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Case Report
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Severe pneumonia in a street rat (*Rattus norvegicus*) caused by *Rodentibacter rarus* strain RMC2

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Abstract

Background: Rodents are one of the most dangerous reservoirs and carriers of infectious diseases. Gradually, rats have become predominant in cities, sometimes staying in close vicinity to humans, pets, and other animals. Consequently, they tend to increase the transmission risk of pathogens.

Case Description: Here, we report an original case of bacterial pneumonia in a street rat (*Rattus norvegicus*). The rat was found dead on a street in the chief town of Marseille (France) after being run over by a car. The necropsy of the corpse revealed generalized granulomatous pneumonia in almost all the pulmonary lobes. Lung lesions and predominantly multiple fibro-inflammatory areas are presumably the witness of an infectious etiology. Bacterial isolation was carried out from lung tissues. Colonies were identified by MALDI-TOF MS and confirmed by 16S rRNA sequencing. The following bacteria were identified: *Staphylococcus cohnii*, *Bordetella bronchiseptica*, *Bordetella parapertussi, Corynebacterium glucuronolyticum*, *Pelistega suis* and *Rodentibacter rarus*. Based on the histopathological diagnosis and the avoidance approach, the most likely etiological agent of pneumonia is therefore *R. rarus*, a little-known Pasteurellales bacterium that is closely related to *Rodentibacter pneumotropicus*.

Conclusion: These data emphasize the severity of *R. rarus* infection in rodents. Thus, pointing out a potential risk for other animals (dogs, cats, and birds), as well as humans. The health monitoring program for rodents and rabbits pasteurellosis should now include *R. rarus*. Therefore, the pathological effect of the *Rodentibacter* species and/or strains needs to be better explored.

Keywords: Rodents, *Rattus norvegicus*, *Rodentibacter rarus,* Pasteurellosis, Pneumonia.

Introduction

Pasteurellaceae bacterium is often involved in pneumonia. They are among the most prevalent commensal and opportunistic bacteria found globally in domestic and wild animals (Wilson *et al.*, 2013). However, the surveillance of these microorganisms is limited to species and/or strains with a virulent effect, such as *Pasteurella pneumotropica*, and *Pasteurella multocida* (Itoh and Kurai, 2018), a well-known pathogen for humans and a wide range of animals. Due to the gravity of the disease and zoonotic risk, the Federation of European Laboratory Animal Science Associations recommended a health monitoring program for laboratory rodents and rabbits for Pasteurellaceae infections (Nicklas *et al.*, 2002; Mähler Convenor *et al.*, 2014), especially *P. pneumotropica*.

Pasteurella pneumotropica was initially isolated and described by Jawetz (1950) from pneumonic lesions of laboratory mice. Later, the human biotype of *P. multocida* was reclassified as *P. pneumotropica* by Henriksen (1962). However, recent advances in clinical microbiology as well as in molecular taxonomic systems, allowed for the reclassification of *P. pneumotropica* to a distinct species within the genus *Rodentibacter*. Two *P. pneumotropica* biotypes, namely Jawetz and Heyl, were reclassified as part of *Rodentibacter pneumotropicus* and *Rodentibacter heylii*, respectively (Adhikary *et al.*, 2017). Other *Rodentibacter* species, namely *R. ratti, Rodentibacter myodis, Rodentibacter heidelbergensis, R. heidelbergensis, R. trehalosifermentans, Rodentibacter mrazii*, and *Rodentibacter rarus* (Adhikary *et al.*, 2017) were derived from some Bisgaard strains (Boot and Bisgaard, 1995). The identification of Pasteurellaceae as an etiological agent of rodents, usually isolated from the nasopharynx (Dafni *et al.*, 2019), is lacking efficiency since the clear-cut distinction between these species/strains relies on a laborious biochemical analysis (Adhikary *et al.*, 2017). Consequently, the diseases they induce remain poorly studied. Nowadays, scant pathological studies on a few *Rodentibacter* species have been reported. *Rodentibacter pneumotropicus* and *R. heylii* are highly virulent pathogens for immunodeficient mice, inducing severe pneumonia,

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septicemia, and conjunctivitis (Kawamoto *et al.*, 2011). *Rodentibacter pneumotropicus* was also involved in bronchopneumonia and septicemia in wildtype mice (Fornefett *et al.*, 2018).

