Veterinary Microbiology 133 (2009) 211–228

Contents lists available at ScienceDirect

Veterinary Microbiology

journal homepage: www.elsevier.com/locate/vetmic

Review

Rat bite fever☆

Wim Gaastra [a], Ron Boot [b], Hoa T.K. Ho [c,d], Len J.A. Lipman [c,*]

[a] Department of Infectious Diseases and Immunology, Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands
[b] Section of Laboratory Animal Microbiology, Diagnostic Laboratory for Infectious Diseases and Perinatal Screening, National Institute of Public Health and the Environment, Bilthoven, The Netherlands
[c] Division of Public Health and Food Safety, Institute for Risk Assessment Sciences, Utrecht University, Yalelaan 2, 3508 TD Utrecht, The Netherlands
[d] Faculty of Animal Husbandry and Veterinary Medicine, Nong Lam University, Ho Chi Minh City, Viet Nam

ARTICLE INFO

Article history:
Received 9 November 2007
Received in revised form 19 September 2008
Accepted 22 September 2008

Keywords:
Streptobacillus moniliformis
Spirillum minus
Zoonosis
Rat bite fever
Haverhill fever

ABSTRACT

Rat bite fever (RBF) is a bacterial zoonosis for which two causal bacterial species have been identified: *Streptobacillis moniliformis* and *Spirillum minus*. Haverhill fever (HF) is a form of *S. moniliformis* infection believed to develop after ingestion of contaminated food or water.

Here the infectious agents, their host species, pathogenicity (virulence factors and host susceptibility), diagnostic methods, therapy, epidemiology, transmission and prevention are described. Special emphasis is given on information from the field of laboratory animal microbiology and suggestions for future research.

Contents

☆ Burning in the patches. Nodular and urticarial eruption: petichial and even haemorrhagic patches on the body: oedematous condition, discoloration and even ulceration of the nodules: lividity of the mucous membranes and haemmorrhagus. Yogaratnakarone, Wagabhatt Shushrut, 300 BC.

* Corresponding author. Tel.: +31 302535342.
E-mail address: L.J.A.Lipman@iras.uu.nl (Len J.A. Lipman).

0378-1135/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.vetmic.2008.09.079

1. Introduction

Rat bite fever (RBF) is a zoonotic infection with two causative bacteria: *Streptobacillus moniliformis* and *Spirillum minus*. The bacteria are transmitted via a bite or a scratch by an infected host animal. If humans become orally infected by *S. moniliformis* the disease is called Haverhill fever (HF).

Worldwide millions of people are bitten by animals each year. Ninety percent of these bites are by dogs and cats (Griego et al., 1995). Rats are responsible for 1% of the bites (Glaser et al., 2000). The relation between humans and animals is changing and many animal species once regarded as pests, are now kept as pets, of which rodents are just examples. Bites from rats and other rodents therefore probably occur in increasing numbers. With an estimated number of 10 billion, rats make up one third of the mammalian population of the world (Wincewicz, 2002). According to one report 40,000 rat bites are recorded annually (Committee on Urban Pest Management, 1980). It is estimated that 2% of rat bites lead to infection (Ordog et al., 1985).

People have known for long that rat bites may result in illness (Roughgarden, 1965). Wagabhatt who lived in India 2300 years ago already referred to the cutaneous lesions produced by rat bites (Row, 1918) and many observers believe that RBF was first recognized in that country. Among the bacteria detected in rat bite wounds are staphylococci, *Leptospira* spp., *Pasteurella* spp., *Corynebacterium* and *Fusobacterium* spp. and the RBF agents *S. moniliformis* and *S. minus* (Krauss et al., 2003). The disease was already reported in the US in 1839 (Wilcox, 1839). For many years great confusion over the etiology of RBF existed. Schottmüller, Blake, Tileston and others described the isolation of "Streptothrix muris ratti" (*S. moniliformis*) from the blood of human patients with recurrent fever following rat bites almost 100 years ago (Schottmüller, 1914; Blake, 1916; Tileston, 1916). A streptothrix-like organism was recognized in the blood of RBF patients before the organism was isolated and characterised in pure culture. Japanese scientists however, showed that RBF was also caused by a spirochetal organism named "Spirochaeta morsus muris" or *Spirillum minus* (Futaki et al., 1916). To date there is no question that RBF can be caused by either *S. moniliformis* or *S. minus*. *S. moniliformis* is the more common cause of RBF occurring worldwide. *S. minus* infection is reported less frequently and occurs mainly in Asia. In Japan the disease is known as sodoku (so = rat, doku = poison).

