

Rickettsia *proWazekii* Infections

Epidemic typhus,
Typhus fever,
Louse-borne typhus fever,
Typhus exanthematicus,
Classical typhus fever,
Sylvatic typhus,
European typhus,
Brill-Zinsser disease, Jail fever

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Importance

Rickettsia prowazekii is a prokaryotic organism that is primarily maintained in human populations, and spreads between people via human body lice. Infected people develop an acute, mild to severe illness that is sometimes complicated by neurological signs, shock, gangrene of the fingers and toes, and other serious signs. Approximately 10-30% of untreated clinical cases are fatal, with even higher mortality rates in debilitated populations and the elderly. People who recover can continue to harbor the organism inapparently. It may re-emerge years later and cause a similar, though generally milder, illness called Brill-Zinsser disease. At one time, *R. prowazekii* regularly caused extensive outbreaks, killing thousands or even millions of people. This gave rise to the most common name for the disease, epidemic typhus. Epidemic typhus no longer occurs in developed countries, except as a sporadic illness in people who have acquired it while traveling, or who have carried the organism for years without clinical signs. In North America, *R. prowazekii* is also maintained in southern flying squirrels (*Glaucomys volans*), resulting in sporadic zoonotic cases. However, serious outbreaks still occur in some resource-poor countries, especially where people are in close contact under conditions of poor hygiene. Epidemics have the potential to emerge anywhere social conditions disintegrate and human body lice spread unchecked.

Etiology

Rickettsia prowazekii is a pleomorphic, obligate intracellular, Gram negative coccobacillus in the family Rickettsiaceae and order Rickettsiales of the α -Proteobacteria. It belongs to the typhus group of the *Rickettsia*. The disease associated with this organism is usually called epidemic typhus, although some authors use the term "sylvatic typhus" for human illnesses associated with flying squirrels. Strains of *R. prowazekii* may differ in virulence; however, a genetic analysis suggested that the strains found in squirrels are similar to other *R. prowazekii* and do not belong to a different subspecies.

Species Affected

In the U.S., the southern flying squirrel (*Glaucomys volans*) serves as a reservoir host for *R. prowazekii*. There was no evidence of infection in nearby eastern gray squirrels (*Sciurus carolinensis*) during some investigations. Antibodies were also absent from white-footed mice (*Peromyscus leucopus*), eastern ground squirrels (*Tamias striatus*), opossums (*Didelphus marsupialis*) and raccoons (*Procyon lotor*). One study found no evidence for *R. prowazekii* in northern flying squirrels (*Glaucomys sabrinus*) in California. Guinea pigs and voles of the genus *Microtus* can be infected experimentally by intraperitoneal inoculation, a route that bypasses normal immune defenses.

There is currently little or no evidence that *R. prowazekii* infects other animals. Some older studies (i.e., from the 1960s or earlier) reported finding antibodies to this organism in various domesticated and wild animals, including wild rodents. However, most commonly used serological tests cross-react with other species of *Rickettsia*, and the significance of these antibodies is unclear. In a few reports from the 1950s and 1960s, *R. prowazekii* was isolated from goats, sheep and a donkey, and from ticks collected from various livestock including ruminants and camels. Other groups were unable to isolate it from various domesticated or wild species, and one study found antibodies to other rickettsia but not *R. prowazekii*. Experimental infections, most dating before 1975, demonstrated limited or no replication in domesticated animals. Infections in lambs seemed to be limited and transient, with little replication of the agent. In one study, organisms were recovered after 5-6 days from the lung, spleen, liver and/or brain (but not lymph nodes or blood) of some lambs inoculated by intravenous or intraperitoneal routes, but only from the injection site of lambs inoculated subcutaneously. Attempts to demonstrate organisms in the blood of a limited number of experimentally infected dogs, donkeys, goat kids, calves and young camels failed. However, in some cases, animals were tested on only a few days and/or blood was not collected until 6-18 days after inoculation. Persistent seroconversion



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was reported in a donkey. Other animals also converted, but sometimes for only short periods before antibodies declined, with responses that were no stronger (and sometimes weaker) than to dead *R. prowazekii*. One group reported that rabbits could be infected experimentally with a very large dose of *R. prowazekii*, while another group could not detect organisms in the blood of rabbits given a lower dose.

