AN OVERVIEW OF THE PATHOGENESIS, TRANSMISSION, AND PREVENTION STRATEGIES OF RAT–BITE FEVER IN HUMANS

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Abstract

Rat bite fever (RBF) is a zoonotic disease caused by the bacteria *Spirillum minus*, *Streptobacillus moniliformis*, and *Streptobacillus notomytis*. In 1926, an *S. moniliformis* outbreak in Haverhill, Massachusetts, linked to contaminated milk, caused "Haverhill Disease." *S. moniliformis* is prevalent in the Americas, while *S. minus* is more common in Asia. In 2018, Okinawa, Japan, documented the first human case of RBF caused by *S. notomytis* (Fukushima et al., 2018). Key animal carriers include rodents such as black rats (*Rattus rattus*) and brown rats (*Rattus norvegicus*), which asymptomatically harbor these bacteria as part of their natural flora. The disease is transmitted to humans through wounds from bites or scratches. Infected individuals typically present with high fever, rash, and painful swelling in the joints. Without treatment, the mortality rate can reach up to 10%, with complications such as myocarditis, pericarditis, and meningitis being potential causes of death. High–risk groups include individuals whose occupations involve frequent contact with rodents or those working in environments prone to rodent infestations, such as food processing facilities that often attract rodents. Treatment involves antibiotics, which significantly reduce the mortality rate. Diagnosing RBF is challenging due to the need for specific environmental conditions to isolate and culture the bacteria. This restriction is a reflection of the present knowledge gaps on the disease's pathogenic mechanisms. Prevention and control strategies focus on maintaining strict hygiene practices and avoiding contact with rodents to minimize the risk of infection.

Keywords: Rat–bite fever, Rats, Zoonosis, Humans

Introduction

Rat bite fever (RBF) is a zoonotic disease caused by three types of bacteria: *Streptobacillus minus*, *Streptobacillus moniliformis*, and *Streptobacillus notomytis*. However, cases of *S. notomytis* infection in humans are relatively rare (Hryciw, Wright & Tan, 2018; Khatib et al., 2020; Pal & Gutama, 2023). A characteristic symptom of the disease is the appearance of a red rash, which has led to an alternative name, Epidemic Arthritic Erythema. This infectious disease has been known for over 2,300 years and continues to be reported today, with numerous cases recorded over the past 50 years following rodent bites (Pannetier & Lombard, 2020). The bacteria responsible for RBF were first identified in 1914 by Christoph Schottmüller, who isolated them from the blood of a person bitten by a rat (Hagelskjaer, Sørensen & Randers, 1998; Wallemacq et al., 2022). The bacterium was initially named *Streptomyces muris ratti*. In 1925, Constantin Levaditi discovered the same bacterium in laboratory workers and subsequently renamed it *S. moniliformis*. This bacterium is rod–shaped, a form known as bacillus (Wang & Wong, 2007).

S. minus was first discovered in Japan in 1916 by the scientist Futaki, who identified it as one of the causative agents of Rat Bite Fever; RBF. The bacterium was given the alternate name Sodoku, derived from two Japanese words: So (Rat) and Doku (Poison) (Gaastra et al., 2009). Although RBF has become less common, it remains a disease that warrants continuous monitoring. In 2005, the U.S. Centers for Disease Control and Prevention; CDC reported two cases of sudden death in previously healthy adults following RBF infection. These cases highlight the severe nature of the disease, particularly for individuals working closely with rodents (Wang & Wong, 2007). RBF can also be transmitted through the consumption of food or water contaminated by rodents, resulting in a condition known as Haverhill Fever (Cunningham, Paller & Katz, 1998). Annually, approximately 40,000 cases of rodent bites are treated in hospitals worldwide. Approximately 2% of these cases 2% result in RBF, ranking third after bites from dogs and cats among mammals causing infections (Gaastra et al., 2009).