2. The infectious agents

2.1. Historical names

2.1.1. Streptobacillus moniliformis

In the older literature several names for this bacterium can be encountered like "Streptothrix muris ratti", "Nocardia muris", "Actinomyces muris ratti" (Borgen and Gaustad, 1948), "Haverhillia multiformis", "Actinomyces muris", "Asterococcus muris" (Heilman, 1941), "Proactinomyces muris", "Haverhillia moniliformis" (Parker and Hudson, 1926), *Actinobacillus muris* (Waterson and Wedgwood, 1953) and "Clostridium actinoides var. muris". In 1925, the organism obtained its present name *Streptobacillus moniliformis* (Levaditi et al., 1925). It is the only species in the genus.

2.1.2. Spirillum minus

S. minus was first described by Futaki et al. (1916) as the cause of RBF. Almost 30 years earlier bacteria named "Spirillum minor" were described in wet mounts from the blood of a wild rat (Carter, 1888). In older literature also several other names such as "Spirochaeta morsis muris", "Spirochaeta laverani", "Spironema minor", "Leptospira morsus minor", "Spirochaeta muris" and "Spirochaeta petit" can be found. The organism was named *S. minus* in

1924 (Robertson, 1924). It should be noted that the organism is not on the Approved List of Bacterial Names (http://www.bacteriocict.fr/) since no type or reference strain for this taxon have been identified.

2.2. Cultural properties

S. moniliformis is fastidious and requires media enriched with 10–20% blood, serum or ascitic fluid for growth. *S. moniliformis* may appear an obligate anaerobe on first isolation, but on subculture it is a facultative anaerobe except isolates from guinea pigs which are obligate anaerobes (Fleming, 1976). In liquid media with serum, the bacterial growth shows a typical "puff-ball" or "bread crumb like" appearance (Fig. 1). The ability to develop cell wall deficient L-forms that are difficult to culture was demonstrated (Freundt, 1956a; Freundt, 1956b; Pins et al., 1996). They are readily formed, likely due to the low glucosamine and muramic acid content of the bacterial cell wall (Smith, 1998). Colonies of L-forms have a "fried egg" appearance, difficult to distinguish from *Mycoplasma* colonies. As for other fastidiously growing bacteria like *Capnocytophaga canimorsus* (Sowden et al., 1995), polyanethole-sulphonate, an anticoagulant frequently present in automatic blood culture systems, inhibits the growth of *S. moniliformis* in concentrations as low as 0.0125% (Lambe et al., 1973; Shanson et al., 1985; Andre et al., 2005). Nevertheless, several successful isolations of *S. moniliformis* using these systems have been reported (Sens et al., 1989; Torres et al., 2003).

