Mahendrar and Rahman, Annals of Veterinary and Animal Science 2015
http://naturepub.org/index.php/journal/navas
[Received:20Dec2014 Accepted: 07Feb2015 Published:28Feb2015]

eISSN: 2313-5514
pISSN: 2312-9123

AVAS
Annals of Veterinary and Animal Science

REVIEW ARTICLE V:2(1) OPEN ACCESS

Rhodococcus equi: An emerging zoonotic pathogen

Mahendrar Pal[1] and Md. Tanvir Rahman[2]*

ABSTRACT

In recent decades, many emerging zoonoses of diverse etiologies have attracted the attention of national and international organization as they caused significant morbidity and mortality in humans as well as animals. Among several zoonotic pathogens, *Rhodococcus equi* is emerging as an important opportunistic intracellular bacterial pathogen of immunosuppressed hosts such as human immunodeficiency virus infected patients. Infection due to *R. equi* has also been recorded in immunocompetent subjects. It is a well-recognized agent causing disease in animals mainly in equines. The natural habitat of *R. equi* is soil, particularly contaminated with animal manure. The exact mode of transmission of *R. equi infection* is not well established. The primary infection occurs in the lungs in approximately 80% of cases. Necrotizing pneumonia is the most common form of infection caused by *R. equi* in human, however, wound infections, and subcutaneous abscess like extrapulmonary infections have also been described. Microbiological, cytological, and molecular techniques are employed to confirm the diagnosis of disease. It is pertinent to differentiate *R. equi* from *Nocardia*, *Mycobacterim*, and diphteroids. Prognosis is grave as mortality may reach up to 50% in HIV patients. Combined antimicrobial agents could be used as therapeutics to reduce the chance of development of antibiotic resistant. Presently, no commercial vaccine is available for immunization. Further research on the pathogenesis, epidemiology, chemotherapy, and vaccinology to protect the equine and humans from rhodococcosis may be rewarding. In this review we focus on etiology, host, transmission, diagnosis and treatment of *R. equi* infection

Key words: Emerging pathogen, Horse, Immunocompromised host, Public health, *Rhodococcus equi,* Zoonosis

INTRODUCTION

Since antiquity, man has domesticated the animals for several purposes. The domestication has brought close contact of humans with animals. This gave an opportunity of several animal pathogens to infect human beings. Many of the infectious diseases that are naturally transmitted from animals to man or vice versa are termed as "zoonoses" (Pal, 2007). Presently, over 300 zoonotic diseases of diverse etiologies are described (Pal, 2013). Horse is one of the domestic animals which can transmit several infections to susceptible individuals (Pal, 2007; Pal et al., 2013). In recent decades, several emerging zoonotic infections which have a significant impact on global economy, public and animal health, have been described (Pal, 2013).

Among such zoonotic agents, *Rhodococcus equi*, the chief cause of equine rhodococcosis, has emerged as a significant pathogen of humans particularly affected with HIV (Weinstock and Brown, 2002). The bacterium was first isolated by Magnusson in1923 from Sweden. It causes an important chronic granulomatous pneumonia, and lung abscesses in foals aged below 4 months, and is a common isolate from cervical lymph nodes in swine. Although rare, infection also occurs in a wide variety of other mammals, often following immunosuppression by various causes. Infections in these unusual hosts commonly include granulomatous pneumonia which develops into lung abscesses, lymphadenitis (often of the mesenteric, bronchial, or cervical lymph nodes), wound infections, and abscesses in various parts of the body.

The role of *R. equi* as a human pathogen was first established in 1967 when the first case was recorded in a 29-year old man with plasma cell hepatitis who developed a cavitary pulmonary lesion after cleaning animal pen at a stockyard (Golub et al., 1967). Before 1983, only 12 cases had been reported in humans (Van Etta et al., 1983). At least 20 additional cases have been

* Corresponding author: tanvirahman@bau.edu.bd
[1]Department of Microbiology, Immunology and Public Health, College of Veterinary Medicine and Agriculture, Addia Ababa University, P.B.No.34, Debre Zeit, Ethiopia. [2]Department of Microbiology and Hygiene, Faculty of Veterinary Science, Bangladesh Agricultural University, Mymensingh-2202, Bangladesh.