In Thailand, the first reported case of RBF caused by *S. minus* occurred in 1938, involving three patients (Buranakitjaroen, Nilganuwong & Gherunpong, 1994). Additionally, Thailand has a long–standing tradition of breeding greater bandicoot rats (*Bandicota indica*) for consumption, which could contribute to potential exposure to rodent–borne diseases (Jaruwatcharaset & Mingmuang, 2023; Suwannarong & Chapman, 2014).

Current studies on RBF still face several limitations in understanding the disease. It is often underreported, likely due to its overlooked nature, which leads to data that may not fully reflect its actual prevalence. This disease is particularly observed among individuals in professions involving close contact with rodents. The purpose of this review article is to provide a comprehensive overview of RBF as a zoonotic disease, with a focus on its public health implications, emphasizing its potential impact on public health systems. By addressing the gaps in knowledge and awareness, this study aims to contribute to better understanding, diagnosis, and management of the disease, ultimately improving public health outcomes.

Historical Outbreaks of Rat Bite Fever

RBF has been responsible for several notable outbreaks throughout history, often drawing attention to the zoonotic transmission of the disease from rodents to humans. These outbreaks have underscored the importance of understanding the disease's transmission, its socio–economic impact, and the challenges in public health intervention.

One of the earliest and most notable outbreaks occurred in 1926 in Haverhill, Massachusetts, where 86 people developed RBF after consuming milk contaminated with rat feces, leading to the term "Haverhill Disease." This event raised awareness about the potential risks of zoonotic diseases and spurred public health campaigns that focused on improving food safety standards, particularly in the dairy industry. The socio–economic implications were significant, as the outbreak caused widespread fear, affecting milk sales and public trust in food safety practices. Furthermore, the medical community faced challenges in diagnosing RBF, as its symptoms often overlapped with other diseases, making the response more complicated (Elliott, 2007).

A similar outbreak occurred in Chester, USA, involving over 400 cases. This outbreak further emphasized the need for effective zoonotic disease surveillance and intervention, particularly in urban areas where rats were more prevalent. The widespread nature of the outbreak also illustrated the vulnerability of the general public to zoonotic diseases transmitted by rodents, particularly in densely populated areas with poor sanitation and rodent control measures (Elliott, 2007).

In 1983, Chelmsford, England, experienced another significant RBF outbreak, involving 304 schoolchildren who fell ill after drinking water contaminated with rat feces. This outbreak highlighted the importance of water sanitation and rodent control in preventing zoonotic transmission.

The socio–economic impact was considerable, as it resulted in hospitalizations, widespread fear, and a loss of productivity among affected families and healthcare systems (Elliott, 2007). In developed countries, the incidence of RBF remains relatively low (Hagelskjaer, Sørensen, & Randers, 1998). In 2018, Okinawa, Japan, reported the first human case of RBF caused by *S. notomytis* (Fukushima et al., 2018).

These outbreaks illustrate the far–reaching effects of RBF, not only in terms of public health but also in socio–economic terms, as they affect healthcare systems, industries, and public confidence. In regions where such outbreaks occurred, public health initiatives and regulations were strengthened to prevent future occurrences. Improved sanitation, rodent control, and public awareness campaigns became central to preventing further outbreaks of RBF.

There are notable regional differences in the prevalence of bacterial species causing RBF. *S. moniliformis* is more commonly identified in North America, whereas *S. minus* is predominantly reported in Asia (Hryciw, Wright & Tan, 2018) Table 1 summarizes the key differences between these two bacteria, which should guide targeted public health responses and preventive measures.