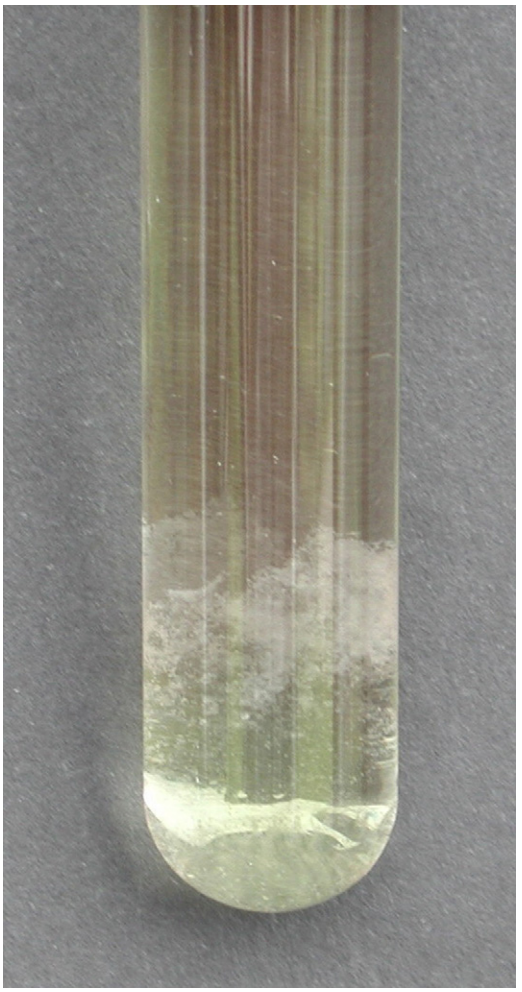

Fig. 1. "Puffball" like growth of *S. moniliformis* strain CCUG 43797 in thioglycollate medium.

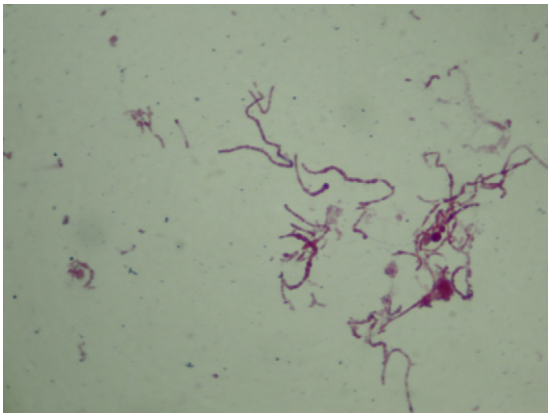

Fig. 2. Gram stain of *S. moniliformis* (strain CCUG 43797) grown in liquid culture.

S. moniliformis is an extremely pleomorphic, non-motile, non-sporulating, non-encapsulated Gram-negative rod (0.1–0.7 × 1–5 μm) with rounded or pointed ends that can form unbranched filaments 10–150 μm long (Fig. 2). The bacterium is less pleomorphic in stains from animal and human tissues than in stains from cultures. Depending on the growth medium and age of the culture, the filaments often are curled or form loops. These loops occasionally show lateral bulbar swellings with the appearance of a "string of beads", hence the specific name *moniliformis* (Latin) meaning in the form of a necklace. *S. moniliformis* sometimes does not stain well in the Gram stain but either carbolfuchsine or Giemsa stains can be used.

2.3. Genetic characteristics

Based on resemblance in colony morphology of L-forms of *S. moniliformis* with *Mycoplasma* colonies, the lack of quinones in cell extracts and the predilection of both bacteria in various animal species for the joint (Adler and Shirfrine, 1960) it was thought for some time that *S. moniliformis* was related to the Mycoplasmatales (Wullenweber, 1995). By one-dimensional SDS-PAGE total protein profiles of *S. moniliformis* strains from different countries and animal species, including humans, were found similar (Costas and Owen, 1987) and quite different from those of *Mycoplasmatales* and "Streptobacillus actinoides" isolated from calves (Gourlay et al., 1982), for which also a relation to *S. moniliformis* has been suggested. The relation of *S. moniliformis* with *Mycoplasma* was eventually proven incorrect by 16S rDNA analysis (Brenner et al., 2005).

The G + C content of *S. moniliformis* DNA is 25% (Savage, 1984). *S. moniliformis* strains of rat, mouse and human origin have been submitted to 16S rDNA sequence analysis. On the basis of these 16S rDNA sequences the genus *Streptobacillus* is now placed with the genera *Fusobacterium*, *Ilyobacter*, *Leptotrichia, Propionigenium*, *Sebaldella* and *Sneathia* within the *Fusobacteriaceae* family (Brenner et al., 2005) which is quite remote from the Mycoplasmatales. A 90% 16S rDNA sequence similarity between an unclassified bacterial fish pathogen and the type strain of *S. moniliformis* was noted (Maher et al., 1995). The 16S rDNA based relationship of *S. moniliformis* with other *Fusobacteriaceae* genera is supported by the outcome of a comparison of 16S–23S rRNA internal transcribed spacer sequences (Conrads et al., 2002). *S. moniliformis* strains from guinea pig, turkey and "S. actinoides" from calves have not been submitted to 16S rDNA sequencing. As these strains were not stored their exact taxonomy is unknown.

