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Rat Bite Fever: An Infectious Under Reported Bacterial Zoonotic Disease

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Abstract Rat bite fever is a potential emerging disease caused with one of two different types of bacteria: *Streptobacillus Species* and *Spirillum minus*. These bacteria are found in the mouth, nose and respiratory tract of rodents (especially rats). After handling rodents that harbor these bacteria, humans may acquire an infection, especially if they are bitten or scratched. Other close encounters with rodents, such as kissing or sharing food with one, might also result in infection. Another type of rat bite fever known as Haverhill fever can be contracted by consuming food or drink that has been contaminated with the causing bacterium. The first case of rat bite fever is in the US that was recorded in 1839. The disease occurs in both sexes, all age groups and in immunocompetent and immunocomromised individuals. In carrier rats, there are typically no clinical symptoms; opportunistic pulmonary infections or abscesses are sporadically observed. The initial symptoms of infection in humans can include headache, fever, and nausea. On the hands and feet, a red, bumpy rash that is not irritating may appear after two to four days. In comparison to typical rat bite fever, Haverhill fever frequently results in severe nausea and vomiting, and the patient may also experience sore throat. The patient with endocarditits have poor prognosis. The most effective way to diagnose rat bite fever is to isolate the pathogen in tissue or blood samples. Unfortunately, these bacteria, especially *S. minus*, can be exceedingly challenging to culture. Although not widely available, a PCR test to identify bacterial DNA would be very helpful. Antibiotics, such as penicillin, are used to treat the initial infection in cases of rat bite fever that have been proven or are highly suspected. If treatment is initiated before complications develop, it is frequently highly effective. Avoiding contact with rats is the best approach to prevent rat bite fever.

Keywords: *rat, rat bite fever, Spirillum minus, Streptobacillus Species, Zoonoses*

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1. Introduction

Emerging and re-emerging zoonoses are significant sources of morbidity and mortality in both developing and developed countries of the world, which occur in sporadic as well as epidemic forms [1,2,3]. Rat-bite fever is caused by two different bacterial strains that produce two separate types of illness; spirillosis and streptobacillosis [4]. The extremely rare Gram-negative coiled rod known as *Spirillum minus*, which is found in Asia, is the cause of spirillosis. Sodoku is another name for it. Rat-bite fever most common form is streptobacillosis, which is also referred to as epidemic arthritic erythema. *Streptobacillus* genus, most frequently *Streptobacillus moniliformis*, is the most common cause of streptobacillosis [5,6]. *Streptobacillus moniliformis* is a Gram-negative, non-motile organism that is frequently found in North America but relatively uncommon in Asia [7].

By coming in contact with rat excretions like saliva, urine, or feces-typically from rat bites or direct contact with rats-humans can become infected. However, humans can also ingest excreta through water and contaminated foods like raw milk, which can result in a condition known as Haverhill fever [4,8]. Relapsing fever, migrating polyarthritis, and a rash that frequently affects the extremities, notably the palms and soles, are the usual symptoms of the disease [9,10]. Since the initial clinical symptoms are ambiguous, clinical cases in both humans and animals may go under-diagnosed. Rat bite fever must be detected using specialized culture conditions or PCR tests [11]. For cases of rat bite fever that have been verified or are highly suspected, penicillin is the treatment of choice [12]. In this review, an effort is made to describe rat bite fever as a potential emerging bacterial zoonosis of public health significance.

2. Etiology

Several strains of the genus *Streptobacillus* and the unrelated bacterium *Spirillum minus* can both cause rat-bite fever [11]. Fastidious Gram-negative bacteria

belonging to the genus *Streptobacillus* can take the form of filaments, chains, or curved rods [13]. *Streptobacillus moniliformis* is most frequently responsible for rat-bite fever [14]. *Streptobacillus moniliformis* is a highly pleomorphic, filamentous, nonmotile, and non-acid-fast rod. Typically, the organism is arranged in clumps that are loosely entangled and chains. Its diameters range from 0.1 to 0.5 μm by 2.0 to 5.0 μm, up to 10 to 15 μm, with long, curved segments up to 100 to 150 μm. It needs specific culture conditions in order to grow, which causes growth delays or cultivation failures [15,16]. A new species of *Streptobacillus* genus that can induce rat bite fever is called *Streptobacillus notomytis*; nonetheless, human infection by this species is uncommon [17,18]. Another new species of the Streptobacillus genus, *S. felis*, has also been linked to human cases of rat bite fever in addition to *S. notomytis* [19]. *Spirillum minus* is a short, thick, gram-negative, tightly coiled spiral rod with two to six helix twists that measures 0.2 to 0.5 μm [20]. The organism has never been grown in synthetic media, and little is known about it, including its taxonomic relationships [11].

