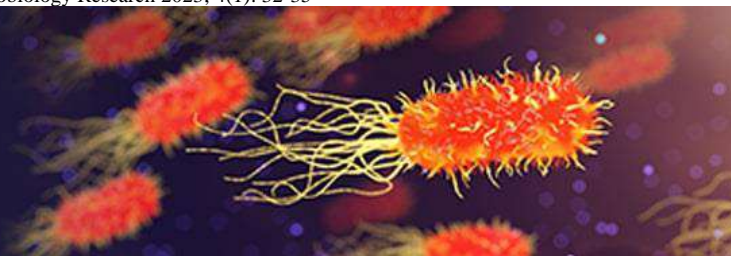


# Journal of Advances in Microbiology Research



E-ISSN: 2709-944X  
P-ISSN: 2709-9431  
JRM 2023; 4(1): 32-35  
© 2023 JAMR  
[www.microbiojournal.com](http://www.microbiojournal.com)  
Received: 02-11-2022  
Accepted: 05-12-2022

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## *Rhodococcus equi*: An emerging bacterial pathogen of public health significance

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### Abstract

*Rhodococcus equi*, a well-known pathogen in equines, is now emerging as an important opportunistic pathogen of humans especially in immunocompromised subjects, such as HIV-infected individuals, causing the lung infection. The soil, particularly polluted with animal manure, is considered as the natural habitat of *R. equi*. The source of infection is exogenous, and transmission occurs through inhalation of organisms from the environment. It is a common cause of disease in foals between the ages of two and six months. *Rhodococcus equi* has several clinical symptoms in foals. Pneumonia with abscess in the lungs is the most prevalent. Intestinal disease, which may or may not be linked with diarrhea, is another less prevalent signs of disease. Many *R. equi*-infected foals recover, but those who are seriously afflicted may not. A bacterial culture and cytology of a transtracheal wash are required for a definitive diagnosis of *Rhodococcus equi* infection. Antibiotics, such as erythromycin (or another macrolide) and rifampin are often used to treat *R. equi* infection. Currently, no vaccine is commercially available for immunization. Infection with *R. equi* is difficult to avoid, however, there are some key management aspects that can help lower the risk of infection. The best ways are good foal management, regular screening, and early identification.

**Keywords:** Emerging zoonosis, Immunosuppressed, Lung infection, Public health, *Rhodococcus equi*

### Introduction

Many emerging zoonoses of various etiologies have drawn the attention of national and international organizations in recent decades because they have caused considerable morbidity and mortality in humans and animals, as well as a significant impact on the global economy (Pal, 2013) [1]. *Rhodococcus equi*, one of several zoonotic pathogens, is emerging as an important opportunistic intracellular bacterial pathogen of immunosuppressed individuals (Pal and Tanvir Rahman, 2015) [2]. *Rhodococcus equi* is a well-known bacterial pathogen in veterinary medicine, having been discovered in the lungs of the foals in Sweden in 1923 (Magnusson, 1923) [3].

*Rhodococcus equi* is a Gram-positive facultative intracellular pathogen that causes bronchopneumonia in foals between the ages of three and five months (AAEP, 2017) [4]. The infection can also be seen in a wide range of other mammals, though it is uncommon. It often develops as a result of immunosuppression caused by a variety of factors (Van Etta *et al.*, 1983) [5]. *Rhodococcus equi* produces a variety of pulmonary infections, including the simple pneumonia, necrotizing pneumonia, lung abscess and lung tumors (Lin *et al.*, 2019) [6].

*Rhodococcus equi* infection in humans was first reported in 1967 in a young guy working in a stockyard who was on immunosuppressive medication (Golub *et al.*, 1967) [7]. The infection is spread by equines to people. *Rhodococcus equi* affects primarily the individuals who are immunocompromised (Pal and Tanvir Rahman, 2015; Pal, 2014) [2, 8]. AIDS/HIV, solid organ and stem cell transplant recipients, leukemia, lymphoma, lung cancer, and following chemotherapy, monoclonal antibodies, or extended steroid usage are all examples of immunocompromised states where the infection has been reported (Vechi *et al.*, 2018) [9]. The major objective of this paper is to describe the role of *Rhodococcus equi* as an emerging pathogen of public health importance.

### Etiology

Rhodococci are members of the *Nocardioform* family, which comprises the *Corynebacterium*, *Mycobacterium*, *Nocardia*, and *Gordonia* genera (Weinstock and Brown, 2002) [10]. *Rhodococcus equi* is an organism that's facultative, intracellular, non-motile, and

does not produce spores. Gram stain reveals pleomorphic Gram-positive rods in a variety of shapes and sizes, ranging from coccoid to long, curved, and clubbed. Depending on the age of the culture and growth conditions, the organism may be inconsistently acid-fast with Ziehl-Neelsen staining (Verville *et al.*, 1994) [11]. It characteristically produces a red pigment, especially in older cultures, although it provides a pale salmon pink color on solid surfaces in younger cultures (Lin *et al.*, 2019; Majidzadeh and Fatahi-Bafghi, 2018) [6, 12]. *Rhodococcus equi* grows best around 30 °C, but it can thrive at temperatures ranging from 10 °C to 40 °C (Walsh *et al.*, 1993) [13]. The presence of catalase, urease, lipase, and phosphatase, as well as the absence of oxidase, DNase, elastase, lecithinase, and protease, distinguishes *R. equi* (Pal, 2014; Prescott, 1991) [8, 14].

