The Body Louse as a Vector of Reemerging Human Diseases

Didier Raoult and Véronique Roux

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
### Table 1. Bacterial infections transmitted by body lice.

<table>
<thead>
<tr>
<th>Infection in lice</th>
<th>Rickettsia prowazekii</th>
<th>Borrelia recurrentis</th>
<th>Bartonella quintana</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease in lice</td>
<td>Gut, intestinal, generalized</td>
<td>Hemolymph</td>
<td>Gut, intestinal</td>
</tr>
<tr>
<td>Human contamination</td>
<td>Yes (red louse)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Survival</td>
<td>Louse feces</td>
<td>Louse hemolymph</td>
<td>Louse feces</td>
</tr>
<tr>
<td>Disease in human relapse</td>
<td>Yes</td>
<td>Yes, usually one, for ~2 days</td>
<td>Yes, usually several (quintan fever)</td>
</tr>
<tr>
<td>Chronic carriage</td>
<td>Human (+ sylvatic)</td>
<td>Human</td>
<td>Human</td>
</tr>
<tr>
<td>Reservoir</td>
<td>Yes</td>
<td>Human</td>
<td>Human</td>
</tr>
<tr>
<td>Disease name</td>
<td>Epidemic typhus, “jail fever”</td>
<td>Relapsing fever (“yellow fever”)</td>
<td>Trench fever, quintan fever</td>
</tr>
<tr>
<td>Fatality rate (without treatment)</td>
<td>30%</td>
<td>10%-40%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Treatment</td>
<td>Doxycycline, 200 mg once</td>
<td>Tetracycline</td>
<td>Doxycycline and gentamicin</td>
</tr>
</tbody>
</table>

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 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

### Table 2. Classification of lice among arthropods of medical interest.

<table>
<thead>
<tr>
<th>Class</th>
<th>Order</th>
<th>Family</th>
<th>Species</th>
<th>Bacteria transmitted</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insecta</td>
<td>Siphonaptera</td>
<td>Pulicidae</td>
<td><em>Rickettsia typhi</em></td>
<td><em>Murine typhus</em></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td><em>Yersinia pestis</em></td>
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<td></td>
<td></td>
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<td><em>Bartonella henselae</em></td>
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<td></td>
<td></td>
<td></td>
<td><em>Rickettsia felis</em></td>
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<tr>
<td></td>
<td>Brachycera</td>
<td>Glossinidae</td>
<td><em>Plague</em></td>
<td></td>
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<tr>
<td></td>
<td>Hemiptera</td>
<td>Cimicidae</td>
<td><em>Cat scratch disease</em></td>
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<tr>
<td></td>
<td></td>
<td>Reduviidae</td>
<td><em>California flea</em></td>
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<td></td>
<td>Diptera</td>
<td>Culicidae</td>
<td><em>Rickettiosis</em></td>
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<td></td>
<td>Anoplura</td>
<td>Pediculidae</td>
<td><em>Bartonella bacilliformis</em></td>
<td></td>
<td><em>Verruga peruana</em></td>
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<tr>
<td>Arachnida</td>
<td>Acarina</td>
<td>Phthiridae</td>
<td><em>Pediculatus capitis</em> (head louse)</td>
<td></td>
<td><em>Trench fever</em></td>
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<td></td>
<td></td>
<td>Ixodidae</td>
<td><em>Pediculatus humanus</em> (body louse)</td>
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<td></td>
<td>Aragasidae</td>
<td><em>Relapsing fever</em></td>
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<td></td>
<td>Trombiculidae</td>
<td><em>Borrelia recurrentis</em></td>
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<tr>
<td></td>
<td>Sacropodida</td>
<td><em>Borrelia species</em></td>
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<td></td>
<td>Macronyssida</td>
<td><em>Ehrlichia species</em></td>
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Body Louse as Disease Vector

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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 subspe-
cies, 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. Eryth-
rocytes 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.