Zoonotic potential

R. prowazekii affects people. In most parts of the world, humans are the only reservoir host for this organism.

Geographic Distribution

Human infections with *R. prowazekii* occur worldwide; however, cases in most countries now typically result from imported or recrudescing infections, rather than from local maintenance of the organism. Foci of endemic disease still exist in some resource-poor parts of Asia, sub-Saharan Africa, and Latin America. The situation in North Africa is unclear. At one time, endemic typhus seemed to have disappeared from this area; however, sporadic cases have since been reported in residents of the highlands of Algeria and visitors to that region.

The only known animal reservoir for *R. prowazekii*, the southern flying squirrel, occurs in eastern North America, including the U.S. and southern Canada. Zoonotic human cases have, to date, been reported only from the U.S.

Transmission

R. prowazekii is transmitted between people by the human body louse (*Pediculus humanus corporis*). Person-to-person transmission does not seem to occur when lice are absent. Lice become infected when they feed on the blood of an infected person, and excrete *R. prowazekii* in their feces after 2 to 6 days. Lice defecate when they feed, and organisms from louse feces or crushed lice can enter the body through the bite wound, other breaks in the skin or mucous membranes. *R. prowazekii* is also infectious by inhalation. Infected lice die prematurely within 2 weeks. However, *R. prowazekii* can survive in louse feces and dead lice for several weeks: in one study, this organism was still detected after 100 days. It can be transmitted between life stages of the louse (transstadial transmission), but does not pass to a new generation in eggs. Other vectors might be able to transmit *R. prowazekii*, although their role, if any, is thought to be minimal. Human head lice (*Pediculus humanus capitis*) have been infected in the laboratory, and can shed this organism. It has also been detected in various species of ticks. Transmission is theoretically possible in blood transfusions, during the period when rickettsia occur in the blood.

R. prowazekii can become latent in people, especially those who are not treated with antibiotics. There is no indication that latent carriers can pass the organism to lice while the infection is quiescent; however, *R. prowazekii* can become reactivated years after infection, probably when stress, concurrent illness or other factors cause immunity to wane. At this time, the organism can reappear in the blood and be transmitted to lice. Where *R. prowazekii* persists in people is not known, but studies in mice suggest it might be harbored in adipose tissues. Transplantation of organs containing latent rickettsia is a theoretical route of exposure.

R. prowazekii is thought to spread between flying squirrels via squirrel lice (*Neohaematopinus scuiropteri*). How squirrels transmit the disease to humans is still unclear. *N. scuiropteri* does not feed on humans, but squirrel fleas (*Orchopeas howardi*), other mammalian fleas and some mites can be infected in the laboratory and might act as mechanical vectors. Another possibility is contact with organisms in infected, dried squirrel louse feces (e.g., via inhalation), or squirrel tissues. Zoonotic infections could be transmitted between people if human body lice were present: zoonotic strains of *R. prowazekii* are capable of infecting these lice. Infections acquired from squirrels can become latent in humans, and later re-emerge.

Disinfection

R. prowazekii is expected to be susceptible to 1% sodium hypochlorite, 70% ethanol, 2% peracetic acid, 3-6% hydrogen peroxide, iodine, glutaraldehyde and formaldehyde, based on the effectiveness of these agents against other Gram negative prokaryotic organisms. *R. prowazekii* can also be inactivated by moist heat (121°C [250°F] for a minimum of 15 minutes) and dry heat (170°C [338°F] for a minimum of an hour).