The brown rat or Norwegian rat (*Rattus norvegicus*) arrived in Europe around 1,750 through international trade vessels. These rodents then became dominant in cities, usually around the port cities by supplanting the black rat (*Rattus rattus*) (Schweinfurth, 2020). In addition to the bad image they give to the cities, they are the most threatening sentinel of public health by propagating a wide range of pathogens. In Marseille, which is the second-largest commune in France with 863,310 inhabitants, we have already conducted studies to identify pathogens in street rats (86 *R. norvegicus* and 22 *R. rattus*): *Hantavirus* (0%) *Bartonella* spp. (30%), *Leptospira interrogans* (9%), *Streptobacillus moniliformis* (13%), *Calodium hepaticum* (44%), *Trichinella* spp. (0%), and *Xenopsylla cheopis* (21%) (Boni *et al.*, 1997; Davoust *et al.*, 1997; Gundi *et al.*, 2004; Socolovschi *et al.*, 2011). More recently, in an urban park near Paris, the brown rats were found to be infected with *Rickettsia* spp. (1.2%), *Bartonella* spp. (53%), *Francisella tularensis* (5%), and *Leptospira* spp. (21%) (Desvars-Larrive *et al.*, 2017). Paradoxically, worldwide, the wild brown rat is one of the most prevalent animals.

Nowadays, studies on pulmonary infectious diseases of brown rats are lacking. These rodents have been investigated for pulmonary infectious diseases only in Vancouver city (631,486 inhabitants) in Canada, a similar city to Marseille (Himsworth *et al.*, 2014a, 2014b). Notably, researchers reported macroscopic and histologic lesions, particularly in the lungs. These data remain the only available ones (Himsworth *et al.*, 2013; Rothenburger *et al.*, 2015), wherein the peribronchiolar and/or perivascular lymphoplasmacytic cuffs were present and were also significantly associated with a cilia-associated respiratory bacillus and *Mycoplasma pulmonis* (Rothenburger *et al.*, 2019). In this context and to extend our knowledge on the pulmonary diseases of brown rats, we present in this article an original case of severe bacterial pneumonia from a street rat in Marseille (France).

Case Details

In December 2019, a rat was struck by a round run in the chief town of Marseille (France) (43°17′06.2 ″N – 5°23′46.7 ″E). The rat corpse was immediately transported to a specific biohazard bag to the veterinary research center at the Institut Hospitalo-Universitaire (IHU) Méditerrannée Infection. The preliminary examination showed that the corpse corresponds to a street rat (*R. norvegicus*), male, weighing 475 g, with a length (head + body) of 25 cm and a tail length of 22 cm. Except for the head, which was strongly damaged, the corpse had a normal appearance. However, a few ectoparasites (*Ornithonyssus* spp.; family Macronyssidae; Acari) were observed.

The rat corpse was necropsied and sampled as described elsewhere (Herbreteau *et al.*, 2011). Visual examination of tissues and visceral organs was carefully carried out. Microscopic examination was carried out using both routine and specific staining techniques and examined at three different magnifications (20×, 80×, and 300×). Besides, the following quantitative polymerase chain reaction (qPCR) screening was carried out on lung tissues to search for the most-known bacteria causing pneumonia: *Mycobacterium* spp. (Bruijnesteijn van Coppenraet *et al.*, 2004), *Pneumocystis jirovecii* (Linssen *et al.*, 2006), *Mycoplasma* species (Cohen-Bacrie *et al.*, 2011), *Mycoplasma pneumonia* and finally, *M. hominis* using a homemade qPCR based on the newly designed primers targeting the 16S rRNA gene of *M. hominis*: Mhom_16S_F_GCTGTTATAAGGGAAGAACATTTGC, Mhom_16S_R_GGCACATAGTTAGCCATCGC and the hydrolysis TaqMan® probe Mhom_16S_P_6FAM-AAATGATTGCAGACTGACGGTACCTTGTCAG.