The genome sizes of *S. moniliformis* (about 1.8 Mbp; Gaastra et al., unpublished) and of its relative *Fusobacterium nucleatum* (2.4 Mbp; Bolstad, 1994) are closer to the 0.6–1.35 Mbp genome size of *Mycoplasma* spp. (Fadiel et al., 2007) than to the 4.4–5.6 Mbp genome size of *E. coli* (Binnewies et al., 2006).

2.3.1. S. minus

S. minus is a spiral shaped Gram-negative (sometimes Gram-variable) bacterium, 0.2–0.5 μm wide and 1.7–5 μm long. The bacterium is actively motile by two to six spirals and bipolar bundles of flagella (Adachi, 1921; see Shwartzman et al., 1951 for an electron micrograph). The bacterium cannot be cultured on artificial media in spite of reports on its successful culture in fluid media, consisting of modified veal infusions incubated under CO_2 atmosphere (Joekes, 1925; Hitzig and Liebesman, 1944; Shwartzman et al., 1951). The taxonomic position of *S. minus* will remain unclear until appropriate nucleic acid based phylogenetic studies have been performed. The failure to grow *S. minus* implies a lack of data with respect to growth requirements, phenotypic and genetic characteristics. Isolation of the organism still requires animal inoculation.

2.4. Phenotypic characteristics

2.4.1. S. moniliformis

The biochemical characteristics for *S. moniliformis* are given in Bergey's Manual of Determinative Bacteriology (1994). The bacterium is catalase, oxidase, indole, and urease negative and does not use nitrate as electron receptor. It ferments a range of carbohydrates and alcohols from which acid without gas is produced. Acid production from fructose, maltose, mannose, salicin, lactose, sucrose, trehalose and xylose is variable depending on the medium used (Cohen et al., 1968; Sens et al., 1989; Wullenweber, 1995). No significant differences in these characteristics were observed for the L-forms of *S. moniliformis* (Cohen et al., 1968, Sens et al., 1989 and Table 1 in Elliott, 2007).

S. moniliformis studied by the API ZYM system consistently showed positive reactions for alkaline phosphatase, butyrate esterase, caprylate esterase, myristate esterase, leucine arylamidase, chymotrypsin and acid phosphatase (Edwards and Finch, 1986; Hofmann, 1994).

The fatty acid profile of *S. moniliformis* shows major peaks of tetradecanoic acid (C14:0), palmitic acid (C16:0), stearic acid (C18:0), oleic acid (C18:1) and linoleic acid (C18:2) (Rowbotham, 1983; Rygg and Bruun, 1992).

3. Host species

S. moniliformis was common in laboratory rats in the first half of the last century (Strangeways, 1933). At that

Table 1
Comparison of rat bite fevers.

Causal organism	*S. moniliformis*	*S. minus*
Shape of organism	Gram-negative rod with bulbous swellings	Gram-negative spirillum
Geographical distribution	World wide	Mainly Asia
Transmission route	Rat bite, scratch or mucosal contact; contaminated food in Haverhill fever)	Rat bite
Bite wound	Rapidly healing	Rapidly healing but development of chancre-like lesion at onset of symptoms
Onset of illness	Fever, chills, vomiting, headache	Fever, chills, vomiting
Regional signs	Mild lymphadenitis	Regional lymphangitis and lymphadenopathy
Fever		
Character	Irregularly relapsing	Regularly relapsing
Onset (average)	2–3 days	2–3 weeks
Arthritis	Common (49% of cases)	Rare
Rash		
Character	Morbilliform to purpuric	Macular, often confluent
%Affected	75%	50%
Untreated mortality	7–13%	6.5%
Diagnosis	Culture, molecular techniques	Microscopy; animal inoculation
First choice antibiotic	Penicillin	Penicillin
Complications	Endocarditis, myocarditis, pericarditis, pneumonitis, anemia, amnionitis, prostatitis, pancreatitis, diarrhoea and abscesses in various organs	Endocarditis (rare), myocarditis, meningitis, hepatitis, nephritis, splenomegaly

