [121, 133–136]. Relapsing fever has been successfully treated with chloramphenicol, penicillin, tetracycline, and erythromycin. When various antibiotic therapy regimens are compared [128, 133–137], the most efficient are based on oral (a single dose of 0.5 g) or iv administration of tetracycline [136]. Erythromycin in a single oral dose (0.5 g) is an equally effective therapy in pregnant women and children of <8 years of age. Antibiotic treatment induces a Jarisch-Herxheimer reaction, which is an exaggeration of the crisis observed in untreated patients. It is characterized by severe rigors, an increase in temperature, a decrease in blood pressure, and leukopenia. It typically starts 1 hour after treatment, with rigor and fever. This is the chill phase. Then the patient feels hot and his or her temperature reaches a maximum, which is associated with the disappearance of spirochete clumping. The patient then experiences the flush phase, with profuse sweats, a drop in blood pressure, and risk of shock and cardiovascular collapse [104, 128] and, possibly, death. The Jarisch-Herxheimer reac-
tion is associated with leukopenia during the chill phase. Penicillin or procaine penicillin is less frequently associated with the Jarisch-Herxheimer reaction (from 1% to 40%) but is less efficient, being followed by relapses in 2%–45% of cases [133, 134, 136]. Some authors suggest starting therapy with penicillin and following this with tetracycline. Severe vasodilatation occurs during the flush phase of the Jarisch-Herxheimer reaction. Supportive treatment with an infusion of physiological saline (0.5–2.0 L according to the patient’s age) is therefore highly recommended when possible. Hydrocortisone does not prevent a Jarisch-Herxheimer reaction and is not recommended [136]. Heparin has not demonstrated benefit on the course of the disease, and no vaccinations are available.

B. quintana

Trench fever was the first clinical manifestation of infection due to Bartonella species to be recognized. The name “trench fever” was chosen because the disease was associated with both Allied and German troops during World War I. The disease is characterized by a 5-day relapsing fever, with severe and persistent pain in the legs. It has been estimated that trench fever affected >1,000,000 people during World War I [99, 138]. Epidemics of the disease were most frequently reported in Russia and on the eastern, central, and western European fronts during the two world wars of this century. The disease was supposedly imported from the Eastern front by German soldiers in 1914, and British troops were responsible for its spread to Mesopotamia [139]. After the war, the incidence of trench fever fell dramatically. During World War II, trench fever reemerged, and large-scale epidemics of the disease were again reported.

The earliest studies for B. quintana were carried out on human volunteers [139, 140] followed by macaques [141]. McNee et al. [142] were the first to suggest that lice had a role in the transmission of trench fever. A rickettsia-like organism, named Rickettsia quintana, was proposed as the etiologic agent of trench fever [41, 141, 143]. Confusion is apparent in early articles on B. quintana, because it was named either Rickettsia quintana, Rickettsia weigli [144], Rickettsia da Rochalimae [145], or Rickettsia pediculi. In 1939, Sparrow [145] reported the presence of Rickettsia quintana in ticks that had fed on patients with trench fever–like illness. The ubiquity of trench fever has been further demonstrated, with cases being reported in Japan [146], China, Mexico [147], and Burundi. Vinson and Fuller [148] reported the first successful axenic cultivation of the agent, which had been reclassified as Rochalimaea quintana [149, 150]. Recent investigations have, however, led to the reemergence of R. quintana as an organism of medical importance. R. quintana was cultured from skin lesions of patients with bacillary angiomatosis by Koehler et al. [10], as well as the newly described Rochalimaea henselae [10]. Moreover, the first identification of Bartonella species in bacillary angiomatosis has been done by amplification by universal primers, based on 16S rRNA sequence and sequencing by Relman et al. [151]. R. quintana, which has been subject to taxonomic reclassification, is now named B. quintana.