3. Hosts

Streptobacillus moniliformis appears to have the rat as its primary natural host, and it is most likely a component of the commensal flora that inhabits the rat's upper respiratory system [13]. This organism has been identified in *Rattus rattus*, the black rat, and *R. norvegicus*, the Norwegian rat, which is the ancestor of the majority of laboratory and pet rats [11]. Infection or colonization may also occur in mice, guinea pigs, gerbils, ferrets, turkeys, cats, and dogs in addition to rats [21,22,23,24]. Streptobacillary disease in turkeys and koalas has been demonstrated, while rat bite fever in nonhuman primates (rhesus macaque and titi monkey) has been documented [25]. Other than rats, no information or evidence of *S. notomytis* harboring in other animals has been documented [18]. Animal infections with *Spirillum minus* are not well understood. Rats are assumed to be the asymptomatic reservoir hosts for this bacterium. *Spirillum minus* has been linked to diseases in experimentally exposed guinea pigs, rhesus macaques, and mice [11]. Rat bite fever is a zoonotic infection, causes disease in humans [4,26].

4. Transmission

Rat bite fever is typically transmitted via a rat bite scratch or by indirect contact with rats. It can also be spread by consuming contaminated food or water with rat feces or urine [4,7,27]. Additionally, humans may consume contaminated food like unpasteurized milk and water, leading to the disease called Haverhill fever [4,8]. *Spirillum minus* is present in asymptomatic rats, but the information on transmission of this pathogen is poorly understood or not definite. Human to human transmission of zoonotic *Streptobacillus* species or *Spirillum minus* has not been reported so far [11].

5. Geographic Distribution

The first case of rat bite fever was recorded in 1839 in the US [28]. Rat bite fever, which is caused by *S. moniliformis*, is not limited to any one particular region [23]. However, infections with *Streptobacillus moniliformis* are the primary cause of the majority of rat-bite fever cases documented in North America and Europe. *Spirillum minus*, which predominates in cases of rat bite fever in Asia, is responsible for additional cases [7,10]. There aren't many reports from Africa, with the exception of one Sodoku case from Kenya [29] and two episodes of an infection linked to squirrel bites in Nigeria [30]. *Streptobacillus. notomytis* has been found as of 2021 in Australia, as well as several regions of Asia and Europe, and it is most likely ubiquitous. *Streptobacillus. felis* are recognized in Europe [11]. This microorganism's true incidence and geographic range are unknown at this time [18].

6. Clinical Signs

In carrier rats, there are typically no symptoms; opportunistic pulmonary infections or abscesses are sporadically observed. The susceptibility varies by strain in mice, and affected mice can present with either a more prolonged septicemia course or abrupt mortality from septicemia. Cervical lymphadenitis, diarrhea, conjunctivitis, cyanosis, haemoglobinuria, and weight loss are typical clinical symptoms. Suppurative polyarthritis, osteomyelitis, and abscesses may be seen in animals that make it through the disease's acute stage [31].

Infection with *S. moniliformis* in humans has been linked to two different clinical syndromes. One of these infections, Haverhill fever, was first identified in 1926 and is contracted by humans by consuming contaminated milk, food, or water that has come in contact with rats. A high incidence of pharyngitis and pronounced vomiting are the disease's hallmarks. Rat-bite fever, on the other hand, is the syndrome connected to *S. moniliformis* infection that is more typical. High fevers that start suddenly, headaches, severe migrating arthralgia, vomiting, and a rash that appears 2-4 days later are the symptoms of this disease [20,32]. Some patients may also have additional complications such meningitis, endocarditis, hepatitis, and/or localized abscesses [10]. In the absence of effective and prompt treatment, the mortality rate for rat bite fever has been reported to be as high as 13% [33]. Up to 53% of morality cases have endocarditis as the leading cause of death [34,35].

The symptoms of rat bite fever, which is caused by an infection with *Streptobacillus notomytis*, include fever, rash, polyarthritis, meningitis, hepatitis, and spondylodiscitis [17,18]. *Spirillum minus* is most likely to be the culprit behind the infection brought on by rat bites in Asia as the disease is often known as sodoku (*so*, rat; *doku*, poison). This condition differs from other rat bite fever both geographically and clinically. The bite site gets indurated and may develop an ulcer after an incubation period of roughly 14 to 18 days, and regional lymphadenopathy is also present. Frequent relapses of fevers are separated by

febrile spells that last 3 to 7 days. A violaceous red-brown macular rash that occasionally contains plaques or urticarial lesions develops in about 50% of patients. Joint symptoms are uncommon [36,37].