described since then, the majority of which have been in patients with AIDS. The increased number of human cases reported recently is partly the result of the spread of AIDS but may also reflect the increasing awareness by medical laboratories of this opportunistic pathogen, and their improved ability to identify it. It can also cause disease in immunocompetent host (Devi et al., 2011). The infection due to *R. equi* are reported from many countries of the world (Weinstock and Brown, 2002; Chen et al., 2009; Devi et al., 2011).The epidemiology of *R. equi* is not clear regarding the means of exposure. Our current understanding of *R. equi* comes primarily from equine research, though it can be applied in part to this opportunistic intracellular human pathogen. The present communication is an attempt to highlight various aspects *i.e.,* etiology, transmission, clinical aspects, diagnosis, treatment, prevention and control of this emerging zoonotic pathogen

ETIOLOGY

Rhodococcosis is caused by *R. equi* which is a Gram positive, facultative intracellular, non-motile, non-spore forming organism that commonly found in soil. Recent literature search in Pubmed has revealed proposed new name of the *R. equi* by some authors as follows: *Prescottella equi* (Sangal et al., 2014) and *Rhodococcus hoagie* (Sangal et al., 2015). In soil the organism can survive for over a year even when exposed to sunlight. The highest numbers of *R. equi* are found in surface soil, whereas almost no bacteria are found in soil at a depth of 30 cm or more underground. Optimal growth of *R. equi* occurs at 30ºC at pH 7.5 (Takai, 1997).

Phylogenetically the genus *Rhodococcus* belongs to group described as nocardioform actinomycetes, which contains the genera *Caseobacter*, *Corynebacterium*, *Mycobacterium, Nocardia, Rhodococcus* and *Tsukamurella* (Goodfellow, 1986). The organism is positive for catalase, urease, nitrate, and phosphatase but negative for indole, methyl red, Voges proskauer, oxidase, gelatinase, esculin hydrolysis, hippurate hydrolysis, and carbohydrate fermentation (Prescott, 1991). Gram stain shows pleomorphic gram-positive rods varying from coccoid to long, curved, and clubbed forms. Largely soil saprophytes, the genus *Rhodococcus* cell wall contain some mycolic acids and the organism may be inconsistently acid-fast with Ziehl-Neelsen staining, depending on the age of culture and growth media. (Verville et al., 1994).

The size of the genome of this facultative intracellular pathogen has been estimated to be around 5 Mb with high GC content. *R. equi* strain ATGC 33701 has extensive homology with the genome of *Mycobacterium tuberculosis* (Rahman et al., 2003), a genetic relatedness to some extent reflected in their pathogenesis, since both can survive and replicate within modified phagocytic vacule inside macrophages. Within the genus recent genomic analyses confirmed close relatedness between *Rhodococcus defluvii* and *Rhodococcus equi* (Sangal et al., 2014) and the observed minor differences which might be associated with host adaptation. The virulent *R. equi* is characterized by the presence of plasmid of 80 to 90 kb size that contain the pathogenicity island having series of virulence genes (*vap* genes *i.e., vapA, vapC, vapD, vapE, vapF, vapR,* ORF8, ORF10) (Takai, 1997). As an opportunistic intracellular pathogen, *R. equi* is found inside the macrophages, where it grows and multiplies. Many of these genes are highly expressed during the growth of *R. equi* inside macrophages and involve with the virulence of the organism (Ren and Prescott, 2013: Rahman et al., 2015). Organisms that lack this plasmid are avirulent in nature.

HOST

Natural infection has been reported in humans as well as in animals which include cats, cattle, deer, dogs, goats, horses, pig, sheep, and wild birds (Prescott, 1991; Takai, 1997; Aiello and Mays, 1998; Sakai et al., 2012; Cohen et al., 2014). Among animals, equine is the most commonly affected species (Takai, 1997).

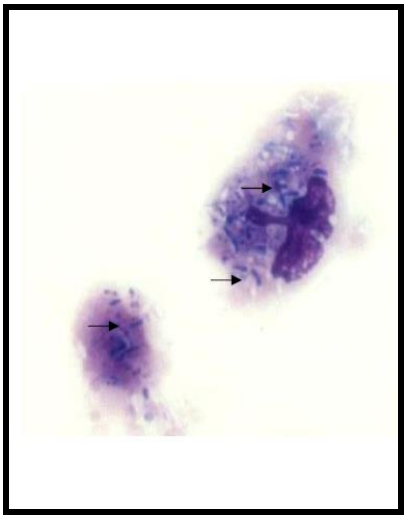

Fig. 1. *R. equi* inside the equine peripheral blood macrophage under *in vitro* condition. Arrows indicate the *R. equi* organisms. The cells were stained with modified Diff-stain.