The bacterium. Brenner et al. [152] proposed the taxonomic unification of the genera Bartonella and Rochalimaea, and the name Bartonella was retained. Then the genus Grahambella was unified with the genus Bartonella, which at present, therefore, contains 10 species (figure 7) [152a]. Comparison of sequences indicates an extremely high homology between the four former Rochalimaea species (from 99.1% to 99.7%) and between these species and B. bacilliformis (from 97.9% to 98.8%) [152]. The genus Bartonella belongs to the α subdivision of the Proteobacteria (figure 4). The classification of the Rochalimaea species into the genus Bartonella also highlights similarities in the pathology of the diseases they cause; B. henselae and B. quintana can induce both bacteremia and

Figure 7. Phylogenetic tree of Bartonella species based on comparison of the sequences for the gene encoding citrate synthase. The evolutionary distance values were determined by the method of Kimura [152b]. These values were used to construct a dendrogram by the neighbor-joining method. Bootstrap values are indicated at the nodes. Boldface indicates the species of interest.
cutaneous angioprolific lesions in infected patients, both presentations also present in Carrion’s disease, which is the manifestation of *B. bacilliformis* infection. The bacteria are defined as short gram-negative rods and closely resemble *Rickettsia* species in morphology and staining properties. Catalase and oxidase reactions are negative, and *Bartonella* can be grown on axenic media [153], either on enriched agar or in broth enriched with amino acids, yeast extract, and fetal bovine serum [154]. Growth is enhanced by increased carbon dioxide pressure and by fetal calf serum [150] and is hemin-dependent [155, 156]. When grown on blood agar, rough colonies, deeply embedded in the agar, are obtained on primary isolation, typically after 12–14 days of incubation at 37°C. Incubation periods required for primary isolation may, however, be as long as 45 days [157]. Cell culture of *B. quintana* has been described; the bacterium grows on the surface of eukaryotic cells such as mouse L cells and within endothelial cells [158, 159]. The genome size of *B. quintana* has been estimated to be 1,700 kb [160, 161].

**Infection in lice.** The natural reservoir of *B. quintana* has not yet been established. Thus far, the human body louse is the only proposed vector for *B. quintana*, and humans remain the only proven host in vivo. Attempts to induce disease in laboratory animals through inoculation with *B. quintana* have succeeded only when primates were used [162]. After the first cases of trench fever were recognized in France in 1915, it rapidly became obvious that the disease occurred primarily when large numbers of people lived together in cramped, unhygienic, louse-infested circumstances. The role of lice in the transmission of infectious diseases had already been demonstrated by Nicolle et al. [163]. Identification of the heavy infestation of World War I troops’ uniforms with body lice led to the proposal that body lice were involved in trench fever as well as in typhus [41]. Lice infected with *B. quintana* remain so until they die. *B. quintana* multiplies widely in louse intestines, and it is easily recognized by staining of sections of the intestine [41, 164]. The association between *B. quintana* and the human host is less well understood. Although the bacteria are usually present in a patient’s blood during the febrile stages of trench fever, infection may persist long after the disappearance of all clinical signs of the disease. The authors recently described completely asymptomatic patients with chronic bacteremia [86], and it has been previously reported in human volunteers feeding lice [41]. It is important to note that persistent bacteremia could facilitate the spread of trench fever by an arthropod vector [41, 140, 141, 148, 165–167]. Infection is thought to be transmitted by feces from infected lice to human beings. *B. quintana* survives very well in louse feces and can remain infectious for up to 1 year [41].

Kostrzewski [41] has reported on the epidemiology of cases that were presented by Pena-Yanez in Spain, Laurell in Sweden, Braslawski in Kiev, and Swinkina in Leningrad. In Poland, Mosing [144] described a laboratory outbreak of disease caused by a new rickettsia-like organism under the name *Rickettsia weigl*; the organism was later shown to be *B. quintana* [41]. Sparrow [145] reported the presence of *B. quintana* in lice that fed on infected patient volunteers in North Africa. Parrot [168] diagnosed a case of trench fever in Algeria in 1945, and the disease was also reported in Egypt [169] and in Addis Ababa [143]. Trench fever has also been recognized in east Asia, with cases being reported in Japan [146] and China. A recent report of trench fever described cases in Mexico City [147, 149].

Recent reports have indicated a reemergence of *B. quintana* infections among the homeless population in modern cities in both Europe and the United States [6, 9, 86, 167]. Significant seroprevalence of *B. quintana* was noted in France [16] and in the United States [170, 171]. The major predisposing factors for these *B. quintana* infections included poor living conditions and chronic alcoholism. These risk factors are also common to HIV-positive patients who develop bacillary angiomatosis [157], suggesting that it may also be transmitted by lice [11, 172]. Moreover, *B. quintana* reemerges in countries where abrupt social changes (such as war) take place, such as Africa [15] and Russia [7], and in countries where it was previously unknown, such as Peru [36].