Table 1 Differences in pathogenesis between *S. moniliformis* and *S. minus*

Item	*S. monoliformis*	*S. minus*
Geographic prevalence	Americas	Asia
Incubation period	10 days	1 to 4 weeks
Mode of Transmission	Bite or ingestion of contaminated food	Rat bite
Joint Pain	Common (Arthralgias)	Rarely observed
Rash Characteristics	Rash on hands and feet	Rash is uncommon
Fever Pattern	Irregular relapsing fever	Regular relapsing fever
Mortality Rate	12.70%	6.50%

Source: Hryciw, Wright & Tan, 2018

The differences between *S. moniliformis* and *S. minus* are crucial for public health interventions. *S. moniliformis*, more common in the Americas, has a shorter incubation period, necessitating rapid diagnosis and treatment. In contrast, *S. minus*, more prevalent in Asia, has a longer incubation period, which can delay symptom onset and complicate early intervention. Additionally, *S. moniliformis* typically presents with more common rash symptoms and joint

pain, whereas these are less frequently observed with *S. minus*, affecting the approach to clinical diagnosis (Elliott, 2007; Hryciw et al., 2018).

Public health measures should focus on the geographical distribution and specific characteristics of each pathogen to optimize diagnostic and therapeutic strategies, particularly in areas with higher rodent populations (Hryciw et al., 2018).

Characteristics of Pathogenic Bacteria

Understanding the characteristics of the bacteria responsible for RBF has significant implications for zoonotic disease management. *S. moniliformis*, *S. notomytis*, and *S. minus* are key pathogens involved in RBF, with distinct characteristics influencing their transmission, diagnosis, and treatment. Effective management of RBF relies on improving surveillance systems to detect outbreaks, ensuring prompt diagnosis, and providing effective antibiotic treatments. Additionally, public health initiatives should focus on improving awareness of the disease's zoonotic nature, particularly in areas with high rodent populations. Zoonotic disease management must also address challenges such as the underreporting of mild or asymptomatic cases in animals and humans, as well as the difficulty in diagnosing RBF due to its nonspecific symptoms (Matsumoto et al., 2017). Enhancing diagnostic capabilities and preventative measures, such as improved hygiene and rodent control, is essential to reducing disease transmission.

S. moniliformis is a Gram–negative bacillus that is facultatively anaerobic, meaning it can survive in both oxygen–rich and oxygen–free environments (Booth, Katz, & Brunton, 2002; Hayakawa et al., 2017). This bacterium is pleomorphic, meaning it has a variety of shapes, and is sometimes observed in clusters that resemble "pearls," which is where the name moniliformis is derived from. The bacterium is nonmotile and cannot tolerate acidic environments (Fenn et al., 2014; Hagelskjaer, Sørensen & Randers, 1998). *S. moniliformis* is typically found in rats, particularly in the oral cavity and upper respiratory tract, including the throat and nose (Elliott, 2007; Hayakawa et al., 2017; Hryciw, Wright & Tan, 2018).

The bacterium coexists in symbiosis with its host, the rat, without causing any disease symptoms. This relationship, where the bacterium lives in the rat's body without causing harm, is referred to as "commensal flora" (Hryciw, Wright & Tan, 2018; Pannetier & Lombard, 2020). Studies indicate that approximately 50–100% of rats carry *S. moniliformis*, making rats a primary

reservoir for this bacterium and capable of transmitting the disease, RBF. *S. moniliformis* is found more frequently than other bacterial strains (Booth, Katz & Brunton, 2002; Pannetier & Lombard, 2020; Wallemacq et al., 2022).

S. minus is a Gram–negative, anaerobic bacillus that survives only in oxygen–free environments (Booth, Katz & Brunton, 2002; Khatib et al., 2020). It has a spiral shape, but previous attempts to culture it in the laboratory have been largely unsuccessful, limiting knowledge about its characteristics and interactions with other bacteria (Pal & Gutama, 2023).

S. notomytis, another bacterium responsible for RBF, causes rare human infections (Khatib et al., 2020; Pal & Gutama, 2023).

The difficulty in cultivating *S. minus* presents a major challenge for diagnosis and treatment development. Unlike *S. moniliformis*, which can be easily cultured, *S. minus* is resistant to isolation and growth in vitro, hindering the creation of rapid diagnostic tests and limiting the study of its pathogenic potential. This complicates timely diagnosis and the development of specific therapies or vaccines (Hryciw et al., 2018). Improved cultivation techniques or alternative diagnostic methods, such as molecular approaches, are needed to better understand *S. minus* infections and its role in RBF.