TRANSMISSION

The organism is widely distributed in soil and manure is main source of infection as this pathogen rapidly grows on volatile organic acids contained within it. This made the removal of the organism from equine stable almost impossible and subsequently, the status of infection with the organism has become endemic in some farms (Katsumi et al., 1991).

R. equi is thought to be acquired primarily by inhalation from the soil, since the organism is readily available in soil particularly where horses are raised (Takai et al., 1991). However, inoculation into a wound or mucous membrane or ingestion and passage through the alimentary tract has also been observed. Exposure to domesticated animals, such as horses and pigs, may play a role in some cases of infection (Golub et al., 1967; Prescott, 1991). It has been noticed that about one-third of all patients with *R. equi* infection have a history of exposure to horses or pigs. Human colonization of *R. equi* and person-to-person transmission, are poorly understood. Rhodococci with biochemical properties identical to those of *R. equi* are among the species that dominate the nasal microbiota of healthy adults (Rasmussen et al., 2000). Raising the intriguing possibility that nasal colonization plays a role in the acquisition of disease. Doig et al. (1991) reported that probably *R. equi* does not colonize the large intestine

There are reports on the nosocomial occurrence of *R. equi* infection (Scotton et al., 2000*)* including those occurred in patient who developed sepsis and hydrocephalus from an infected ventricular shunt two weeks after being hospitalized. Patient-to-patient transmission was implicated in two HIV-infected patients who developed *R. equi* infections after sharing a room with another HIV infected patient who had *R. equi* pneumonia (Donisi et al., 1996). The occupational acquisition of *R. equi* infection by an immunocompetent laboratory worker has been reported (Egawa et al., 1991). Researchers believe that the consumption of undercooked meat of pig and wild boar may be a route of infection (Sakai et al., 2012), however, the exact role of animal in the transmission of *R. equi* to humans is not clearly established.

CLINICAL SPECTRUM

Human (As zoonoses): *R. equi* infection is considered as an emerging zoonotic pathogen particularly in immunocompromised patients such as those suffering with HIV (Spiliopoulou et al., 2014). In the patient, the organism can causes respiratory infection *e.g.,* pyogranulomatous pneumonia. However, the sources and routes of human infection are not fully known, though *R. equi* was detected in tissues of animals intended for human consumption (Witkowski et al., 2011).

The disease is also observed occasionally in healthy people e.g., people having healthy normal immune system (immunocompetent), but the infection remain localized and may appear as wound infections. However, in human, the onset of *R equi* infections is generally insidious, and presenting symptoms vary according to the infection site. Symptoms in immunocompetent patients do not differ from those in immunocompromised patients. In infections secondary to trauma, such as endophthalmitis, septic arthritis, and traumatic meningitis, symptoms may present

within 24 hours of the trauma. The patients affected with pulmonary *R equi* infections exhibit fever and cough (>80% of patients with pulmonary *R equi* infections), malaise, chest pain, dyspnea, haemoptysis, and weight loss. Other presentations of *R equi* infection include lymphadenopathy, eye drainage and pain, joint pain, altered level of consciousness, bloody diarrhoea, and fever of unknown origin. Anemia caused by colonic polyps infected with *R equi* has also been reported (Talanin et al., 1998). Recently Gundelly et al. (2014) reported *R. equi* associated pericarditis in a patient living with HIV/AIDS.

Animal: The infection in foal is slowly progressive, with acute to sub-acute clinical manifestations. Clinical signs of the disease could be difficult to detect until the pulmonary infection reaches a critical mass, resulting in decompensation of the foal. Pulmonary lesions comprises of subacute to chronic suppurative bronchopneumonia, pulmonary abscessation, and suppurative lymphadenitis. At the onset of clinical signs, most foals are lethargic, febrile, and tachypneic. Diarrhoea is seen in one-third of foals with *R equi* pneumonia, and may be caused by colonic microabscessation. Cough is a variable clinical sign and purulent nasal discharge is less common. Thoracic auscultation reveals crackles and wheezes with asymmetric/regional distribution. In subclinical infections in foals, abscesses of small to moderate-sized are observed. It causes suppurative lesions in cats, cattle, goats, and sheep (Takai, 1997; Aiello and Mays, 1998).