**Pathophysiology.** Pathological lesions, characteristic of *B. quintana*– or *B. henselae*–induced bacillary angiomatosis, reveal tumor-like capillary lobules [173]. Proliferating endothelial cells may protrude into or occlude the vascular lumina. Interactions between members of the genus *Bartonella* and eukaryotic cells have been investigated for a long time. Recent work in our laboratory confirms these findings; experiments suggest that *B. quintana* is phagocytosed by endothelial cells in vitro and exists intracellularly in vacuoles [158]. The association of *Bartonella* species with neovascularization and the regression of lesions when antimicrobial agents are administered suggest that the microorganisms themselves stimulate the angiogenesis [173]. Koehler et al. [10] recently reported that when *B. quintana* is inoculated into bovine endothelial cells, the cell monolayers remain intact and viable for longer periods than do the uninfected monolayers. Cell growth was clearly enhanced in infected cultures, and infected cells became larger and more spindle-shaped [174]. As this in vitro model reproduced some of the histological findings associated with bacillary angiomatosis, we have suggested that *B. quintana* may induce neovascularization through the secretion of angiogenic factors, as previously proposed for *B. bacilliformis* [100, 174]. An extracellular round to icoshedral particle with a diameter of 40 nm has been detected in the supernatant collected from cultures of *B. henselae* [175]. This contained a 14-kb linear DNA segment and corresponded to a bacteriophage particle [98, 176]. It encodes a 36-kDa protein named PapA. Although some pathophysiological mechanisms for the induction of bacillary angiomatosis lesions by *B. quintana* have been proposed, angioprolific lesions have not been reported to occur
either in patients with trench fever or in patients with \textit{B. quintana}–induced endocarditis.

\textbf{Clinical manifestations.} Trench fever is the main clinical form of \textit{B. quintana} infection. The incubation period is between 15 and 25 days. Clinical manifestations range from asymptomatic to severe, life-threatening illness. The presentation most often reported corresponds to a febrile illness of acute onset of a periodic nature accompanied by headache and pain in the legs. Headache is most often severe, at the front of the head and behind the eyes. Symptoms may therefore suggest meningitis. Pain may spread to legs and is often felt in the bones. Conjunctival congestion is frequently noticed. Splenomegaly is often present. Fever is periodic, and the interval between attacks is usually between 4 and 8 days, with 5 days being the most commonly observed period. The term “quin-tan fever” refers to the recurring 5-day attacks. Each succeeding attack is usually less severe. Major polymorphonuclear leukocytosis is often observed. Persistent bacteremia has long been recognized [41]. Recently, many patients with \textit{B. quintana} infections have been from deprived backgrounds, usually being homeless; the poor underlying state of health of these people and the unhygienic conditions in which they live are clearly comparable to the lifestyles of patients with trench fever [177].

Kostrzewski [41] carried out a unique experiment by surveying louse feeders enrolled for typhus vaccine production. Among the 100 participants exposed, all were infected; 90 were sick and 10 were asymptomatic, of which 5 were chronically bacteremic. Among the symptomatic patients, two-thirds experienced several episodes of trench fever; these were not relapses, being several months apart. Asymptomatic carriers do not frequently have antibodies. Symptomatic patients presented with three clinical forms: classic relapsing trench fever; typhoidal with prolonged fever, splenomegaly, and a rash, resembling epidemic typhus; and an extremely mild aborting fever, in which the usual symptom was pharyngitis. Of the 10 bacteremic patients in Seattle reported by Spach et al. [167], 7 were febrile and 2 had splenomegaly. We [86] recently observed 10 homeless patients with bacteremia, of whom 8 were not febrile, 1 had pharyngitis, and none had typical trench fever. These reports emphasize the fact that there are chronic blood carriers of \textit{B. quintana} who are paucisymptomatic or asymptomatic and who constitute a reservoir of the disease.