Infections in Animals

Little has been published about the effects of *R. prowazekii* on southern flying squirrels; however, exposure seems to be common in some squirrel populations in the eastern U.S. Infections usually peak in the fall and early winter, when squirrel populations are concentrated in nests. One study reported that southern flying squirrels inoculated intraperitoneally with the highest doses of *R. prowazekii* died. No clinical signs were mentioned in squirrels that received more moderate doses and had rickettsia in the blood.

Experimental infections of domesticated animals including dogs, lambs, goat kids, calves, donkeys and young camels, did not result in clinical signs.

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Infections in Humans

Incubation Period

The incubation period is 1-2 weeks, with most infections becoming evident after 10-14 days. Recrudescence cases can occur years after the initial infection.

Clinical Signs

The symptoms often begin suddenly, with nonspecific initial signs that may include headache, chills, fever, myalgia (which is often severe) and malaise. Some, but not all, patients develop a rash after a few days. Small pink macules usually appear first on the upper trunk or axillae, and can spread to almost the entire body, typically sparing the face, palms and soles. As the disease progresses, the rash can become dark and maculopapular, petechial or even purpuric. However, some patients only have a transient rash. Petechiae may occasionally appear on the conjunctiva and/or soft palate. Rashes are more difficult to detect on darker skin. Other frequently reported signs include arthralgia, splenomegaly, abdominal pain, nausea, vomiting and mild thrombocytopenia. Coughing is common, and some patients develop pulmonary complications including secondary bacterial pneumonia. Conjunctivitis, diarrhea and hematuria have been reported. CNS signs of varying severity (e.g., confusion, drowsiness, seizures, coma, hearing loss) can be seen in some patients. There may also be other serious complications, including shock, renal dysfunction, myocarditis and multiple organ dysfunction. Ischemia from vasculitis can result in gangrene, usually symmetrical, of the distal fingers and toes. More extensive involvement of the extremities is possible but uncommon. The acute, febrile stage of epidemic typhus lasts approximately 2 weeks in untreated patients, but full recovery may be slow, sometimes taking up to 2-3 months. A significant number of untreated cases are fatal. Residual neurological defects are reported to be rare in patients who survive.

Brill–Zinsser disease (recrudescence typhus) resembles acute epidemic typhus, but tends to be milder, with a lower risk of death and a shorter course. Epidemic typhus acquired from flying squirrels has also been milder and shorter in many cases, although severe illnesses have been reported. Rash was barely visible or absent in some people with the zoonotic form.

Diagnostic Tests

Epidemic typhus is often diagnosed by serology. A fourfold rise in titer is diagnostic. Titers usually become detectable during the second week; thus, this test is most useful for retrospective confirmation. A number of serological tests have been described. They include indirect fluorescence antibody (IFA) tests, various agglutination tests (e.g., plate microagglutination, latex agglutination) and enzyme immunoassays such as

ELISAs and dot blot assays. Complement fixation tests were also used in the past, and may still be employed in some countries. *R. prowazekii* can cross-react with *R. typhi*, the agent of murine typhus, in some tests. Differential reactions in immunoblotting, and cross-adsorption assays, performed at reference laboratories, can distinguish these reactions. Patients with Brill–Zinsser disease usually have elevations in specific IgG but not IgM.

Organisms can be identified directly in tissue samples, including skin biopsies of the rash, with immunohistochemical or immunofluorescent staining, or polymerase chain reaction (PCR) assays. Blood can also be collected for PCR, which can distinguish *R. prowazekii* from other rickettsia, including *R. typhi*. Culture and identification of *R. prowazekii* is not usually available outside reference laboratories, as rickettsia are both fastidious and dangerous to laboratory personnel. If necessary, this organism can be cultured with a shell-vial assay using L929 cells. Inoculation into guinea pigs or embryonated eggs was commonly used in the past.

Test availability may be limited at diagnostic laboratories in areas where epidemic typhus is uncommon.