Bacterial isolation was carried out by inoculating three pieces from the lung tissue into Columbia agar medium supplemented with 5% sheep blood (bioMérieux, Marcy l'Etoile, France). The culture was carried out for 24 hours at 37°C. Once isolated, bacterial colonies were subjected individually to MALDI-TOF MS identification as previously described (Seng *et al.*, 2009). Subsequently, genomic DNA was extracted from each bacterial colony using the EZ1 DNA tissue kit (Qiagen, Courtaboeuf, France) and subjected to the 16S sequencing (Weisburg *et al.*, 1991). Species resolution was carried out using BLASTn analysis (Altschul *et al.*, 1990).

Molecular phylogenetic analysis was conducted essentially for bacterial strains identified as the most likely species to be involved in pneumonia. Multiple alignments against the homologous GenBank sequences was conducted using multiple alignment using fast Fourier transform (MAFFT) (Katoh *et al.*, 2002). The Best fit model and maximum likelihood phylogeny were conducted on MEGA 6 (Tamura *et al.*, 2013). Phylogram was edited using iTOL v4 software (Letunic *et al.*, 2019). Additionally, the interspecific nucleotide pairwise distance (NPD) was evaluated to estimate the genetic divergence between the bacterial strains we isolated herein and those from the GenBank database using MEGA 6 (Tamura *et al.*, 2013).

Finally, this bacterium was subjected to the antimicrobial susceptibility test according to the European Committee on Antimicrobial Susceptibility Testing.

See SI Materials and Methods for complete details on the materials and methods.

The necropsy examination revealed that the cause of death was due to severe brain injury caused by a round run. Furthermore, the necropsy revealed generalized granulomatous pneumonia lesions. Granulomas appeared to be consistently hard and whitish with up to 2 mm in diameter and were distributed throughout all the lung tissues (Fig. 1). On the liver, we observed

multiple small nodules composed of whitish fibrosis, suggesting *C. hepaticum* parasitism. Finally, few necrosis foci were observed in the kidneys.

Histological analysis of the lung tissues revealed the presence of several fibro-inflammatory areas of up 2 mm in diameter (Fig. 2a). These foci were dominated by the presence of a hyaline fibrous scar containing inflammatory cells, mainly epithelioid macrophages with a rim of lymphocytes (Fig. 2b). We also noted a small number of multinucleated giant cells (MGC) in these lesions. However, central necrosis and bacteria were not present (Fig. 2c).

Additionally, the lung tissue showed the foci of inflammatory cells with a patchy distribution, and the alveoli filled mainly with lymphocytes and alveolar macrophages (Fig. 3a). Arterial vessels were surrounded by chronic inflammatory cells (Fig. 3b).

Accordingly, the histologic analysis of the whitish hepatic nodules confirmed the presence of the parasitic nematode *C. hepaticum* (formerly known as *Capillaria hepatica*; Trichocephalida, Capillariidae). Nematode eggs were visualized in great number surrounding the fibrous tissue. These hepatic nodules measured 0.5–2 mm in diameter and were distributed under the hepatic capsule inside the parenchyma.

All lung tissue samples were qPCR negative for *Mycobacterium* spp., *Mycoplasma* spp., *M. pneumoniae*, *M. hominis*, and *P. jirovecii*.

Bacterial growth was observed among all the inoculated lung tissues on the agar medium at 37°C. MALDI-TOF MS and 16S sequencing yielded the identification of at least ten bacterial colonies (Table 1).

Phylogenetic analysis of the 16S sequences (Fig. 4) showed that the bacterial strain of *R. rarus* from the colony RMC2 was clustered together with *R. rarus* strains (NR156996 and AY362902) and the other *Rodentibacter* species isolated from rats (*R. mrazii, R. ratti, R. heidelbergensis* and *R. trehalosifermentans*). This group of rat-associated *Rodentibacter* formed a monophyletic clade with mouse-associated *Rodentibacter* (*R. pneumotropicus* and *R. heylii*). Similarly, the lowest (0.002; 0.003) NPD of *R. rarus* (RMC2) herein we isolated was observed with *R. rarus* strains.