Bacillary angiomatosis is the name given to a vascular proliferative disease that affects the skin [178]. Bacillary angiomatosis has been described in HIV-infected and immunocompetent patients [179]. Both \textit{B. quintana} and \textit{B. henselae} are considered to be etiologic agents of bacillary angiomatosis [10, 179, 180]. Several organs may also be involved, including spleen, bone marrow, and lymph nodes. Cutaneous lesions may be solitary or multiple. A specific feature is that lesions may bleed profusely when punctured. Leukopenia and CD4 cell counts of <100/mm\textsuperscript{3} have been reported most frequently in HIV-infected patients with bacillary angiomatosis [180]. In HIV-infected patients, bacillary angiomatosis may be associated with hepatic peliosis [11, 181]. Two recent works on the clinical and epidemiological aspects of HIV-infected patients with peliosis and bacillary angiomatosis outlined some specific features associated with the causative agent [11, 172]. Patients with disease due to \textit{B. quintana} were more likely to be homeless, to be alcoholic, and to have body lice than were those infected with \textit{B. henselae}. Peliosis was associated with \textit{B. henselae}, as well as lymph node lesions. Bone lesions and subcutaneous mass were associated with \textit{B. quintana}. \textit{B. quintana} has also recently been isolated from patients with bacterial endocarditis [40, 182–184], and rare cases of meningoencephalitis were reported [185].

\textbf{Diagnosis.} The three most widely used methods for isolation of \textit{B. quintana} are direct plating onto solid media, blood culture in broth, and cocultivation in cell culture [10, 40, 157, 167, 186–188]. A combination of two methods may be useful for optimizing the recovery of \textit{Bartonella} species. On blood-enriched agar, \textit{Bartonella} species are best cultivated in a humid, CO\textsubscript{2}-rich (5\%) atmosphere [148, 153, 155]. Primary isolation from the blood of infected patients may require up to 45 days of incubation before colonies become apparent. Horse and rabbit blood are reported to be more effective supplements than sheep blood [10]; in any case, freshly prepared blood-supplemented agar plates must be used [188]. Recent investigations have demonstrated the hemin dependence of \textit{Bartonella} species at 50–250 \textmu g/mL [189, 190]. The use of lysis centrifugation has been shown to enhance the recovery of \textit{Bartonella} species as well as sample congelation from blood [191]. \textit{B. quintana} was first isolated from a patient with bacillary angiomatosis by Koehler et al. [10] following the cocultivation of cutaneous biopsy material with a bovine endothelial cell line. We [40, 184] recently reported this approach when isolating \textit{B. quintana} from the blood of homeless patients with endocarditis and from the blood of two patients with chronic lymphadenopathy and lymphopenia [101, 187].

Several methods for confirming the identity of presumptive \textit{Bartonella} species have been described. The most convenient way of differentiating \textit{Bartonella} species is through the use of polyvalent antiserum [157, 192]. Cell wall fatty acid analysis has been attempted on \textit{Bartonella} species [40], but differences cannot be considered suitable markers for the confident differentiation of species. Members of the genus \textit{Bartonella} can be differentiated by the application of an extensive range of genotyping, including 16S rRNA gene sequencing [151, 157, 179, 193–195], citrate synthase gene analysis [40, 152b, 157, 179, 194, 196], DNA hybridizations, and pulsed-field gel electrophoresis of genomic DNA [157, 161]. Further genotypic methods have been used to demonstrate intraspecies differences [161, 197].

Serological diagnosis of trench fever originally relied on passive hemaggulination [198]. The current authors described a cross-reaction with 1 of 11 sera taken from patients with Q fever. Presently, diagnosis of infections due to \textit{Bartonella} species relies
on the immunofluorescent antibody test and ELISAs. However, in most HIV-infected patients, a significant antibody response is not obtained. In persons with *Bartonella*-induced endocarditis, very high levels of antibodies have been detected [40]. Finally, in our laboratory, trench fever or bacteremia in the homeless population is usually associated with a low titer by immunofluorescent antibody testing (100–400), endocarditis is associated with higher titers (≥800), and patients with bacillary angiomatosis have no antibodies. The specificity of antibody estimation tests has been questioned. A current serological test may not distinguish a response to *B. quintana* from that to *B. henselae*. Only antibodies to *B. quintana* are obtained for trench fever, and in cat scratch disease, half of patients have significantly more antibodies to *B. henselae* than to *B. quintana*. Endocarditis cannot usually be attributable to the specific pathogen on the basis of serology alone.