### Epidemiology

*Rhodococcus equi* infection has been reported on every continent except Antarctica (Cisek *et al.*, 2014) [15]. The organism can be found in abundance in soil, particularly where domesticated animals graze. The soil pollution comes from horses' and other animals' feces. Human infection is caused by exposure to the environment where the organisms are present (Pal, 2014; Prescott, 1991) [8, 14]. It was first identified as a human pathogen in 1967 and described as a cause of disease in immunocompromised individuals. The infection can spread to humans and animals through inhalation or ingestion of infected material, as well as traumatic inoculation or wound super infection. Although horses and foals are the most common hosts, the virus has also been reported in sheep, goats, cattle, cats, dogs, and wild birds (Pal, 2014; Ayoade and Alam, 2021) [8, 16].

### Transmission

The most common route for virulent *R. equi* to infect foals is through inhalation. The ingestion of the organism is a common route of exposure and likely of vaccination, but it seldom leads to hematogenously acquired pneumonia unless a foal has many exposures to exceptionally large quantities of germs (AAEP, 2017) [4]. *Rhodococcus equi* infected foals can shed the bacteria in their feces, causing the pathogen to become endemic on the breeding farm and causing disease in the foal crop year after year (Young, 2020) [17]. Human colonization and person-to-person transmission are two further ways of *R. equi* acquisition that are poorly understood (Rasmussen, 2000) [18].

### Clinical spectrum

#### In Humans

Immunocompromised people, such as those with HIV, are more vulnerable to *R. equi* infection (Spiliopoulou *et al.*, 2014) [19]. Though *R. equi* was found in tissues of animals intended for human consumption, the sources and routes of human infection are unknown (Witkowski *et al.*, 2011) [20]. The clinical manifestation is determined by the organ or system affected. The pulmonary involvement is the most prevalent, accounting for up to 80% of all cases. Extrapulmonary involvement (most typically the brain and skin) can occur in conjunction with a lung infection. Necrotizing pneumonia is a common occurrence that can spread to other structures, resulting in empyema, mediastinitis, and bacteremia. Fever, cough (which may or may not be productive), weight loss, exhaustion, and occasionally hemoptysis, which can be severe and

necessitate a transfusion or pneumonectomy, are all common symptoms (Pal, 2014; Ayoade and Alam, 2021) [8, 16]. Lymphadenopathy, eye discharge and pain, joint pain, altered state of awareness, and bloody diarrhea is some of the other symptoms of *R. equi* infection. Anemia induced by *R. equi*-infected colonic polyps has also been documented (Talanin *et al.*, 1998) [21].

#### In Animals

*Rhodococcus equi* infection progresses slowly, with symptoms ranging from acute to subacute. Clinical indications of disease are difficult to detect until the lung infection has reached a critical mass, causing the foal to decompensate (MVM, 2012) [22]. Fever, cough, elevated respiratory and heart rates, and aberrant tracheal and lung sounds on auscultation are the most common symptoms in foals. In some circumstances, nasal discharge may occur. Pneumonia progresses slowly, and lung lesions might already be extremely widespread before clinical symptoms manifest. Rarely, the disease manifests itself as a per-acute form, in which previously healthy foals acquire respiratory distress with a rapid onset and death in less than 48 hours. Extrapulmonary indications of *R. equi* infection can also be seen in foals. Diarrhea, colic, and weight loss are the most common symptoms. Extrapulmonary diseases are frequently associated with a greater mortality rate (Reuss *et al.*, 2009; Tarancón *et al.*, 2009) [23, 24]. At those farms, the most common form of *R. equi* infection is a subclinical form, in which foals develop sonographic evidence of peripheral lung consolidation or abscessation without displaying clinical signs (AAEP, 2017) [4].

#### Diagnosis

*Rhodococcus equi* is diagnosed based on a history of cases on the farm (showing the presence of the bacterium on the premises), ultrasound and/or x-ray evidence of pulmonary abscesses, blood tests, and identification of the organism via culture and/or PCR testing (Pal, 2014; Young, 2020) [8, 17]. *Rhodococcus equi* replicates slowly, and unless culture plates are incubated for 48–72 hours, visible colonies may not form. Large quantities of white blood cells with pleomorphic and Gram-positive coccobacilli are found in Gram-stained sputum from patients with *R. equi* infection. Because *R. equi* on a culture plate could indicate "normal respiratory flora," some researchers have suggested that microscopic analysis of Gram-stained material be given more attention (Lin *et al.*, 2019) [6]. The distinction between *R. equi*-induced lower respiratory tract infections and those caused by other pathogens is difficult to make, especially on farms without a history of *R. equi* infections. Complete blood count (CBC), fibrinogen concentration measurement, ultrasonography, radiography, and serology may help identify *R. equi* pneumonia from pneumonia caused by other organisms (Leclere *et al.*, 2009) [25]. To achieve a definitive diagnosis of *R. equi* pneumonia, polymerase chain reaction (PCR) amplification of the vapA gene and cytological analysis of a tracheobronchial aspirate (TBA) are required (Pusterla *et al.*, 2009; Rodriguez-Lazarro *et al.*, 2006) [26, 27].