time laboratory animals were kept under poor hygienic conditions and their microbiologic status is now termed "conventional" which is synonymous with "infected by various pathogenic micro-organisms". In 1962 the first publication appeared on the breeding of so-called "disease-free animals" (Foster, 1962). These animals were obtained by hysterectomy shortly before natural delivery from conventional donor animals. The germfree (GF) animals obtained have been used to constitute breeding colonies free from devastating infections. Due to the absence of a wide variety of named (specified) pathogenic micro-organisms these animals are described as specified pathogen free (SPF) animals. Their SPF status is maintained by high animal care standards and all these preventive hygienic measures taken are laid down in the term "SPF barrier measures" (Boot et al., 2001; Weisbroth et al., 2006). The success of the barrier (exclusion of pathogens) is periodically evaluated by testing animals for the absence of unwanted micro-organisms (Nicklas et al., 2002).

Inherent to the re-derivation are two important consequences for the microbial ecology of contemporary SPF laboratory animals in comparison to conventional animals. The first is the elimination of a wide range of pathogenic micro-organisms including zoonotic agents. The second, inevitable side effect, is that also the non-pathogenic autochthonous (synonyms: normal or indigenous) micro flora living on mucous membranes has been lost. Therefore, GF animals differ considerably from conventional animals with respect to their microbial ecology and microbial flora associated anatomical and physiological characteristics (Coates and Gustafsson, 1984). The differences are most striking in the intestinal tract where the indigenous micro flora is the first line of defence against pathogens by the establishment of colonization resistance (Van der Waaij, 1989). The intestinal flora is further involved in host nutrition, mucosal defence and the development of the immune system. Enteric flora is host specific (Boot et al., 1985) and in conventional animals contains several hundreds of bacterial species (Tannock, 1999).

To compensate the loss of the host specific indigenous flora and to normalize the anatomical and physiological abnormalities, GF animals have deliberately been dosed a complex colonization resistant enteric flora (Van der Waaij et al., 1971) or the so-called Schaedler flora which consists of eight bacterial strains (Dewhirst et al., 1999). Flora associated animals are used to start SPF breeding colonies. Inherent to the direct contact with animal caretakers SPF animals become spontaneously colonized by human and environmental bacteria and have as a consequence a non-standardised microbial ecology. SPF animals are often susceptible to opportunistic infections by micro-organisms that are rarely encountered as pathogens in conventional counterparts (Boot et al., 1989; ILAR, 1998).

Outside the field of laboratory animal science, the different microbial ecology of SPF animals and conventional counterparts has not been considered in the evaluation of the occurrence, pathogenicity and epidemiology of *S. moniliformis*.

3.1. Non human hosts

3.1.1. Rodents

3.1.1.1. Rat. It is generally assumed that conventional rats are the natural host and asymptomatic carriers of *S. moniliformis*. This applies both to *Rattus rattus* (the black rat) and *R. norvegicus* (the Norwegian rat) which is the species kept as laboratory rat and as pet. The non-pathogenicity in its natural host insures its survival. Remarkably, in a number of RBF cases caused by pet rats, the death of the rat shortly after the bite incident was mentioned explicitly (Rygg and Bruun, 1992; Prager and Frenck, 1994; Ojukwu and Christy, 2002; Andre et al., 2005; Clarke et al., 2005; Donker et al., 2005). A bite from a dying rat (Hudsmith et al., 2001) and the death of a pet rat on the first day of illness of the human patient were likewise noted (Freels and Elliott, 2004). Illness in these rats may have been the reason for the bite but involvement of *S. moniliformis* in the death of the rats seems unlikely.

Despite higher animal care standards and the use of hysterectomy derived—SPF barrier maintained animals streptobacillosis occurred in the past 20 years in SPF rat breeding colonies (Boot et al., 2006) and the bacterium has been cultured from the middle ear of SPF rats used for experimental induction of effusion (Koopman et al., 1991).

S. minus has been isolated from the oropharynx, blood and exudate from infected eyes of up to 25% of wild (conventional) rats, but carrier rates among rats vary widely in different geographical regions (MacLean, 1979). Nasopharyngeal carriage rates of 50–100% in wild rats and before 1970 in 10–100% of conventional laboratory rats have been reported (Signorini et al., 2002; Washburn, 2005).