**Treatment.** There are very few data on the antibiotic susceptibility of *B. quintana* in axenic media [199, 200]. We evaluated the susceptibilities of nine *B. quintana* isolates in horse blood-supplemented Columbia agar [201]. All isolates were highly susceptible to β-lactams but not to oxacillin and cephalothin. The MIC<sub>90</sub> of aminoglycosides ranged from 1 to 4 μg/mL, with gentamicin being more effective. Erythromycin, doxycycline, and rifampin were also efficient, as well as roxithromycin, azithromycin, and clarithromycin. Large variations were noted in susceptibility to the fluoroquinolone compounds.

Published observations on efficacy of antibiotic therapy are scarce because most cases of trench fever were reported before the antibiotic era. Successful treatments with tetracycline [202] or chloramphenicol [140] have, however, been reported. Data on the requirements for the effective treatment of *Bartonella*-induced endocarditis are scarce because few cases have yet been reported. Successful treatment has been reported with complex regimens consisting of intravenous amoxicillin combined with gentamicin [40]. Isolation of *Bartonella* species was reported in one patient with bacillary angiomatosis receiving gentamicin and one receiving cephalosporin, but neither patient received either macrolides or tetracyclines, the preferred antibiotic treatment [11]. We currently recommend the combination of doxycycline and gentamicin.

**R. prowazekii**

The origin of typhus is controversial. Some authors consider it to be an old European disease that caused the Athens plague. Others believe that the reservoir is extrahuman and is of American origin, as shown by its presence in isolates from flying squirrels. However, as Zinsser [1] stated, epidemic typhus has probably caused more deaths than all of the wars in history. Transmission of epidemic typhus by the body louse was demonstrated by Nicolle, who obtained the Nobel prize for this discovery [42, 163, 203]. The main reservoir, except in the United States, appears to be in humans, because lice die of the infection. Humans who contract typhus retain some rickettsiae for the rest of their lives. Under certain stressful conditions, they may relapse and develop Brill-Zinsser disease, a milder but bacteremic form of typhus [204]. The bacteremia may then allow feeding lice to become infected and to start a new epidemic. During this century, more cases of typhus have been observed in Russia than in any other country. It is difficult to confirm that diseases classically considered to be typhus were in fact epidemic typhus before the description of the clinical entity and before its epidemiological situation was defined [205, 206]. However, the Napoleonic Wars were an example of the terrible consequences of a combination of war and cold: the Grand Army marched to Moscow with 550,000 men and only 3,000 came back. It is likely that 20% of the troops died of typhus [1]. Typhus reemerged during World War I, but the Russians experienced the most terrible outbreak during the revolution between 1917 and 1925, when 25 million people were infected and 3 million died [32]. During World War II, typhus was prevalent in northern Africa and southern Italy in Naples and in central and eastern Europe, where terrible outbreaks occurred in concentration camps [207]. Typhus has slowly declined since the end of World War II, and the last reports of outbreaks were in Africa [208–213]. Only a few reports have mentioned its presence in the Americas, such as in Guatemala [214] and in the United States in association with flying squirrels [208–213, 215, 216]. It has also been reported in China [34]. Until recently, typhus was considered a disease of the past, and in 1995 it was suspected to be prevalent only in Ethiopia [217]. No cases had been recorded in eastern Europe, including Russia, since the 1980s, nor in Rwanda, Burundi, Uganda, and Nigeria, which were regular foci [82]. Few data were obtained from other mountainous tropical countries, such as Tibet, Nepal, or Peru, which were still louse-infested. However, since 1995, typhus has dramatically reemerged. A large outbreak was reported in Burundi in 1997 [15, 17, 218], in which 100,000 people were estimated to be infected. Sporadic cases were reported in northern Africa [219]. Small outbreaks were observed in Russia in 1997 [103] and in Peru in 1998 [36], and a case from Algeria was observed in 1998 (unpublished data). Typhus should be considered a serious threat, even in developed countries, when body lice are prevalent, as it has the most serious epidemic potential of all rickettsiae.

**The bacterium.** Bacteria of the Rickettsiales order are short, gram-negative bacillary microorganisms that retain basic fuchsin when stained by the Gimenez method [91] and grow in axenic media [199, 200]. They are often enclosed in a vacuole [92, 220]. The typhus group rickettsial genome size is small (1.1
Mb) and consists of a single circular chromosome when whole sequencing is performed [221].