Rodentibacter rarus was considered here as the most likely etiological agent of rat-pneumonia. The 16S sequence of *R. rarus* strain RMC2 was deposited in the GenBank database under MT860347, while the bacterial isolate was deposited in the strain collection (Collection de Souches de l'Unité des Rickettsies WDCM 875) under accession number Q4538.

Rodentibacter rarus RMC2 strain was sensitive for all tested antibiotics except for ciprofloxacin against which the bacteria showed a resistance expressed by 22 mm disk diameter (Table 2).

Discussion

We describe here the histopathological lesions in bacterial pneumonia potentially caused by *R. rarus* in a street rat. The necropsy examination revealed an unexpected lung lesion never encountered in previous

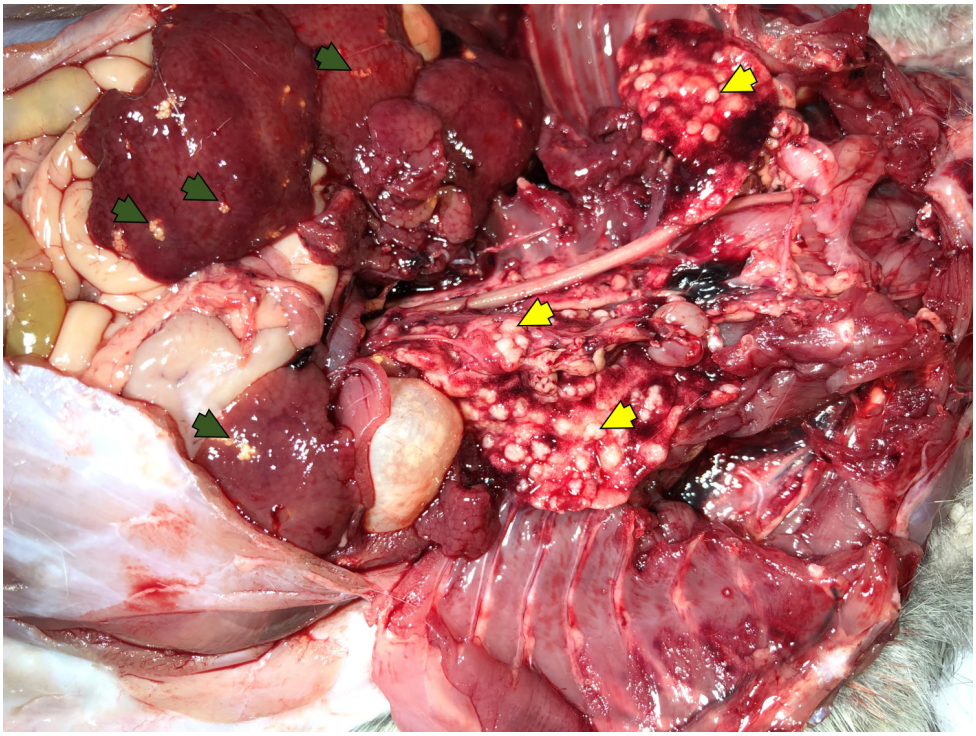

Fig. 1. Necropsy examination of the rat corpse showing the thoracic and abdominal viscera. Arrowed lesions indicate whitish colored nodules distributed throughout the lung (yellow arrows) and liver (green arrows) parenchyma.