Pathogenesis

The exact mechanism behind the development of RBF remains unclear due to the relatively low incidence of the disease (Elliott, 2007; Zhang et al., 2019). Additionally, the mortality rate is relatively low if treatment is administered promptly (Elliott, 2007). Initial hypotheses regarding the impact of the disease on the body include various effects on cells, such as erythrophagocytosis (The process where white blood cells consume red blood cells), as well as impacts on organs like the liver and spleen, which may become enlarged (Hepatosplenomegaly). Other observed effects include inflammation of the alveolar walls (Interstitial pneumonia), enlargement of lymph nodes (Lymph node sinus hyperplasia), and inflammation of the heart's membrane (Endocarditis), the heart muscle (Myocarditis), and the blood vessels of the skin (Leukocytoclastic vasculitis) (Elliott, 2007).

In experimental studies involving rats, Glastonbury, Morton & Matthews, (1996) observed that when the bacteria were introduced into the body of a rat, they traveled through the bloodstream to the lymph nodes throughout the body. This caused inflammation around the joints, which was categorized into three stages:

1) Acute Septicemia: During this phase, pathological changes are minimal.

2) Subacute Septicemia: This stage is characterized by distinctive features, such as multifocal suppurative embolic interstitial nephritis.

3) Arthritic Septicemia: This stage is marked by the formation of abscesses throughout the body, with skin lesions presenting as diffuse neutrophilic dermatitis, leading to scabs on the skin. Additionally, areas around the joints exhibit fibrinopurulent synovitis.

These pathological findings help to understand how the infection progresses and manifests in rats, which may also provide insights into human cases of RBF.

Animal models provide valuable insights into RBF pathogenesis and transmission but differ from human cases in key ways. Rodents may develop infections similar to RBF but often lack symptoms like fever or rash, complicating disease impact assessment (Matsumoto et al., 2017). Transmission routes and immune responses also vary between species, with rats not showing clinical symptoms despite being carriers (Hryciw et al., 2018). These differences must be considered when applying animal data to human healthcare, as immune responses and disease progression can differ (Fukushima et al., 2018). While animal models aid in developing treatments, human clinical trials are essential to confirm safety and efficacy (Bermudez et al., 2020). Understanding these distinctions is crucial for refining RBF prevention, diagnosis, and treatment strategies in humans.

Transmission and Spread of the Disease

The spread of RBF occurs primarily through contact with rodents, which are the main carriers of the disease. The primary mode of transmission is via bites or scratches from these animals, with bites being the most common route of transmission. Additionally, the disease can spread through direct contact with the skin or exposure to excretions from infected rodents, such as saliva, urine, or feces (Fenn et al., 2014; Hryciw, Wright & Tan, 2018).

Ingesting contaminated food or water can also lead to RBF, a condition known as Haverhill fever, which is associated with similar symptoms (Fenn et al., 2014; Pannetier & Lombard, 2020). However, current studies indicate that human–to–human transmission has not been observed for this disease (Pal & Gutama, 2023).

Although rodent bites and contamination from rodent excretions are known transmission routes, further research is needed to fully understand the potential for other transmission pathways.

Factors Contributing to the Severity of the Disease

The virulence factors of Streptobacillus include adhesins, which play a crucial role in enabling the bacterium to successfully infect the host. Previous studies have shown that adhesins help the bacteria bind to the host's blood cells (Eisenberg et al., 2016). The presence of DNase at high levels is released without affecting bacterial growth, and lipopolysaccharides are a key component that contributes to the symptoms of RBF. Furthermore, studies suggest that genetic factors may influence susceptibility to infection, such as differences in rat strains, which indicate varying immune responses. Therefore, further study of virulence factors and other related factors is necessary to better understand the full range of virulence factors in Streptobacillus infections (Eisenberg et al., 2016). By exploring these factors, researchers can better understand the dynamics of the disease and potentially develop more effective preventive and therapeutic strategies.