Phylogenetic analysis of the rickettsiae is based on comparisons of 16S rRNA and citrate synthase gene sequences [222–224]. These studies have confirmed the evolutionary unity of the genus (figures 4 and 8). Traditional identification methods used in bacteriology cannot be applied to rickettsiae because of their strictly intracellular nature. For a long time, serological typing by microimmunofluorescence with mouse antisera has remained the reference method for the identification of rickettsiae [225]. Regnery et al. [226] described the usefulness of restriction fragment length polymorphism analysis of PCR-amplified fragments of the citrate synthase. This was later coupled with restriction fragment length polymorphism analysis of an rOmpB-encoding gene fragment [227, 228]. Restriction fragment length polymorphism analysis of the gene coding for a 17-kDa protein has also been used [229].

**Infection in lice.** The louse acquires *R. prowazekii* after feeding on an infected human but does not become infective until 5–7 days later. Transmission of *R. prowazekii* from the louse to the human occurs by contamination of the bite site with feces containing rickettsiae or by contamination of conjunctivae or mucous membranes with the crushed bodies or feces of infected lice. Infection through aerosols of feces-infected dust has been reported and provides the main risk of contraction of typhus for the physician. Persons with Brill-Zinsser disease provide a mechanism for the interepidemic survival of *R. prowazekii*. If a person with recurrent *R. prowazekii* infection is simultaneously infested with lice, an epidemic focus of *R. prowazekii* can become established. When rickettsiae are ingested as part of a blood meal, they infect the midgut epithelial cells of the louse and multiply rapidly. As a result of the excessive growth of *R. prowazekii*, infected epithelial cells enlarge and eventually burst, releasing the rickettsiae into the gut lumen. Massive quantities of rickettsiae are discharged in the feces and can remain infective for up to 100 days. As ruptured epithelial cells are not replaced, infection with *R. prowazekii* leads to the death of the louse. The rupture of digestive epithelium allows the blood to pass through the intestine and the louse becomes red. Infected red lice die shortly thereafter. Typhus has also been named “red louse disease.” Bozeman et al. [211] were able to isolate *R. prowazekii* from *Glaucomys volans volans*, the eastern flying squirrel, in the United States. Fleas and lice from flying squirrels were also shown to be infected.

**Pathophysiology.** Studies on the difference in virulence between *R. prowazekii* isolates have shown no correlation between fatality rates in humans and those in guinea pigs or mice [230, 231]. Isolates from fatal human cases are unable to produce fatal illness in guinea pigs and, consequently, results of studies on animals used in experiments cannot be compared with disease in humans. A highly virulent strain, Madrid, became avirulent for guinea pigs after a few passages in embryonated eggs [232]. It was not pathogenic in human volunteers and was proposed as an attenuated vaccine.

After inoculation, rickettsiae spread throughout the body via the bloodstream, enter endothelial cells, and proliferate intracellularly until the cell bursts and releases rickettsiae into the extracellular space. *R. prowazekii* has the ability to injure cells directly in the absence of immune and inflammatory responses. Cellular injury results in the pathological hallmarks of all rickettsial infections: widespread vasculitis with increased vascular permeability, edema, and activation of humoral inflammatory and coagulation mechanisms. As illness advances, progressive endothelial damage leads to widespread vascular dysfunction. In addition, rickettsia-induced cell damage leads to the accumulation of lymphocytes and macrophages around small blood vessels. In severe infection, endothelial damage results in permeability changes and the passage of plasma and plasma proteins from the intravascular compartments to the interstitium. In addition, endothelial injury leads to disruption of vessel integrity, manifesting as microscopic and macroscopic foci of hemorrhage [233].
Table 5. Clinical symptoms and laboratory data for patients with epidemic typhus.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>[15] 60</td>
</tr>
<tr>
<td>Fever</td>
<td>100 100</td>
</tr>
<tr>
<td>Headaches</td>
<td>100 100</td>
</tr>
<tr>
<td>Myalgias</td>
<td>100 70</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>43</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase level</td>
<td>63</td>
</tr>
<tr>
<td>Increased alanine aminotransferase level</td>
<td>35</td>
</tr>
<tr>
<td>Increased bilirubin level</td>
<td>20</td>
</tr>
<tr>
<td>Increased serum creatinine level</td>
<td>2</td>
</tr>
<tr>
<td>Hematuria</td>
<td>44</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>28</td>
</tr>
<tr>
<td>Rash (any)</td>
<td>25 38</td>
</tr>
<tr>
<td>Purpuric eruption</td>
<td>10 33</td>
</tr>
<tr>
<td>Delirium or confusion</td>
<td>80 18</td>
</tr>
<tr>
<td>Coma</td>
<td>4</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>56 42</td>
</tr>
<tr>
<td>Cough</td>
<td>70 38</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 7</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>8 13</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>15 53</td>
</tr>
</tbody>
</table>