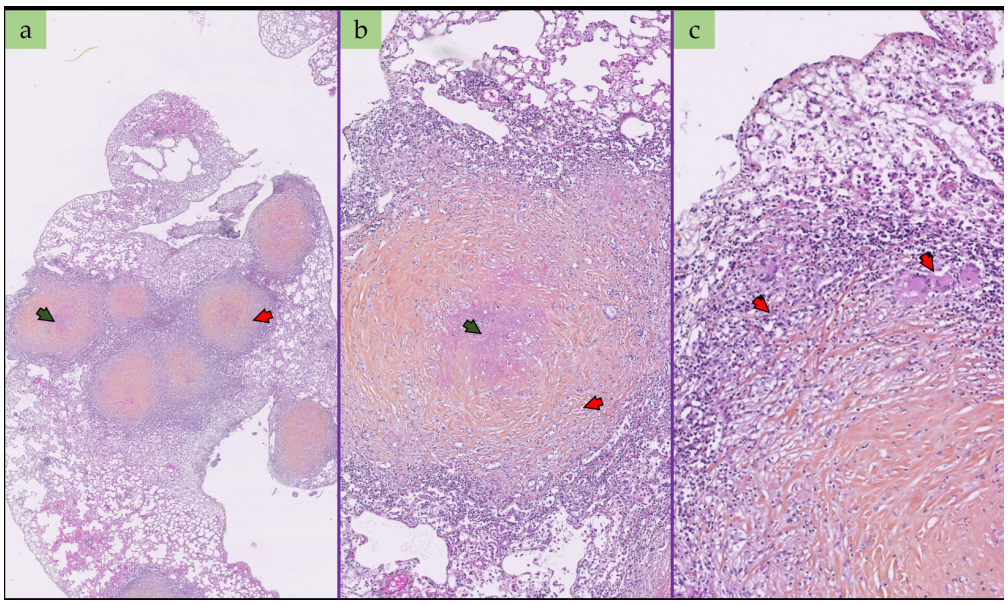

Fig. 2. Hematoxylin eosin saffron staining of the lung section examined at 20× (a), 80× (b), and 150× (c) magnifications showing the histopathological aspect of the lung. (a and b) Lesions containing mononuclear inflammatory cells (green arrows) surrounded by fibrous tissue (red arrows). (c) Pulmonary granuloma with MGC (red arrows).

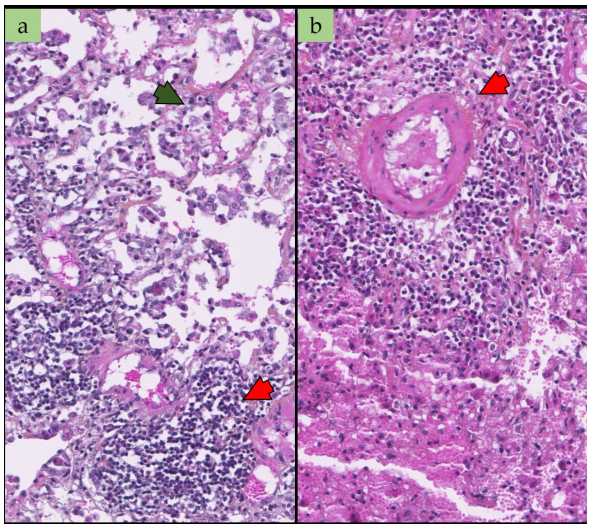

Fig. 3. Hematoxylin eosin saffron staining of the lung section examined at 300× magnification. (a) Dense inflammatory infiltrate composed of lymphocytes (red arrow) and alveolar macrophages (green arrow). (b) Alveolar inflammatory infiltrates around an arterial vessel (red arrow).

studies (Davoust *et al.*, 1997; Boni *et al.*, 1997; Gundi *et al.*, 2004; Socolovschi *et al.*, 2011). Since the infection is natural, which could involve several potential pathogens, we used the experiential avoidance approach relying on the full exploration of pathogens following a one-by-one elimination of the detected microorganisms according to their known pathological status, if it had been already described.

In the present study, we searched for the possible bacterial agent that could be involved in rat pneumonia, while no search for viruses has been undertaken. According to the histopathological lesions and literature, no virus is known to induce such lesions in rats (Rothenburger *et al.*, 2015; Kling, 2011). Therefore, the extension of the granulomatous lesions to almost all the pulmonary lobes supported the exclusion of parasitic origin.

Pneumocystis jirovecii infection was, however, investigated. Since the PCR was negative and pathological analysis did not reveal any cystic forms in the pulmonary alveoli, this etiology was discarded. *P. carinii* has been consistently identified as a causative agent in the pneumonia of wild brown rats co-infected with *M. pulmonis* (Rothenburger *et al.*, 2015). *Mycoplasma pulmonis* is the most common cause of bronchopneumonia in rats (Kling, 2011) and causes purulent pneumonia, not granulomatous. Our macroscopic and histological observations were not in favor of this diagnosis, and it was further excluded by the mycoplasma-negative PCR. In this study, neither *P. carinii*, *Mycoplasma pneumoniae* nor *M. hominis* were detected.