#### Treatment

##### In Humans

A single drug, such as an extended-spectrum macrolide or a fluoroquinolone, may be sufficient for treating immunocompetent hosts. However, two or more agents, at

least one with strong macrophage penetration, are desirable for the treatment of immunocompromised hosts. Vancomycin, linezolid, carbapenems, fluoroquinolones, aminoglycosides, macrolides, and rifampin are examples of antibiotics that should be chosen based on susceptibility results (Pal, 2014; Willingham-Lane *et al.*, 2019; Cui *et al.*, 2018) [8, 28, 29]. In many cases, notably in AIDS patients, definitive therapy is often followed by suppressive therapy until immunological reconstitution occurs. A combination of rifampin and a macrolide, doxycycline, or quinolone could be used as suppressive therapy. Because restoration of cellular immunity is linked to increased survival, antiretroviral medication should be started as soon as possible in HIV patients with *R. equi* infection. In the case of lung infections, additional surgical intervention may be required. This could include abscess or empyema drainage, as well as lobectomy if antibiotics are not working (Ayoade and Alam, 2021) [16].

### In Animals

Treatment is usually time-consuming, costly, and, worst of all, ineffective (Cohen *et al.*, 2015) [30]. *Rhodococcus equi* pneumonia is typically undetected until it has progressed to the point where it is impossible to treat (AAEP, 2017) [4]. The scarcity of effective antimicrobial medications and rising resistance are the two most pressing issues in treating *Rhodococcus equi* infections. Rifampicin + Erythromycin once a day for 4–9 weeks, Rifampicin + Clarithromycin once a day for 3–12 weeks, Rifampicin + Azithromycin once a day for 6 weeks, Doxycycline in monotherapy twice a day for 6 weeks, Doxycycline + Azithromycin once a day for 6 weeks, Tulathromycin in monotherapy once a week for 6 weeks, and Gamithromycin in monotherapy once per week for 6 weeks are recommended treatment. Antibiotic groups utilized in equine medicine are generally limited, and antimicrobial resistance has increased dramatically in recent decades (Rakowska *et al.*, 2020) [31].

### Prevention and control

Despite the fact that various ways have been investigated, there is no effective rhodococcosis preventative strategy (Huber *et al.*, 2019) [32]. Hyperimmune plasma (HIP), which is a regular treatment on many breeding farms in the United States, can help to prevent rhodococcal pneumonia in equines (Kahn *et al.*, 2019) [33]. Limiting foal overpopulation and ensuring that they are housed in well-ventilated spaces with minimal dust are all important aspects of good management. Dirt paddocks should be avoided at all possible. Foals that look to be infected should be removed from the group and their excrement managed properly (Ayoade and Alam, 2021) [16]. Early correct diagnosis and prompt therapy is advised in order to prevent the suffering to the affected individuals (Pal, 2014) [8]. Vaccines against *R. equi* are eagerly anticipated and are frequently used as a form of prophylaxis. Unfortunately, despite numerous trials, none of them were found to be sufficiently successful to be commercially available (Rakowska *et al.*, 2020) [31].

### Conclusion

*Rhodococcus equi* is a bacterium that lives in the soil and can cause pneumonia in young foals and in rare cases, in immunodeficient adult horses. The disease's prevalence varies by region, farm, and year, but *R. equi* can be found on

nearly every horse farm on the world. In humans, *R. equi* causes pulmonary infections ranging from simple pneumonia to necrotizing pneumonia, lung abscess and lung masses. Maximum cases of *R. equi* infection have been described in immunosuppressed hosts, most commonly in those with untreated AIDS, but also in individuals with hematological malignancies, organ transplants and those receiving immunosuppressive medications. The infection is typically less severe in immunocompetent individuals. It is emphasized that in immunocompromised patients, prompt diagnosis and directed therapy utilizing two or more medications are frequently required to obtain a satisfactory outcome. Further work on the immunopathology, risk factors, transmission dynamic, molecular epidemiology, and chemotherapy on *R. equi* infection is required.

### Acknowledgements

The authors wish to thank to Prof. Dr. R. K. Narayan for giving his suggestions during the preparation of the manuscript. This paper is dedicated to the scientists who did commendable work in the field of *Rhodococcus equi*.

### Contribution of Authors

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 conflict of interest.

### Source of Financial Grant

There was no financial support for this manuscript.

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#### How to Cite This Article

Pal M, Gutama KP, Singh S, Botton S. *Rhodococcus equi*: An emerging bacterial pathogen of public health significance. *Journal of Advances in Microbiology Research* 2023; 4(1): 32-35. DOI: <https://doi.org/>

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