DIAGNOSIS

The insidious course of *R. equi* infection and the difficulties in the isolation of the microorganism has contributed to the delay in the diagnosis and to the high mortality rate of this opportunistic infection (Corti et al., 2014). Many diagnostic tests including complete blood count (CBC), measurement of fibrinogen concentrations, ultrasonography, radiographs, and serology may help distinguish pneumonia caused by *R. equi* from that caused by other pathogens. In one study, white cell counts >20,000 cells/ul, fibrinogen concentrations >700 mg/dl, and evidence of thoracic abscessation were more likely to be found in foals with pneumonia caused by *R. equi* than in foals with pneumonia caused by other bacterial pathogens. However, bacteriologic culture and/or and cytological examination of a tracheobronchial aspirate (TBA) are necessary to make a definitive diagnosis of pneumonia caused by *R. equi*. For conform diagnosis polymerase chain reaction (PCR) targeting virulence plasmid encoding *vapA* gene is recommended (Sellon et al., 2001; Rodriguez-Lazaro et al., 2006; Pusterela et al., 2007).

However, culture offers the advantage of detecting other bacterial pathogens present, and permits *in vitro* susceptibility testing of the recovered pathogens. As a result, PCR amplification of the *vapA* gene may be done in association with, but should not replace, bacterial culture. On endemic farms, many foals without clinical disease have *R. equi* in their trachea as a result of inhalation of contaminated dust or as a result of a subclinical infection (Ardans et al., 1986). For this reason, culture or PCR amplification of *R. equi* from a TBA should be interpreted in the context of cytological evaluation and clinical examination. Several independent studies have recently evaluated the performance of available serological tests for diagnosis of infection caused by *R. equi* on endemic farms. The serological tests evaluated were found to either have low sensitivity, low specificity, or both (Martens et al., 2002).

TREATMENT

Antibiotic failure in patient with *R. equi* infection has been reported in many cases (Cisek et al., 2014; Ursales et al., 2014). Therefore it is crucial to do determine the antibiogram of the isolates for effective treatment. *R.equi*, has shown *in vitro* susceptibility to erythromycin, ciprofloxacin, vancomycin, aminoglycosides, rifampin, imipenem, meropenem, and resistant to penicillins (Golub et al., 1967). The intracellular survival of the organism has led

to recommendations that *R. equi* infections be treated with lipophilic antibiotics that penetrate cells. Combined antimicrobial therapy involving parentral glycopeptide plus imipenem for at least three weeks, followed by an oral combination of rifampin, plus either macrolides or tetracycline has been recommended in humans. The combination of erythromycin (25 mg/kg, PO, qid), and rifampin (5–10 mg/kg, PO, bid) has become the treatment of choice for *R. equi* infections in foals. (Nordmann and Ronco, 1992). It is recommended that combination antimicrobial therapy should be used to prevent the risk of drug resistance.

PREVENTION AND CONTROL

Many of the infectious disease are controlled by vaccination, however, till now no well-developed effective vaccines are available for the control of *R. equi* infection in foals (Giguere et al., 2011). Because of the intracellular nature of the organism, it is speculated that Th1 immunity could be more effective for the control of *R. equi* infection than Th2 type immunity.

There is a progressive buildup of infection on horse farms where large numbers of foals are kept on bare, dusty, manure containing paddocks. This will result in heavy challenge, with clinical disease maintaining virulent bacteria. Pasture must be rotated to decrease dust formation and by consequent inhalation of *R. equi*. Any sandy or dirt areas should ideally be planted with grass and made "off limits" to foals or, alternatively, irrigation may be useful in decreasing dust formation. Early recognition of *R. equi* cases with isolation and treatment of infected foals will reduce losses, prevent the spread of virulent organism and limit the cost of therapy. Careful daily observation of foals, daily recording of foal's temperatures, measurement of plasma fibrinogen every two weeks, periodic ultrasonographic examination of the lungs, and serological surveillance have all been used to successfully promote early diagnosis on enzootic farms (Giguère and Prescott, 1997). The use of one liter of hyperimmune plasma obtained from donors vaccinated with *R. equi* antigens has become the mainstay of prevention of this disease in foals on enzootically affected farms, since it has proved to be highly effective in reducing illness, and death (Hurley and Begg, 1995; Erganis et al., 2014).