Risk factors for exposure to the disease

Risk factors for exposure to the disease include the following:

1) Occupational groups working with rats: This includes laboratory personnel, individuals working in animal research facilities, pet owners, and employees in pet stores who regularly handle rodents. These groups are at high risk of exposure to rodents through bites, saliva, and other bodily fluids, which are the primary routes of transmission of the bacteria causing RBF (Hryciw, Wright & Tan, 2018).

2) Country status: RBF is rarely found in developed countries, with only a few cases reported each year (Wallemacq et al., 2022). However, it is more common in developing countries, which are considered higher–risk areas due to living conditions that may increase exposure to rodents (Hryciw, Wright & Tan, 2018).

3) Animal species: Studies have identified natural hosts that can carry the disease, such as the black rat (*R. rattus*) and the brown rat (*R. norvegicus*), which is also known by several names, including Norway rat, house rat, or brown rat. These rat species are asymptomatic carriers of the disease (Gaastra et al., 2009). The natural habitat of R. norvegicus includes urban drainpipes, and these rats are known for their behavior of exploring and digging burrows for movement between locations. This behavior contributes to the spread of zoonotic diseases,

including parasites and severe epidemics like plague, typhus, leptospirosis, as well as toxoplasmosis and tetanus, which have historically had significant impacts on humans (Hirschhorn & Hodge, 1999).

Studies have shown that both domestic rats and laboratory rats exhibit a prevalence of *S. moniliformis* in their bodies, with 10% to 100% of rats tested carrying the bacterium. This means that for every 10 rats, at least one may be carrying the bacterium. If bitten by such a rat, there is a 10% chance of contracting the bacteria (Elliott, 2007; Hagelskjaer, Sørensen & Randers, 1998). Other studies have found that wild rats may carry the bacterium in 50% to 100% of cases, suggesting they may be more likely to act as vectors for the disease (Elliott, 2007).

Other animals that may harbor the bacterium include various rat species such as the bandicoot rat, guinea pigs, desert rats, ferrets, poultry, and certain mammals such as dogs, cats, cows, sheep, koalas, and macaque monkeys. However, there is no conclusive evidence that these animals serve as vectors capable of transmitting RBF to humans (Eisenberg et al., 2016; Elliott, 2007; Pal & Gutama, 2023).

1) Establishments: Locations such as homes, apartments, basements, shops, warehouses, and food processing areas, including slaughterhouses, are places where rats commonly enter, as they provide food sources and nesting sites for survival (Hirschhorn & Hodge, 1999). Ports, where goods are loaded and unloaded, and sewer systems, which are underground waste disposal pipes, are particularly favored due to their darkness and abundance of hiding places. The primary habitat of R. norvegicus is the sewer system, which is why it is often referred to as the "sewer rat." Sewers provide an ideal environment for *R. norvegicus* to live and move around (Hirschhorn & Hodge, 1999).

People living in areas with high rat populations, particularly those in unsanitary and overcrowded conditions, are at increased risk of rat bites. Previous reports indicate that large rat populations are often found in such environments, making them a significant risk factor for injury from rat bites (Booth, Katz, & Brunton, 2002).

Symptoms in Humans

The symptoms of RBF in humans can be categorized into three main groups: 1) High fever, 2) Polyarthritis (joint inflammation), commonly presenting as joint pain in the knees or elbows, and 3) Red rashes on the skin, with the appearance of the rash varying from person to

person (Mohamed, Albahra & Haley, 2023). *S. moniliformis* is more likely to cause red rashes compared to *S. minus* (Booth, Katz & Brunton, 2002). The onset of symptoms for RBF typically occurs within 3 to 10 days after exposure (Mohamed, Albahra & Haley, 2023), though sometimes it may take up to two weeks, depending on the bacterial strain involved (Hryciw, Wright & Tan, 2018; Khatib et al., 2020). The incubation period for both bacterial species is on average 5 days for *S. moniliformis* and 13 days for *S. minus* (Cunningham, Paller & Katz, 1998).