7. Diagnosis

It is crucial to make early investigations to identify potential infections because a rat bite fever sign resembles those of other diseases such as hemolytic uremic syndrome, Lyme disease, rheumatoid arthritis, and post infectious arthritis [38,39]. *Streptobacillus* infections can be identified using serology, molecular methods, or organism isolation. *Streptobacillus* spp. can be challenging to culture from clinical specimens because they are fastidious, require media enriched with serum, blood, or ascitic fluid to grow, and are easily overgrown by other bacteria. Sodium polyanethole sulfonate, a frequent component of aerobic blood culture media, may inhibit *Streptobacillus moniliformis* growth, and thus, leads to low negative predictive values [11,16].

Isolating the organism from the clinical specimens is the gold standard diagnostic method. In most clinical microbiology laboratories, the usual negative biochemical reactions like catalase, oxidase, nitrate, indole, citrate, and urease should be sufficient for identifying *S. moniliformis*. These characteristics include high pleomorphism, "string of beads" appearance along with cotton balls and intertwining wavy filamentous forms [40]. Several additional tests, such as gas-liquid chromatography, PCR, and 16S rRNA sequencing, are more sensitive than culture for detecting *S. moniliformis* [41]. High-throughput sequencing methods like mNGS are currently playing a bigger role in the detection of uncommon infections. With the aid of this cutting-edge technology, rat bite fever can be diagnosed and treated quickly, with remarkable results anticipated [12].

Artificial media cannot be used to culture *Spirillum minus*. Finding organisms with the typical morphology in darkfield or phase contrast preparations, or after Giemsa, Wright, or silver staining, has been the primary method for finding this organism. In cases involving humans, inoculation into mice, guinea pigs, or *Sp. minus*-free rats has been utilized to make a diagnosis if microscopy is ineffective. Using dark-field microscopy, spirochetes can be discovered in the blood of these animals after 5–15 days. There are no serological or molecular (PCR) testing available since *Sp. minus* cannot be grown [11]. Therefore, it is advised to undertake further research to develop immunological and molecular techniques for the diagnosis of *Sp. minus* infection.

8. Treatment

In the absence of complications, penicillin G is the drug of choice for the treatment of rat bite fever and 7–14-day course (400,000–600,000 IU/ day) is recommended for adults. The dose can be increased to 1.2 million IU per day, if no response is observed within 2 days. Ceftriaxone (adult dose: 1 to 2 g every 24 hours) for two weeks is also recommended [12]. Patients with penicillin allergies can take doxycycline (100 mg dose) [33]. *Steptobacillus moniliformis* is also susceptible to clindamycin, tetracycline, and erythromycin, although the standard treatment durations need to be established [10]. Additional research on chemotherapy of rat bite fever is needed.

9. Prevention and Control

There are steps that can be taken to decrease the incidence of rat bite fever cases. Rats can be eliminated from metropolitan environments, where unintentional exposure is most prevalent. People can be made aware of the dangers of possibly contaminated water and food, such as unpasteurized milk [42]. Avoid contact with rats, wash your hands and face after any contact, and apply antiseptic to any scratches [4]. Following rodent bites or scratches, the effect of prophylactic chemoprophylaxis is unknown. Sanitation, sewage, and laboratory employees must take protective measures against exposure. Never handle wild rats, whether they are living or dead [43]. Owners of exotic pets and lab workers should get immediate medical attention if they experience the typical signs of a rat bite [44].

10. Conclusion

Rat bite fever is an under-recognized and under-reported disease with an approximately 10% fatality rate, which is characterized by an abrupt onset of fever, rigors, and migratory polyarthralgias. By coming into touch with rat excretions like saliva, urine, or feces typically from rat bites or direct contact with rats-humans can become infected. Humans can also consume excreta through water and contaminated foods like raw milk. Molecular diagnosis is required, particularly in patients who have no prior history of animal exposure because the diagnosis is challenging. Clinicians should be aware of this diagnosis when the exposure history is suggestive, as the symptoms are nonspecific and can be variable. Early diagnosis and prompt treatment with antibiotics is important to avoid progression to later stages and disease complications. Further research on pathophysiology, and epidemiology is emphasized.

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Author's Contribution

All the authors contributed equally. They read the final version, and approved it for the publication.

Conflict of Interest

The authors declare that they do not have any conflict of interest.

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