Treatment

Epidemic typhus can be treated with tetracyclines. Chloramphenicol may also be used, but it is reported to be less effective, and also carries a risk of serious drug-related side effects.

Prevention

Outside North America, epidemic typhus can be prevented by avoiding human lice. Bathing removes lice from the body, and insecticide treatment may also be recommended. Lice on clothing can be killed by laundering at 50°C (122°F). Because body lice are obligate parasites of humans and usually die within 5 days in the environment, another possibility is to keep infested clothing isolated for a week. In North America, flying squirrels should not be allowed to take up residence in attics, porches, walls or other areas of human residences. Close contact with these animals should be avoided.

There are no commercial vaccines for epidemic typhus. Experimental vaccines have sometimes been produced by the military (e.g., in the U.S.) and might be available for high-risk situations. The relevant authorities should be consulted for current information about vaccines.

Morbidity and Mortality

In most parts of the world, epidemic typhus now occurs only as sporadic cases, originating from recrudescence or imported infections. Occasional zoonotic cases are also described in North America, typically between November and February.

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Outbreaks usually occur in populations living in unsanitary, crowded conditions where lice are difficult to control. They are often associated with wars, famines, floods, and other disasters, and can occur in refugee camps. These outbreaks can be explosive. Historical outbreaks sometimes caused thousands or even millions of deaths, and serious outbreaks can still be seen in some countries. In 1997, epidemic typhus is thought to have affected more than 40,000 people in Burundi. Most epidemics occur during the colder months, when closer contact and heavier clothing facilitate lice infestations and person-to-person transmission. Underreporting may be an issue in some remote areas, particularly when the illness is mild.

The severity of a clinical case can vary with general health, age and the form of the disease. Children under the age of 10 years tend to have relatively mild cases compared to adults, while elderly or debilitated patients are particularly susceptible to serious complications. Case fatality rates up to 60% or more have been reported in untreated primary infections; however, the highest mortality rates were described in highly vulnerable populations, such as the elderly, or people who were severely undernourished. Some sources estimate that, overall, the case fatality rate is probably 10-30% in untreated cases. It is reported to be < 5% when treated.

Recrudescing typhus and zoonotic typhus are often less severe than primary, human louse-transmitted typhus, with an estimated mortality rate of 1% in recrudescing disease. Recrudescing typhus (Brill-Zinsser disease) seems to be uncommon in patients who were treated with antibiotics effective against *R. prowazekii*. No fatalities have been reported, to date, in zoonotic typhus. Nevertheless, there have been some severe cases that required intensive care.

Internet Resources

- Centers for Disease Control and Prevention (CDC)
Rickettsial (Spotted & Typhus Fevers) & Related Infections
<https://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-travel/rickettsial-spotted-typhus-fevers-related-infections-anaplasmosis-ehrlichiosis>
- European Centre for Disease Prevention and Control (ECDC). Epidemic Louse-borne Typhus
http://ecdc.europa.eu/en/healthtopics/emerging_and_vector-borne_diseases/lice-borne-diseases/Pages/Epidemic-lice-borne-typhus.aspx
- PHAC. Pathogen Safety Data Sheets
<http://www.phac-aspc.gc.ca/lab-bio/res/psds-ftss/index-eng.php>