A key characteristic of RBF is the development of a rash, which is commonly observed in 75% of cases caused by *S. moniliformis* and 50% of cases caused by *S. minus*. This suggests that there is a high likelihood of a rash when symptoms of RBF appear (Banerjee, Ali & Fowler, 2011; Rosser, Wiselka & Pareek, 2014). The rash is typically found on the palms of the hands and soles of the feet, a distribution pattern known as "Acral distribution" (Rosser, Wiselka & Pareek, 2014). Additional symptoms include chills, or Rigors, which are more commonly seen in cases of *S. moniliformis* than *S. minus*, and joint pain, which is more pronounced in *S. moniliformis* infections (Wallemacq et al., 2022). Other symptoms that may occur include fatigue, vomiting, muscle pain, headache, and sore throat, which are similar to cold or allergic reactions (Banerjee, Ali & Fowler, 2011; Hryciw, Wright & Tan, 2018).

If left untreated, the infection may lead to severe complications, such as multiorgan failure, including myocarditis, pericarditis, meningitis, osteomyelitis, pericardial effusion, pneumonia, and meningitis. These complications can lead to a high mortality rate, with up to 50% of cases resulting in death (Akter et al., 2016; Hryciw, Wright & Tan, 2018; Khatib et al., 2020; Pannetier & Lombard, 2020). Additionally, the infection can impact the immune system, causing the rash due to inflammation of the blood vessels and resulting in low blood protein levels, which can lead to Cryoglobulinemia. This condition involves abnormal proteins in the blood, which can trigger further inflammation (Akter et al., 2016).

Diagnosis of the Disease

The diagnosis of RBF begins with taking a patient history, which typically includes the three main symptoms: fever, rash, and polyarthritis (Joint pain). Laboratory tests are essential for confirmation, with common samples including blood, joint fluid, and pus (Hagelskjaer, Sørensen & Randers, 1998). Diagnosing RBF can be challenging, especially if the patient's history does not confirm exposure to rats (Hryciw, Wright & Tan, 2018). Although laboratory testing,

such as bacterial culture, remains the gold standard for diagnosis (Pal & Gutama, 2023), it can be difficult to culture *S. moniliformis* and *S. minus* because they require specific growth conditions, including 20% sterile rabbit serum and a controlled carbon dioxide concentration (5–10%), incubated at 35°C. Even under these conditions, bacterial cultures may take up to five days to grow. Additionally, some substances, like Sodium polyanethol sulfonate; SPS, added at low concentrations to stop the growth of other bacteria, may affect the growth of *S. moniliformis* and *S. minus* (Eisenberg et al., 2016; Flannery et al., 2017; Hayakawa et al., 2017).

Molecular diagnostic methods, such as PCR testing for 16S rDNA, have also been developed to confirm the diagnosis of RBF (Pannetier & Lombard, 2020). For differential diagnosis, RBF should be distinguished from a variety of infectious diseases, including bacterial infections such as *Streptococcus pyogenes*, *S. aureus*, disseminated gonorrhea, meningococcemia, brucellosis, leptospirosis, syphilis, typhoid fever, and Borrelia infections. It should also be differentiated from protozoal infections like Lyme disease, ehrlichiosis, and malaria, as well as viral infections such as Epstein–Barr virus, parvovirus B19, and non–infectious conditions like autoimmune diseases or drug allergies (Elliott, 2007).

Preventive Strategies and Effectiveness

Preventive measures, such as maintaining proper hygiene, controlling rodent populations, and using personal protective equipment (PPE) like gloves and face masks, are essential in reducing the risk of RBF transmission. Prompt antibiotic treatment is effective in most cases, with medications such as Ceftriaxone, Doxycycline, Penicillin, Clindamycin, and others proving beneficial (Clement, Frans & Van Ranst, 2003; Hryciw, Wright & Tan, 2018). However, the success of these measures depends on local factors, such as healthcare infrastructure and rodent prevalence. In high–risk areas, such as urban slums, public health interventions need to include education, improved water sanitation, and enhanced rodent control to reduce RBF risks.