On the other hand, the importance of the fibrosis inside the granulomas suggested an old bacterial infection that is not in favor of mycobacteriosis that causes granulomatous inflammatory reactions, forming both caseating and noncaseating granulomas. Therefore, the presence of mycobacterial infections was also excluded by both PCR and Ziehl–Neelsen staining.

Thanks to the bacterial culture, followed by MALDI-TOF MS and 16S sequencing, we initially identified four bacterial strains (*Staphylococcus cohnii, Pelistega*

Table 1. MALDI-TOF MS and 16S rRNA identifications of isolated colonies.

Isolate	MALDI-TOF MS	16 sequencing		
Colony Id.	Species name	Accession no.	Species name	Identity (%)
RMC 1	*S. cohnii*	HG941657	*S. cohnii*	99.9
RMC 2	Unidentified	KX858113	*R. rarus*	99.04
RMC 3	*B. bronchiseptica*	E03742/CP052851	*B. bronchiseptica/B. parapertussis*	100
RMC 4	*Bordetella holnesii*	CP018899	*B. holnesii*	99.5
RMC 5	*Corynebacterium glucuronolyticum*	AJ277970	*C. glucuronolyticum*	100
RMC 6	Unidentified	E03742/CP052851	*B. bronchiseptica/B. parapertussis*	100
RMC 7	Unidentified	E03742/CP052851	*B. bronchiseptica/B. parapertussis*	100
RMC 8	Unidentified	NR_145928 strain (3340-03)	*P. suis*	99.16
RMC 9	Unidentified		*P. suis*	99.16
RMC 10	Unidentified	NR156996	*R. rarus*	99.02