Primary prophylaxis against *R. equi* is not routinely recommended, because no data are available to support its efficacy and because the infection is rare. Macrolide prophylaxis against *Mycobacterium avium* complex infection may offer some protection against *R. equi* infection for patients suffering from AIDS. Immunocompromised patients with significant exposure to domesticated animals should be cautioned regarding the possible risk of *R. equi* infection. Some investigators have advocated isolation of hospitalized patients with *R. equi* pneumonia, to prevent nosocomial spread, and this practice may be reasonable, especially considering our poor understanding of *R. equi* transmission and the previous reports of nosocomial spread (Arlotti et al., 1996; Scotton et al., 2000*).*

CONCLUSION

Rhodococcus equi, a well-recognized etiologic agent of equine rhodococcosis, is emerging as a significant opportunistic pathogen of immunocompromised host. The infection is recorded in many countries of the world including India. It affects primarily foals 2 to 6 months of age, and hoses above 6 months old are resistance unless immunosuppressed. The source of infection may be exogenous as organism occurs in the environment. The role of animals in the transmission of *R. equi* to humans remains unclear. Bacteriologic culture combined with cytological examination of trachea-bronchial aspirate remains the most definite method of an unequivocal diagnosis of *R. equi* pneumonia. The antibiotic combination of choice is erythromycin with rifampin. Frequent removal of manure from stable and keeping the foal in a clean, well ventilated, and hygienic pen will prevent buildup of *R. equi* in the immediate environment of animal.

Presently, no effective vaccination protocols for foals or dam have been described to date.

The role of *R. equi* in many clinical disorders of humans as well as animals should be further investigated. Attempts should also be made to study the epidemiology so that better foal management system could be developed. In addition, research towards the development of safe, potent and cheap *R. equi* vaccine for control purpose. Not only could the plasmid encoded *vap* genes, chromosomal genes also should be focused for the development of effective vaccine.

ACKNOWLEDGEMENT

We thank Segni Shimelis and Tilaye Shiberu for providing some literature on the subject.

REFERENCES

1. Aiello SE, Mays A (1998). (Ed.).The Merck Veterinary Manual.8th Ed. Merck and Co.INC, Whitehouse Station, NJ., USA.
2. Ardans AA, Hietala SK, Spensley MS (1986). Studies of naturally occuring and experimental *Rhodococcus equi*, in *Proceedings.* 32nd Annual Convention of the American Association of Equine Practioners. 129–144.
3. Arlotti M, Zoboli G, Moscatelli GL (1996). *Rhodococcus equi* infection in HIV-positive subjects: a retrospective analysis of 24 cases. Scandinavian J. Inf. Dis. 28: 4663-467.
4. Camponovo R, Garcia P (2006) . *Rhodococcus equi*. Review Child Infec. 23: 155-156.
5. Chen X, Xu F, Xia J, Cheng Y, Yang Y (2009). Bacteremia due to *Rhodococcus equi:* a case report and review of literature. J. Zhejiang Univ. Sci. 10: 933-936.
6. Cisek AA, Rzewuska M, Witkowski L, Binek M (2014). Antimicrobial resistance in *Rhodococcus equi*. Acta Biochim Pol. 2014 Nov 4.
7. Cohen ND (2014). *Rhodococcus equi* Foal Pneumonia. Vet Clin North Am Equine Pract. 2014 Oct 1. pii: S0749-0739(14)00068-6. doi: 10.1016/j.cveq.2014.08.010.
8. Corti M, Solari R, De Carolis L, Palmieri O, Rollet R, Shah HN (2014). *Rhodococcus equi* infection in AIDS patients: retrospective analysis of 13 patients in Argentina. Rev Children Infec. 2014 Aug;31(4):411-6. doi: 10.4067/S0716-10182014000400006.
9. Devi P, Mehrotra S, Chadha A (2011). Bacteremia due to *Rhodococcus equi* in an immunocompetent infant. Indian J. Medical Microbiol. 29: 65-68.
10. Doig C, Gill MH, Church DL (1991). *Rhodococcus equi:* an easily missed opportunistic pathogen. Scandinavian J. Infect. Dis. 23: 1-6.
11. Donisi A, Suardi MG, Casari S (1996). *Rhodococcus equi* infection in HIV-infected patients. AIDS 10: 359-362
12. Egawa T, Hara H, Kawase I (1990). Human pulmonary infection with *Corynebacterium equi*. European Resp. J. 3: 240-242.
13. Erganis O, Sayin Z, Hadimli HH, Sakmanoglu A, Pinarkara Y, Ozdemir O, Maden N (2014). The Effectiveness of Anti-R. equi Hyperimmune Plasma against R. equi Challenge in Thoroughbred Arabian Foals of Mares Vaccinated with R. equi Vaccine. The Scientific World Journal. Volume 2014 (2014), Article ID 480732, 10 pages. http://dx.doi.org/10.1155/2014/480732
14 .Giguere S, Cohen ND, Chaffin MK, Hines SA, Hondalus MK, Prescott JF, Slovis NM (2011). *Rhodococcus equi:* Clinical Manifestations, Virulence, and Immunity. Review J Vet Intern Med. 25:1221-1230.
15. Giguère S, Prescott JF (1997). Strategies for the control of *Rhodococcus equi* infections on enzootic farms. Proceed. American Assoc. Equine Pract. 43: 65-70.
16. Goodfellow M (1987). The taxonomic status of *Rhodococcus equi*. Vet. Microbiol. 14: 205-209.