3.1.1.2. Mouse. Also with respect to laboratory mice it is necessary to discriminate between conventional and SPF mice. Wild mice (*Mus musculus*) are not considered a natural host of *S. moniliformis*. This may explain that only a few human RBF cases have been reported after a mouse bite (Arkless, 1970; Gilbert et al., 1971). *S. moniliformis* was however isolated from chronically abscess forming joints in wild mice on a farm in Australia (Taylor et al., 1994). Notably the carpi and tarsi were affected and the joints were ankylosed and deformed. Loss of digits and the tail was observed regularly. Subcutaneous and liver abscesses occurred also. In an outbreak in a conventional laboratory mouse colony, random bred Swiss mice died from subacute *S. moniliformis* sepsis and had polyarthritis. More than 50% of the mice had brown crusts on their mammae due to a severe, acute and diffusely spreading neutrophilic dermatitis. Mice with subacute sepsis had acute multifocal suppurative embolic interstitial nephritis and the polyarthritis was characterised by numerous subcutaneous and peri-articular abscesses (Savage et al., 1981; Glastonbury et al., 1996).

Natural infection of pregnant mice resulted in arrested pregnancy and abortions (Mackie et al., 1933; Sawicki et al., 1962). The chronic infection can last for 6 months. The mobility of mice and their capacity to reproduce is reduced by streptobacillary arthritis. Recently, mice were suggested as the cause of RBF in a retired microbiologist

who maintained mice to feed his pet snake (Irvine and Wills, 2006). *S. moniliformis* was isolated from the patient but isolation from the mouse was not attempted.

Most cases of natural clinical infection in laboratory mice have been reported before the introduction of SPF mice (Levaditi et al., 1932; Mackie et al., 1933; Freundt, 1956b; Sawicki et al., 1962). Due to poor housing standards mice may occasionally have been infected from laboratory rats held in the same room or vicinity via aerosols or handling by animal caretakers (Freundt, 1956b). The most recent report on streptobacillosis in laboratory mice explicitly mentioned that wild rats were trapped in the farm shed (Glastonbury et al., 1996).

Despite higher hygienic standards in contemporary laboratory animals an outbreak of streptobacillosis occurred in an SPF mouse breeding colony which was separated from rats. The source of the infection was not elucidated (Wullenweber et al., 1990; Kaspareit-Rittinghausen et al., 1990). The colony housed various mouse strains and C57Bl/6J mice but no other mouse strains showed distinct swellings of the hind feet and hock joints and some had nodular swellings of the tail and the anterior feet. Gross lesions included enlargement of cervical lymph nodes and occasionally of the axillary and inguinal lymph nodes.

3.1.1.3. Spinifex hopping mouse. Sudden deaths occurred within a couple of days in spinifex hopping mice (*Notomys alexis*) in a zoo. In the months before, rats had broken into their cage. Bite wounds were observed on several dead mice and numerous micro-abscesses were present in the livers. *S. moniliformis* was cultured from several mice. Intraperitoneal injection of these isolates in laboratory mice induced lameness and swelling of joints (Hopkinson and Lloyd, 1981).

3.1.1.4. Gerbil. RBF occurred in a 39-year-old male after the bite of a gerbil (*Meriones unguiculatus*) (Wilkins et al., 1988). The patient bred conventional gerbils (but no other animal species) for years and was never bitten before. Clinical symptoms (i.e. rash) and the isolation of Gram-negative bacteria showing filaments in chains with numerous bulbous swellings and the typical "fluff ball" growth in serum-broth were characteristic for *S. moniliformis*. No attempts to demonstrate *S. moniliformis* in the gerbils were reported. Nothing is known about the pathogenicity of *S. moniliformis* to this animal species.

Most contemporary gerbils come from SPF breeding colonies but gerbil colonies are not periodically monitored for absence of the bacterium (Nicklas et al., 2002).