![Figure 1. Body louse observed by electron microscopy.](image1)

![Figure 2. Egg of body louse in cotton tissue (electron microscopy).](image2)

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 mat-
ing 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 ad-
here 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 physi-
ology. 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 dura-
bulity 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 thus 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.ashing the worn clothes with hot water allows them to be wrung 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 a 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 in 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. Louse-transmitted diseases, especially epidemic typhus, are more frequently reported during winter and early spring [32]. 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, 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, and in Peru [36]. In infested communities, the proportion of people parasitized by lice can be very high. A recent study showed that two-thirds of Ethiopian students are infested with lice [35]. The louse is transmitted by body contact; thus, ural promiscuity also favors infestation. Infestation with lice more frequent during wars, in trenches and in jail, where soldiers 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 lice have remained extant but have been slowly declining, as witnessed by the fall in the number of reports of louse-associated diseases in the 1980s. Widespread louse infestation is thought 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, 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, fatigue, 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
R. prowazekii can remain viable in feces for 3 months, louse body. 34% had >25, and only 5% had >200 [35]. As study found that 36% of infected students had < 10 lice on their 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 antibiotic 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].

Boucharine 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].

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 does not seem to be a practical solution.
Body Louse as Disease Vector

Requesting the detection of bacteria in blood-sucking arthropods, such as body lice, is an important aspect of disease control. In this context, the body louse is a significant vector for transmitting bacterial pathogens. The body louse can transmit various bacterial diseases, including typhus and lice-borne relapsing fever.

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 clothing 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.

Recommendations of the World Health Organization for e-scale use of insecticides.

Potential an appropriate method in most countries, but spraying 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 refined method, which has some lasting benefit in reducing the number of vectors, is the use of insecticides such as 10% DDT, 1% malathion, or 1% permethrin dust [65]. Since body lice spend a significant part of their life in clothing, where they also lay their eggs, there is no need to take any delousing action on the linen. Neither shaving nor bathing is necessary to rid the body of lice [26]. In addition, there is no need to disinfect blankets, sheets, or other belongings, with the exception of recently used blankets or clothes. Recently, the therapeutic efficacy of compounds orally eradicated lice has been reported. Ivermectin, a macrocyclic lactone, causes paralysis in many nematodes and arthropods [66]. It has also been used successfully in the treatment of onchocerciasis and is effective for the treatment of lice-infected swine [66]. It is mainly used for the treatment of onchocerciasis. It has been used for the treatment of lice-infected wounds 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 for 10 days to avoid relapses [69, 70]. Crotamoxazole has also been reported as efficient in the treatment of head lice. However, these compounds are not currently recommended for body lice.

In the future, large-scale use of insecticides is necessary, the proposal by the World Health Organization [39] (figure 2) should be used.

Detection of Bacterial Pathogens in the Body Louse

Detection of bacteria in blood-sucking arthropods, such as 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, and the ITS1 and the primers BF/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
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 mummified Egyptians [2] and pre-Columbian Incas [1]. Thus, speciation of the louse predatesthe 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 duttoni, 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-
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 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
organisms/mm³ 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 mammalian 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 epistaxis 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>
<thead>
<tr>
<th>Condition</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
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</tr>
<tr>
<td>Headaches</td>
<td>84</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>52</td>
</tr>
<tr>
<td>Myalgias</td>
<td>38</td>
</tr>
<tr>
<td>Joint pain</td>
<td>29</td>
</tr>
<tr>
<td>Disturbed consciousness</td>
<td>9</td>
</tr>
<tr>
<td>Vomiting or nausea</td>
<td>35</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4</td>
</tr>
<tr>
<td>Cough</td>
<td>44</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>13</td>
</tr>
<tr>
<td>Jaundice</td>
<td>10</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>27</td>
</tr>
<tr>
<td>Splenomegaly</td>
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</tr>
<tr>
<td>Conjunctivitis</td>
<td>21</td>
</tr>
<tr>
<td>Petechial spots</td>
<td>34</td>
</tr>
<tr>
<td>Mucosal bleeding</td>
<td>9</td>
</tr>
<tr>
<td>Death ratio</td>
<td>4 (treated)</td>
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</tbody>
</table>

Reference

Table 3. Symptoms associated with louse-borne relapsing fever.