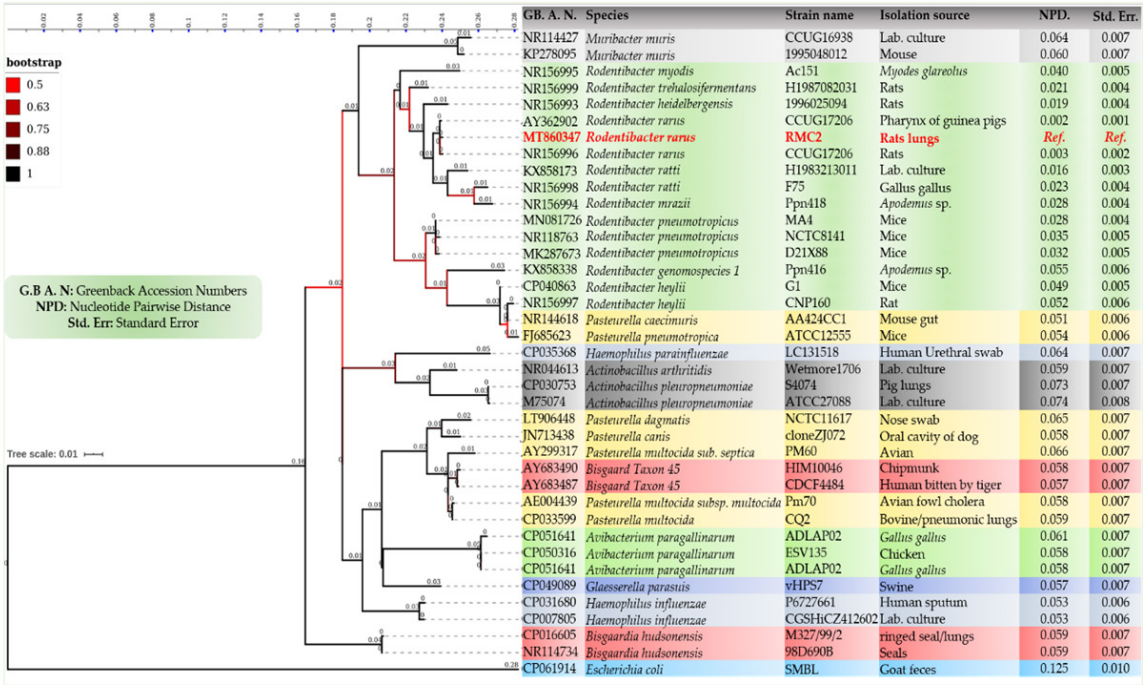

Fig. 4. Phylogenetic tree showing the position of *R. rarus* strain isolated in the present study (indicated in red) among the representative members of the *Pasteurellacea* family. The tree was inferred using the Maximum Likelihood method based on 1000 bootstraps and the Kimura 2-parameter model. The analysis involved 39 nearly complete (1409) 16S rRNA sequences. Outgroup taxons *Escherichia coli* (CP061914) are drawn at the root. A discrete Gamma distribution was used to model evolutionary rate differences among sites [five categories (+G. parameter = 0.2834)]. The rate variation model allowed for some sites to be evolutionarily invariable [(+I). 59.6971% sites]. Log likelihood was −6,365.9530. The axis showed the global distance observed throughout the trees. The value above branches indicates branch length. Branches are color-coded according to the bootstrap's percent. The identity of each taxon is color-coded according to the genus. GenBank accession numbers, strain name, and isolation source are indicated at each node. The number of base substitutions per site from between the *R. rarus* strain isolated in the present study and the GenBank strains is shown. Standard error estimate(s) are shown in the last column. Analyses were conducted using the Maximum Composite Likelihood model in MEGA 6. All ambiguous positions were removed for each sequence pair (pairwise deletion option).

Table 2. Detailed results of the antimicrobial susceptibility testing of *R. rarus* strain MRC2.

Abbreviation	Antibiotic	Concentration (µg/ml)	Ø (mm)	S/R
TIC	Ticarcillin	75	40.5	S
TCC	Ticarcillin/Clavulanic acid	10	40.4	S
TPZ	Piperacillin/Tazobactam	36	38.5	S
ATM	Aztreonam	40	39.8	S
CAZ	Ceftazidime	30	33.4	S
FEP	Cefepime	30	43.2	S
MER	Meropenem	10	34.5	S
IPM	Imipenem	10	36.3	S
FF	Fosfomycin	200	41.3	S
RA	Rifampicin	300	27.8	S
SXT	Trimethoprim/Sulfamethoxazole	25	39.4	S
AK	Amikacin	30	20.2	S
CIP	Ciprofloxacin	5	22	R
DO	Doxycycline	30	29	S
CT	Colistin	50	25.2	S
CN	Gentamicin	15	29	S

S = Sensitive; R = Resistant.

suis, Bordetella parapertussis, and *R. rarus*) that could be the potential cause of this pneumonia.

Staphylococcus cohnii is a coagulase-negative staphylococci bacterium colonizing skin and mucous membranes of humans, farm, and companion animals (Mendoza-Olazarán *et al.*, 2017). It may have been the cause of a few cases of nosocomial infections (Hu *et al.*, 2014). In rats, staphylococci infections cause skin abscesses but never pneumonia (Heilmann *et al.*, 2019). Exceptionally, this bacterium was found to be transmitted by rat bite in one of 40 rats studied (Himsworth *et al.*, 2014c). With regard to other coagulase-negative staphylococci, *S. cohnii* is frequently detected as contaminants of microbiological cultures from clinical specimens (Mendoza-Olazarán *et al.*, 2017).

Pelistega suis was initially isolated from the tonsils swab samples of pigs and wild boars (Vela *et al.*, 2015). However, there is no reported data on its pneumonic pathogenicity neither in their type of hosts nor in rats, While *B. parapertussis* is the agent of a mild form of whooping cough (20% of the cases), a highly contagious disease of the upper respiratory tract in humans. The involvement of this bacterium in rat pneumonia remains completely avoided since humans are the only known reservoir and there were no available data from rodent hosts (Guiso, 2015). On the contrary, *Bordetella bronchiseptica* causes respiratory infections in many different mammals, including mice, rats, rabbits, cats, dogs, ferrets, foxes, pigs, hedgehogs, sheep, horses, and, occasionally, humans (Mattoo and Cherry, 2005). *Bordetella bronchiseptica* causes in rats multifocal bronchopneumonia with polymorphonuclear cell and lymphocytic infiltration with peribronchial lymphoid hyperplasia as revealed in the microscopic examination (Kling, 2011). However, *B. bronchiseptica* infection could not be confirmed in this study, since the clear-cut distinction between *B. bronchiseptica* and *B. parapertussis* was not possible by the 16S sequencing. Therefore, the histopathological lesions were not in favor of *B. bronchiseptica* infection.