3.1.1.5. Squirrel. Schottmüller described purulent skin lesions and pyemia following the bite of a South African squirrel (Schottmüller, 1914). The rash and pustules on the body of his patient strongly resembled those seen in RBF (Fig. 3). Due to differences in growth characteristics compared to the "Streptothrix muris ratti" isolated from a second patient he named the Gram-negative rod which grew in filaments "Streptothrix taraxeri cepapi" after the squirrel, suggesting that the source of the infection was *Paraxerus cepapi* (Smith's bush squirrel) which belongs to the Sciuridae. Two episodes of squirrel bite associated disease were reported from Nigeria (Gray, 1967). Recurrent fever and maculo palpular rash all over the body in both patients resembled RBF, and both recovered after penicillin injections. However, as the author states "to discover the causative agent of squirrel bite fever smears and cultures from the blood of patients and the mouth of squirrels should have been made".

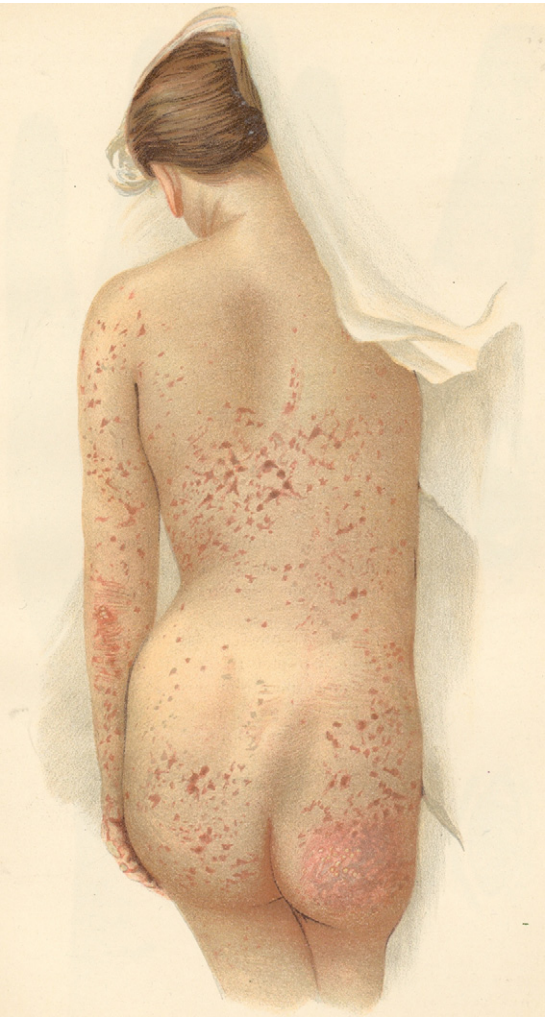

Fig. 3. Photograph of a painting by Johannes Arndt Jepa, showing the rash on the body of a woman bitten by a squirrel. Reproduced from Schottmüller (1914) with permission from Thieme Verlag, Germany.

3.1.1.6. Guinea pig. Guinea pigs (*Cavia aperea porcellus*) are susceptible to natural *S. moniliformis* infection. Fleming (1976) reported a high incidence of cervical lymphadenitis in stocks of conventional guinea pigs at several research laboratories. The bacterium was isolated from cervical lymphnodes and cervical abscesses (Smith, 1941; Aldred et al., 1974; Fleming, 1976). The isolation of *S. moniliformis* from a guinea pig with granulomatous bronchopneumonia has been reported (Kirchner et al., 1992); it cannot be decided whether the animal came from a conventional or an SPF colony. Most contemporary guinea pigs come from

SPF breeding colonies and these colonies are periodically monitored for absence of the bacterium (Nicklas et al., 2002).

3.1.2. Carnivores

Many textbooks mention that RBF can also be contracted through the bite of an animal that feeds on rats or at least has had a rat in its snout. Carnivores including dogs, cats, ferrets and weasels that mouth or feed on rats (Sigge et al., 2007), however apparently seldom transmit the disease by bite or scratch.

3.1.2.1. Cat. RBF was reported in a previously healthy male bitten by a cat (Mock and Morrow, 1932). The etiological agent was not directly isolated from the patient but a spirillum was isolated in very low numbers from the blood of a guinea pig inoculated with material from the patient. This combined with laboratory tests lead to the RBF diagnosis.