<table>
<thead>
<tr>
<th>Symptom</th>
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<th>[107]</th>
<th>[109]</th>
<th>[127]</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
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<td>37</td>
<td>389</td>
<td>2,073</td>
</tr>
<tr>
<td>Fever</td>
<td>100</td>
<td>73</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>Headaches</td>
<td>84</td>
<td>88</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>52</td>
<td>25</td>
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<td></td>
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<tr>
<td>Myalgias</td>
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<tr>
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<td>51</td>
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<td>Disturbed conscious</td>
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<td>19</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4</td>
<td>32</td>
<td>9</td>
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<tr>
<td>Cough</td>
<td>44</td>
<td>66</td>
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<tr>
<td>Epistaxis</td>
<td>13</td>
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<tr>
<td>Jaundice</td>
<td>10</td>
<td>0</td>
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<tr>
<td>Hepatomegaly</td>
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<td>54</td>
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<tr>
<td>Mucosal bleeding</td>
<td>9</td>
<td>29</td>
<td></td>
<td></td>
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</tbody>
</table>

NOTE. Data are %. Missing data were not reported.

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 10⁸ organisms/mm³ of blood. Between febrile periods, blood
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 hemoptyisis, hematemesis, 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 micro-

![Figure 6. Detection of Borrelia by Giemsa staining of a blood smear. Magnification, ×1,000.](cid:1999/29/October)
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 weigil [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 Grahamella 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 reclassification 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...
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, 156–167]. 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].

Kostrewski [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 isosahedral 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 B. quintana–induced endocarditis.

Clinical manifestations. Trench fever is the main clinical form of 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 “quintan fever” refers to the recurring 5-day attacks.

Several methods for confirming the identity of presumptive Bartonella species have been described. The most convenient way of differentiating Bartonella species is through the use of polyvalent antisera [157, 192]. Cell wall fatty acid analysis has been attempted on Bartonella species [40], but differences cannot be considered suitable markers for the confident differentiation of species. Members of the genus 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 hemagglutination [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 Bartonella species relies...
United States, appears to be in humans, because lice die of the infection. Humans who contract typhus retain some rickettsiae discovery [42, 163, 203]. The main reservoir, except in the Joan of Arc, was the body louse. Transmission of epidemic typhus by the body louse was demonstrated by Nicolle, who obtained the Nobel prize for this discovery [42, 163, 203].

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 re-emerged. 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 association with eukaryotic cells. The advent of molecular taxonomic methods, specifically 16S rRNA analysis, has enabled the determination of phylogenetic relationships between bacterial species [89] and placed Rickettsia species within the α subgroup of Proteobacteria [195] (figure 8). Rickettsiae live only intracellularly, although not enclosed by a vacuole [92, 220]. The typhus group rickettsial genome size is small (1.1
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 Glaucomyys 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].
Thrombocytopenia 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 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 of 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]. Epidemic and endemic typhus (due to *R. typhi*) cannot be differentiated by serology, unless Western blot and/or cross-adsorptions of sera are done [15, 17, 238]. 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 and Brill-Zinsser disease [237]. 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].

**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]</td>
</tr>
<tr>
<td>Fever</td>
<td>[82]</td>
</tr>
<tr>
<td>Headaches</td>
<td>102</td>
</tr>
<tr>
<td>Myalgias</td>
<td>100</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>43</td>
</tr>
<tr>
<td>Increased aspartate</td>
<td>63</td>
</tr>
<tr>
<td>aminotransferase level</td>
<td>35</td>
</tr>
<tr>
<td>Increased bilirubin level</td>
<td>20</td>
</tr>
<tr>
<td>Increased serum creatinine</td>
<td>2</td>
</tr>
<tr>
<td>level</td>
<td>44</td>
</tr>
<tr>
<td>Hematuria</td>
<td>28</td>
</tr>
<tr>
<td>Rash (any)</td>
<td>25</td>
</tr>
<tr>
<td>Purpuric eruption</td>
<td>10</td>
</tr>
<tr>
<td>Delirium or confusion</td>
<td>80</td>
</tr>
<tr>
<td>Coma</td>
<td>4</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>56</td>
</tr>
<tr>
<td>Cough</td>
<td>70</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>8</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>15</td>
</tr>
</tbody>
</table>

**NOTE.** Data are %.
Body Louse as Disease Vector

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 meningococemia 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 a 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