RBF, if left untreated, can lead to mortality rates of 7% to 10% due to complications like myocarditis, pericarditis, and meningitis (Hryciw, Wright & Tan, 2018). However, the use of antibiotics can significantly reduce mortality. While S. moniliformis is resistant to the Trimethoprim–sulfamethoxazole group (Wallemacq et al., 2022), treatment usually lasts around 14 days, though severe cases may require longer durations of 4 to 6 weeks (Wallemacq et al., 2022). It is also important to administer a tetanus vaccine if warranted by risk factors (Himsworth

et al., 2014). Rabies is not a concern with rats, but its potential transmission may need to be considered based on individual circumstances.

Control and Prevention

Effective RBF control and prevention require several strategies. Ensuring food and water hygiene is critical to avoid contamination by rat excretions. For instance, pasteurized milk should be preferred, as raw milk can carry the bacteria (Pal & Gutama, 2023). Occupational groups with frequent rat exposure should take precautions, including wearing PPE such as gloves and face masks (Hagelskjaer, Sørensen & Randers, 1998; Pal & Gutama, 2023). Immediate washing of any bite or scratch with soap and water is crucial to minimize bacterial contact and should be followed by seeking medical attention promptly (Pal & Gutama, 2023).

Key Findings and Implications for Future Research and Public Health Policies

This review has highlighted the critical role of Streptobacillus moniliformis, Streptobacillus notomytis, and Spirillum minus in the transmission of Rat–Bite Fever (RBF), with a focus on their distinct pathogenic characteristics and geographical prevalence. The findings emphasize the importance of understanding these differences in developing effective diagnostic tools, treatment protocols, and prevention strategies (Hryciw et al., 2018). Additionally, historical outbreaks demonstrate the significant public health impact of RBF, underlining the need for better surveillance, rodent control, and hygiene practices, particularly in high–risk urban environments (Elliott, 2007).

Limitations and Knowledge Gaps

Despite the progress made in understanding RBF, several limitations remain in current research. The difficulty in isolating *S. minus* for laboratory studies has significantly hindered progress in understanding its full pathogenic potential, making diagnostic methods and treatment options for *S. minus*–related RBF more limited (Hryciw et al., 2018). Furthermore, much of the existing data on RBF comes from isolated case studies or small–scale outbreaks, leaving many aspects of the disease's epidemiology, including risk factors, incubation periods, and long–term consequences, inadequately explored. Future research should aim to address

these gaps by focusing on better cultivation techniques, large–scale surveillance programs, and clinical trials.

Conclusion

In conclusion, strengthening the connection to the study's objective involves emphasizing how improved understanding of RBF's transmission, symptoms, and public health implications can enhance both diagnosis and prevention efforts. By addressing gaps in current knowledge, this article helps shed light on RBF's zoonotic nature, aiding in more effective management strategies and better preparedness for outbreaks.

One key challenge in RBF management is the under–recognition of the disease, particularly in regions with limited healthcare infrastructure. Despite the availability of effective antibiotic treatments, misdiagnosis or delayed treatment can still pose significant risks. Preventive measures, such as hygiene practices and protective gear for those at risk, are often neglected, exacerbating transmission. Additionally, a lack of awareness about the disease's potential impact on public health systems further complicates prevention and control efforts.

The implications of RBF on public health systems, especially in areas with high rodent populations, are profound. In endemic regions, frequent cases of rat–bite fever can place a strain on healthcare resources, especially if timely diagnosis and treatment are not consistently provided. Strengthening public health systems to address zoonotic diseases like RBF by improving surveillance, raising awareness, and ensuring access to prompt medical care can significantly reduce the disease burden and protect vulnerable populations. The knowledge gaps highlighted in this article emphasize the need for continued research and better prevention strategies to minimize the risk of RBF outbreaks in the future.

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