Finally, *R. rarus* is one of the frequent Pasteurellales agents of rats. Phylogenetic characterization revealed its placement with rat-associated *Rodentibacter* species. These species were also monophyletic with the known virulent strains of rat and mouse-associated *Rodentibacter*. Furthermore, *R. rarus* was close to *R. pneumotropica*, the agent of rodent pneumonia and septicemia (Frebourg *et al.*, 2002).

The genome-based description of *R. rarus* was recently made on the type of species of *R. rarus* (CCUG number: 17206, DSM number: 103980, NCBI: txid1908260) (Adhikary *et al.*, 2017), initially isolated from a rat in Denmark and later from the mouse as the reference strain of taxon 17 of Bisgaard (1993). Despite the low host specificity of the *Rodentibacter* species, the phylogenetic analysis we conducted herein revealed that rat and mouse-associated *Rodentibacter* are grouped according to their hosts. Therefore, we confirm the previous phenotypic characterization of the *Rodentibacter* species (Adhikary *et al.*, 2017).

The problem in rodent Pasteurellaceae infections is evident. Since the latest molecular-based

reclassifications, there is an emergence of several *Rodentibacter* species from *Pasteurella* species, and the clear-cut identification of the etiological agent of the Pasteurellales diseases is difficult. Although the investigation conducted by Hayashimoto in 2008 on the pathological effect of different *P. pneumotropica* strains revealed that pulmonary lesions were observed within *P. pneumotropica* ATCC 35149 and CNP 160 strains. However, the possibility that these strains are one of the *Rodentibacter* variants could not be ruled out in the absence of molecular data (Hayashimoto *et al.*, 2008). Rodents are the main hosts of *Rodentibacter* bacteria causing pneumonia. Usually, immunocompetent rodents are asymptomatic carriers. Experimental infections of severe combined immunodeficient (SCID) mice cause the appearance of pneumonia lesions (Sasaki *et al.*, 2018). Another study showed that a highly virulent strain of *R. pneumotropicus* causes severe pneumonia and septicemia after intranasal infection of C57BL/6 and BALB/c mice (Fornefett *et al.*, 2018). Alveoli and bronchioles of this mouse were infiltrated with a high number of neutrophils. *Rodentibacter pneumotropicus* is best known in laboratory rodents (rat and mouse) as an opportunistic microbe that can seriously affect the health of rodents and thus disrupt experiments (Benga *et al.*, 2018).

So far, data on the pathogenicity of *R. rarus* in rodents are lacking and have never been studied in other hosts. Here, we report the first isolation of a pathogenic strain of *R. rarus* from a street rat. The bacterium was genetically close to rat-associated *Rodentibacter* with a close relatedness to the virulent strain of *R. pneumotropicus*.

Conclusion

From all the results, the clear-cut distinction between the opportunistic or the strictly virulent character of *R. rarus* we isolated herein cannot be ruled out yet. Further investigation on the virulence of this strain is needed. Obviously, our results need to be confirmed or disproved by an experimental model of *R. rarus* infections for the purpose of health monitoring of laboratory rodents (Otto and Myles, 2020; Fingas *et al.*, 2019). Our initial work on the detection of pathogenic microorganisms in brown rats must be part of our ongoing efforts to inform health authorities about the risks these animals may present. Moreover, this case of pneumonia associated with *R. rarus* is of great importance as it concerns a species of commensal rodent living in the vicinity of other animals (dogs, cats, and birds) and humans. The World Health Organization is working to bring together experts in the control of rodent commensal reservoirs and potential vectors of zoonoses and to publish recommendations (Colombe *et al.*, 2019).

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Conflicts of interest

The authors declare that there is no conflict of interest.

Authors' contribution

Conceptualization: BD; formal analysis and investigation: HM, YL, BS, HL, and HD; writing and original draft preparation: BD, HM, YL, and HD; writing review: BD and HM; supervision: OM and BD. All authors read and approved the published version of the manuscript.

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