The Merck Manual

<http://www.merckmanuals.com/professional>

World Health Organization

<http://www.who.int/>

References

- Angelakis E, Bechah Y, Raoult D. The history of epidemic typhus. *Microbiol Spectr*. 2016;4(4).
- Azad AF, Beard CB. Rickettsial pathogens and their arthropod vectors. *Emerg Infect Dis*. 1998;4(2). Available at: <http://www.cfsresearch.org/rickettsia/other/9nf.htm>.*. Accessed 4 Dec 2002.
- Badiaga S, Brouqui P. Human louse-transmitted infectious diseases. *Clin Microbiol Infect*. 2012;18(4):332-7.
- Baxter JD. The typhus group. *Clin Derm*. 1996;14:271-5.
- Bechah Y, Capo C, Mege JL, Raoult D. Epidemic typhus. *Lancet Infect Dis*. 2008;8(7):417-26.
- Bechah Y, Paddock CD, Capo C, Mege JL, Raoult D. Adipose tissue serves as a reservoir for recrudescing *Rickettsia prowazekii* infection in a mouse model. *PLoS One*. 2010;5(1):e8547.
- Botelho-Nevers E, Raoult D. Host, pathogen and treatment-related prognostic factors in rickettsioses. *Eur J Clin Microbiol Infect Dis*. 2011;30(10):1139-50.
- Bozeman FM, Sonenshine DE, Williams MS, Chadwick DP, Lauer DM, Elisberg BL. Experimental infection of ectoparasitic arthropods with *Rickettsia prowazekii* (GvF-16 strain) and transmission to flying squirrels. *Am J Trop Med Hyg*. 1981;30(1):253-63.
- Breitschwerdt EB, Hegarty BC, Davidson MG, Szabados NSA. Evaluation of the pathogenic potential of *Rickettsia canada* and *Rickettsia prowazekii* organisms in dogs. *J Am Vet Med Assoc*. 1995;207(1):58-63.
- Centers for Disease Control and Prevention (CDC). Epidemic typhus associated with flying squirrels — United States. *MMWR Morb Mortal Wkly Rep*. 1982;31(41): 555–6;561.
- Foley JE, Nieto NC, Clueit SB, Foley P, Nicholson WN, Brown RN. Survey for zoonotic rickettsial pathogens in northern flying squirrels, *Glaucomys sabrinus*, in California. *J Wildl Dis*. 2007;43(4):684-9.
- Ge H, Tong M, Jiang J, Dasch GA, Richards AL. Genotypic comparison of five isolates of *Rickettsia prowazekii* by multilocus sequence typing. *FEMS Microbiol Lett*. 2007;271(1):112-7.
- Graves S, Stenos J. Rickettsioses in Australia. *Ann N Y Acad Sci*. 2009;1166:151-5.
- Huffman J, Nettles V. Typhus and flying squirrels. Southeastern Cooperative Wildlife Disease Study (SCWDS) Briefs. 1999;15(3). Available at: http://www.uga.edu/scwds/topic_index/1999/TyphusandFlyingSquirrels.pdf.*. Accessed 3 Dec 2002.
- Imam Z, Imam E, Alfay L. Evidence of typhus infection in domestic animals in Egypt. *Bull World Health Organ*. 1966; 35(2): 123-6.
- Labruna MB. Ecology of rickettsia in South America. *Ann N Y Acad Sci*. 2009;1166:156-66.