NOTE. Data are %.

Thrombopenia often occurs in patients with advanced and severe illness. Vasculitis may be accompanied by mural and intimal thrombi in small vessels surrounded by inflammatory infiltrates consisting of macrophages, lymphocytes, and plasma cells. These lesions may occur focally throughout the CNS, where they are called typhus nodules. These lesions may be associated with secondary changes induced by minute foci of hemorrhage. As the vasculitis of *R. prowazekii* infection is generalized, virtually any organ may be involved [164, 234].

**Clinical manifestations.** Typhus begins abruptly (table 5). Headache, myalgias, and nonspecific constitutional symptoms such as malaise, anorexia, chills, and fever are common. After an incubation period of 10–14 days, the majority of patients with epidemic typhus develop a malaise and vague symptoms before the onset of fever and severe headache [82]. Most patients complains of fever, chills, myalgias,arthralgias, and anorexia early in the course of their illness. In a recent study in Burundi, a coughing attitude due to myalgia, named “sutama,” was reported [15]. A cough is frequent, as well as confusion and stupor. Most patients develop a skin rash that classically begins on the trunk and spreads to the periphery. The rash may be macular, maculopapular, or petechial and it may be difficult to detect on dark-skinned persons. Rarely, patients with severe cases may develop gangrene of the distal extremities, necessitating amputation. The majority of patients with epidemic typhus manifest one or more abnormalities of function of the CNS, such as signs of meningeal irritation or signs of focal or generalized cortical dysfunction ranging from seizures to confusion, drowsiness, and coma as well as hearing loss [235]. Thrombocytopenia, jaundice, and abnormal liver function tests may occur in severe cases. Clinical and electrocardiographic evidence of myocarditis [236] may occur in a small percentage of patients. Pulmonary involvement may manifest as interstitial pneumonitis, bronchitis, or bronchiolitis [236]. The disease is fatal in 10%–30% of patients, depending on underlying diseases and on the nutritional state of the host. Since a single dose of 200 mg of doxycycline will save the patient, any suspected case should be treated, as prompt reaction to this treatment could be diagnostic for the infection. Recrudescence typhus or Brill-Zinsser disease can appear in patients who had totally recovered from epidemic typhus, years after the onset of the first infection [204].