17. Golub B, Falk G and Spink WW (1967). Lung abscess due to *Corynebacterium equi:* report of first human infection. Anna. Internal Med. 66:1174-1177.
18. Hurley JR, Begg AP (1995). Failure of hyperimmune plasma to prevent pneumonia caused by *Rhodococcus equi* in foals. Australian Vet. J. 72: 418-420.
19. Katsumi M, Kodoma N, Miki Y, Kikuchi N, Nakazawa M (1991). Typing of *Rhodococcus equi* isolated from submaxillary lymph nodes of in Japan. J. Vet. Med. 38: 299-302.
20. Magnusson H (1923). Spezifische infektiose pneumonie beim fohlen: ein neuer eitererreger beimpferd [in German]. Arch Wiss Prakt Tierheilkd, 50:22–38.
21. Martens RJ, Cohen ND, Chaffin MK (2002). Evaluation of 5 serologic assays to detect *Rhodococcus equi* pneumonia in foals. J. American Vet. Med. Associat. 221:825-83.
22. Nordmann P, Ronco E (1992). In-vitro antimicrobial susceptibility of *Rhodococcus equi*. J Antimicrobial Chemoth. 29: 383-393.
23. Pal M (2007). Zoonoses. 2nd Ed. Satyam Publishers, Jaipur, India.
24. Pal M (2013). Public health concerns due to emerging and re-emerging zoonoses. Int. J. Livest. Res. 3: 56-62.
25. Pal M, Tesfaye S, Dave, P (2013). Zoonoses occupationally acquired by abattoir workers. J. Environ. Occup. Sci. 2:155-162.
26. Prescott JF (1991). *Rhodococcus equi:* an animal and human pathogen. Clin. Microbiol. Rev. 4: 20-34.
27. Pusterla N, Wilson WD, Mapes S (2007). Diagnostic evaluation of real-time PCR in the detection of *Rhodococcus equi* in faeces and nasopharyngeal swabs from foals with pneumonia. Vet. Record 161: 272-275.
28. Rahman MT, Herron LL, Kapur V, Meijer WG, Byrne BA, Ren J, Nicholson VM, Prescott JF (2003). Partial genome sequencing of Rhodococcus equi ATCC 33701. Vet. Microbiol. 94: 143-158.
29. Rahman MT, Parreira VP, Prescott JF. (2005). In vitro and intra-macrophage gene expression by *Rhodococcus equi* strain 103. Vet. Microbiol. 110: 131-140.
30. Ren J, Prescott JF, 2003. Analysis of virulence plasmid gene expression of intra-macrophage and in vitro grown *Rhodococcus equi* ATCC 33701. Vet. Microbiol. 94, 167–182.
31. Rasmussen TT, Kirkeby LP, Poulsen K, Reinholdt J, Kilian M (2000). Resident aerobic microbiota of the adult human nasal cavity. APMIS 108: 663-675.
32. Rodriguez-Lazaro D, Lewis DA, Ocampo-Sosa AA (2006). Internally controlled real-time PCR method for quantitative species-specific detection and vapA genotyping of *Rhodococcus equi*. Appl. Environ. Microbiol. 72: 4256-4263.
33. Sakai M, Ohno R, Higuchi C, Sudo M, Suzuki K, Sato H, Maeda K, SakaiY, Kakuda T, Takai S (2012).Isolation of *Rhodococcus equi* from wild boar (Sus scrofa) in Japan. J. Wildlife Dis. 48: 815-817.
34. Sangal V, Jones AL, Goodfellow M, Hoskisson PA, Kämpfer P, Sutcliffe IC (2014). Genomic analyses confirm close relatedness between *Rhodococcus defluvii* and *Rhodococcus equi* (*Rhodococcus hoagii*). Arch Microbiol. 2014 Nov 20.
35. Sangal V, Jones AL, Goodfellow M, Sutcliffe IC, Hoskisson PA. (2014). Comparative genomic analyses reveal a lack of a substantial signature of host adaptation in *Rhodococcus equi* ('*Prescottella equi*'). Pathog Dis. 71(3):352-6.
36. Sangal V, Jones AL, Goodfellow M, Hoskisson PA, Kämpfer P, Sutcliffe IC. (2015). Genomic analyses confirm close relatedness between *Rhodococcus defluvii* and *Rhodococcus equi (Rhodococcus hoagii).* Arch Microbiol. 197(1):113-6.
37. Scotton PG, Tonon E, Giobbia M, Gallucci M, Rigoli R, Vaglia A (2000). *Rhodococcus*