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- Letaief A. Epidemiology of rickettsioses in North Africa. *Ann NY Acad Sci.* 2006;1078:34-41.
- McDade JE. Flying squirrels and their ectoparasites: disseminators of epidemic typhus. *Parasitol Today.* 1987;3(3):85-7.
- McQuiston JH, Knights EB, Demartino PJ, Paparello SF, Nicholson WL, Singleton J, Brown CM, Massung RF, Urbanowski JC. Brill-Zinsser disease in a patient following infection with sylvatic epidemic typhus associated with flying squirrels. *Clin Infect Dis.* 2010;51(6):712-5.
- Mokrani K, Fournier PE, Dalichaouche M, Tebbal S, Aouati A, Raoult D. Reemerging threat of epidemic typhus in Algeria. *J Clin Microbiol.* 2004;42(8):3898-900.
- Ormsbee R, Burgdorfer W, Peacock M, Hildebrandt P. Experimental infections of *Rickettsia prowazekii* among domestic livestock and ticks. *Am J Trop Med Hyg.* 1971;20(1):117-24.
- Ormsbee RA, Peacock MG, Bell EJ, Burgdorfer W. Experimental infections of lambs with *Rickettsia prowazekii*. *Am J Trop Med Hyg.* 1971;20(6):950-7.
- Parola P. Rickettsioses in sub-Saharan Africa. *Ann N Y Acad Sci.* 2006;1078:42-7.
- Perine PL, Chandler BP, Krause DK, McCardle P, Awoke S, Habte-Gabr E, Wisseman CL Jr, McDade JE. A clinico-epidemiological study of epidemic typhus in Africa. *Clin Infect Dis.* 1992;14(5):1149-58.
- Petri WA. Epidemic typhus. In: Porter RS, Kaplan JL, Lynn RB, Reddy M, eds. *The Merck manual* [monograph online]. Merck and Co.; 2017. Available at: <http://www.merckmanuals.com/professional/infectious-diseases/rickettsiae-and-related-organisms/epidemic-typhus>. Accessed 16 Feb 2017.
- Philip CB, Hoogstraal H, Reiss-Gutfreund R, Clifford CM. Evidence of rickettsial disease agents in ticks from Ethiopian cattle. *Bull World Health Organ.* 1966;35(2):127-31.
- Philip CB, Hughes LE, Lackman DB, Bell EJ. Susceptibility of certain domestic animals to experimental infection with *Rickettsia prowazekii*. *Am J Trop Med Hyg.* 1967;16(6):758-61.
- Prusinski MA, White JL, Wong SJ, Conlon MA, Egan C, Kelly-Cirino CD, Laniewicz BR, Backenson PB, Nicholson WL, Eremeeva ME, Karpathy SE, Dasch GA, White DJ. Sylvatic typhus associated with flying squirrels (*Glaucomys volans*) in New York State, United States. *Vector Borne Zoonotic Dis.* 2014;14(4):240-4.
- Public Health Agency of Canada (PHAC). Pathogen Safety Data Sheet: *Rickettsia prowazekii* [online]. Pathogen Regulation Directorate, PHAC; 2010 Jul. Available at: <http://www.phac-aspc.gc.ca/lab-bio/res/psds-ftss/rickettsia-prowazekii-eng.php>. Accessed 14 Feb 2017.
- Robinson D, Leo N, Prociw P, Barker SC. Potential role of head lice, *Pediculus humanus capitis*, as vectors of *Rickettsia prowazekii*. *Parasitol Res.* 2003;90(3):209-11.
- Sarycheva NI, Chirov PA. [Experimental infection of domestic animals with *R. prowazekii* and *R. canada*]. *Zh Mikrobiol Epidemiol Immunobiol.* 1976 Sep(9):101-4.
- Sonenshine DE, Bozeman FM, Williams MS, Masiello SA, Chadwick DP, Stocks NI, Lauer DM, Elisberg BL. Epizootiology of epidemic typhus (*Rickettsia prowazekii*) in flying squirrels. *Am J Trop Med Hyg.* 1978;27(2 Pt 1):339-49.
- Svraka S, Rolain JM, Bechah Y, Gatabazi J, Raoult D. *Rickettsia prowazekii* and real-time polymerase chain reaction. *Emerg Infect Dis.* 2006;12(3):428-32.
- Tarasevich IV, Mediannikov OY. Rickettsial diseases in Russia. *Ann N Y Acad Sci.* 2006;1078:48-59.
- Walker DH. Rickettsiae. In: Baron S, ed. *Medical microbiology*. 4th ed. New York; Churchill Livingstone: 1996. Available at: <http://www.gsbs.utmb.edu/microbook/ch038.htm>.* Accessed 4 Dec 2002.
- Washington State Department of Health. Surveillance and reporting guidelines for typhus. 2002 Oct. Available at: <http://www.doh.wa.gov/notify/guidelines/typhus.htm>.* Accessed 4 Dec 2002.
- Woodman DR, Weiss E, Dasch GA, Bozeman FM. Biological properties of *Rickettsia prowazekii* strains isolated from flying squirrels. *Infect Immun.* 1977; 16(3): 853-60.

*Link defunct as of 2017