**Diagnosis.** Typhus is usually suggested by the presence of typical clinical findings such as fever, headaches, and skin rash in patients with body lice or in persons who are living in crowded, cold, and unhygienic circumstances. Typhus often occurs in clusters, but it may also occur as isolated illness. Differentiation between increases in IgG and IgM antibody titers may not help to distinguish between a primary infection and Brill-Zinsser disease [237]. As with other rickettsial diseases, a diagnosis of typhus can be confirmed by culture at a few large medical or research centers. Biopsy of a skin rash can lead to a definitive diagnosis by demonstrating the characteristic changes of rickettsial vasculitis and the presence of rickettsiae in tissue by use of fluorescent antibody conjugates. A diagnosis of recent epidemic or murine typhus rickettsial infection can be established by demonstrating a fourfold or greater rise in titer of antibody in properly collected acute and convalescent serum samples. The immunofluorescent antibody test can lead to a definitive diagnosis by demonstrating the characteristic changes of rickettsial vasculitis and the presence of rickettsiae in tissue by use of fluorescent antibody conjugates. A diagnosis of recent epidemic or murine typhus rickettsial infection can be established by demonstrating a fourfold or greater rise in titer of antibody in properly collected acute and convalescent serum samples. The immunofluorescent antibody test can distinguish between IgM and IgG antibody responses. For decades, the Weil-Felix reaction, which is based on cross-reaction between antibodies to rickettsiae and *Proteus* antigens, has been used to diagnose the various forms of typhus fever. Both false-negative and false-positive results are noted and are important problems. Techniques using PCR technology have been used to diagnose typhus in blood and to detect these organisms in their vectors [15, 17, 231, 239]. The limited availability of PCR technology makes this diagnostic method impractical and largely limited to research centers. In our laboratory, we use both lice and blood collected as drops on filter paper to perform serological testing on a large scale for field samples [240, 241]. Both techniques are extremely efficient methods of collecting diagnostic samples and can be sent to reference laboratories without any specific transportation system. Serological testing can be done by ELISA [242, 243], latex test [244], or immunofluorescence [243, 245, 246]. Cross-reactions occur within the typhus group [15], between typhus and spotted fever agents [247], and between *Rickettsia, Legionella*, and *Proteus* species [248].
Treatment. In vitro susceptibility has been tested in lice [45, 249] and in cells [250, 251]. Tetracycline and chloramphenicol are the only effective treatments for epidemic typhus [252–254]. In areas of the world where diagnostic facilities are unavailable or inaccessible, chloramphenicol is widely used as an empirical treatment, since its broad spectrum includes other serious illness, such as meningococcemia and typhoid fever, illnesses that can initially mimic epidemic typhus. However, many physicians prefer to use tetracycline for all typhus diseases, as it is cheaper and safer. Most patients treated with either antibiotic improve markedly within 48 hours after initiation of therapy. In fact, failure to show a response within 48–72 hours of starting empirical treatment is often considered to be clinical evidence that a rickettsial disease is not present.

A single dose of 200 mg of doxycycline is extremely efficient [15]. Few or no relapses are observed [137, 254, 255] with this treatment, which should be prescribed for any suspected case, including those in children, as the risk of tooth staining with such a regimen is not demonstrated. Ciprofloxacin should be avoided, following evidence from a case report of a patient misdiagnosed as having typhoid who died from typhus after treatment with this compound, despite in vitro efficiency [256].

Vaccination. The first vaccine was developed by Weigl in Poland in lice [249]. Later, the Madrid E nonpathogenic strain, the Cox vaccine egg (embryo-grown), and the Durand vaccine (rat-grown) were used successfully [43]. However, because antibiotic treatment is so efficient, vaccine was not considered a priority. The huge recent outbreak in Africa has resulted in different opinion as to the potential use of a vaccine. Indeed, an outbreak of meningococcal meningitis was controlled within 3 months with a vaccine [257], whereas >1 year was necessary for the eradication of typhus [15].

Conclusions

It is feasible that lice can transmit any agent of chronic bacteremia that is ingested with the blood meal and capable of surviving in the insect’s midgut. Indeed, lice have been demonstrated to be capable mechanical transmitters for virtually all microorganisms tested, including Rickettsia species and Coxiella burnetii [95]. However, as yet, only R. prowazekii among the rickettsiae has been implicated in in vivo transmission. The transmission potential of the louse may be influenced not only by factors intrinsic to the vector but also by the length of the bacteremic period in the host. Thus, bacteria, such as spotted fever group rickettsiae and C. burnetii, that infect blood for only a short length of time during their pathogenic processes are likely to be far more difficult to disseminate by transmission by horizontal vectors. Among the Bartonella species, B. bacilliformis may have a good potential to be louse-transmitted. Like B. quintana, this bacterium is thought to infect only humans, and infection can manifest as chronic bacteremia [100]. These bacteremias can be clinically asymptomatic, and therefore their duration is not curtailed by treatment. The massive HIV epidemics provide a greatly enlarged number of persons specifically susceptible to B. henselae bacteremia. As these epidemics are more devastating in less-developed countries where hygiene may be poor, the dissemination of this species by lice is feasible. Other tick-borne Borrelia species may be transmitted by lice, and although as yet no viruses have been identified as being transmitted by this vector, this should be considered. It is impossible to predict the body louse’s future, as this depends mainly on socioeconomic parameters. We are lucky that head lice, which are so prevalent in developed countries despite repeated efforts to eradicate them [2, 4], do not presently transmit diseases. However, should this situation change, it would undoubtedly lead to a whole new spectrum of louse-transmitted diseases.

References