equi nosocomial meningitis cured by levofloxacin and shunt removal. Clinic. Infect. Dis. 30: 223-224.

38. Sellon DC, Besser TE, Vivrette SL (2001). Comparison of nucleic acid amplification, serology, and microbiologic culture for diagnosis of *Rhodococcus equi* pneumonia in foals. J. Clinic. Microbiol. 39: 1289-1293.
39. Spiliopoulou A, Assimakopoulos SF, Foka A, Kolonitsiou F, Lagadinou M, Petinaki E, Anastassiou ED, Spiliopoulou I, Marangos M. 2014. Pulmonary infection by *Rhodococcus equi* presenting with positive Ziehl-Neelsen stain in a patient with human immunodeficiency virus: a case report. J Med Case Rep. 8(1):423.
40. Takai S (1997). Epidemiology of *Rhodococcus equi* infections. Vet. Microbiol. 56:167-176.
41. Takai S, Sasaki Y, Ikeda T, Uchida Y, Tsubaki S, Sekizaki T (1994). Virulence of *Rhodococcus equi* isolates from patients with and without AIDS. J. Clinic. Microbiol. 32: 457-460.
42. Talanin NY, Donabedian H, Kaw M (1998). Colonic polyps and disseminated infection associated with *Rhodococcus equi* in a patient with AIDS. *Clinic. Infect. Dis.* 26:1241-1242.
43. Ursales A, Klein JA, Beal SG, Koch M, Clement-Kruzel S, Melton LB, Spak CW (2014). Antibiotic failure in a renal transplant patient with Rhodococcus equi infection: an indication for surgical lobectomy. Transpl. Infect. Dis. 2014 Nov 21. doi: 10.1111/tid.12314
44. Van Etta LL, Filice GA, Ferguson RM, Gerding DN (1983). *Corynebacterium equi:* a review of 12 cases of human infection. Rev. Infect. Dise. 5:1012-1018.
45. Verville TD, Huycke MM, Greenfield RA, Fine DP, Kuhls TL, Slater LN (1994). *Rhodococcus equi* infections of humans. 12 cases and a review of the literature. Medicine. 73: 119-32.
46. Witkowski L, Rzewuska M, Rzewuska D, Kizerwetter-Swida M, Frymus T, Kita J (2011). *Rhodococcus equi* infections in animals and humans. Wiad Lek. 64(4):306-309.Weinstock DM, Brown AE (2002). *Rhodococcus equi:* an emerging pathogen. Clinic. Infect. Dis. 34:1379-1485.