3.1.2.2. Dog. Approximately 1 in 20 dogs will bite a human being during the dogs lifetime (Griego et al., 1995). The number of proven cases of *S. moniliformis* infection after a dog bite is however limited to three Australian reports (Gilbert et al., 1971; Maynard et al., 1986; Peel, 1993) of which the latter two were possibly on the same case. The involvement of a greyhound, a breed that eats rats, was explicitly mentioned (Peel, 1993).

In another case report two male team mates (age 15) both had RBF symptoms (confirmed by culture in one). Potential sources of infection comprised exposure to the same dog and ingestion of water from an open irrigation ditch that might have been contaminated with rat faeces (MMWR, 1998). Mucosal contact with two family dogs, known to catch and kill rodents and bring them into the living room was suggested to be the route of transmission in a case of *S. moniliformis* amnionitis. The agent was isolated from amniotic fluid of the patient, but no attempts to isolate the agent from the dogs were reported (Faro et al., 1980).

In a first case of clinical *S. moniliformis* infection in a dog (Ditchfield et al., 1961) the animal suffered from diarrhoea, vomiting, anorexia and arthritis in the hind legs and died after 10 days of hospitalisation, despite antimicrobial therapy with penicillin and chloramphenicol. Post-mortem examination showed purulent polyarthritis, endocarditis and pneumonia. Gram-negative highly pleomorhic bacilli with numerous pear-shaped swellings were isolated on blood agar from blood samples and taken as an indication of *S. moniliformis* infection. No history of exposure to rats was known, nor were there any apparent bite wounds. Since the dog ate garbage and illness started with acute gastroenteritis, this may indicate a HF case in this particular dog but other causes of infection are imaginable. In a second case *S. moniliformis* was claimed to be isolated from the aspirate of an abscess in a dog (Das, 1986). The growth characteristics and antibiotic susceptibility of the dog isolate were however not fully in accordance with those of *S. moniliformis* (see Wullenweber, 1995).

The presence of *S. moniliformis* DNA in the mouth of 15% of dogs known to have been in contact with rats has been demonstrated by PCR (Wouters et al., 2008).

Human RBF due to *S. minus* acquired from a dog has been described (Ripley and van Sant, 1934) in two medical students that both had been in contact with experimental dogs at the physiology laboratory. They reported at the hospital with a month in between, both showing signs of RBF. A positive diagnosis of *S. minus* RBF was made upon dark-field examination of blood smears from mice and guinea pigs inoculated intraperitoneally with blood of the patients.

3.1.2.3. Ferret. In 1914, Nixon observed RBF symptoms in a ratter bitten by a ferret and cited a similar case (Nixon, 1914).

3.1.2.4. Weasel. A *S. moniliformis*-like bacterium (“Streptothrix”) was isolated from the blood of a boy bitten by a weasel (Dick and Tunnicliff, 1918). The clinical picture resembled RBF, but the authors noted morphological and cultural differences with isolates from other RBF cases. Sera from seven rats with bronchopneumonia showed complement fixing antibodies to both the isolate from the weasel bite and four isolates from human RBF, which suggests the isolate being *S. moniliformis* but in contrast to expectation some guinea pigs and rats inoculated intraperitoneally with the weasel isolate died.

3.1.3. Other non-human hosts

3.1.3.1. Calve. The isolation of *S. moniliformis*-like organisms (“S. actinoides”) from pneumonic lungs of calves was described (Gourlay et al., 1982). The Gram-negative rods with bulbous swellings, showed “puff-ball” growth in liquid medium, “fried egg” colonies on agar, dependence on blood or serum for growth and biochemical properties in agreement with *S. moniliformis*. The isolates did however not induce illness in C57Bl/6 mice and the taxonomic status of the organism remains unclear by lack of 16S rDNA sequence data. The authors summarized literature on the isolation of similar *S. moniliformis*-like organisms from pneumonic lungs of calves, sheep and seminal vesicles of bulls.

3.1.3.2. Pig. RBF from a pig bite was reported once (Smallwood, 1929) in a woman bitten in the forefinger. Very painful swollen joints of the finger, rash on arms, legs, abdomen and neck and periods with high fever, led to the diagnosis. The patient was cured by therapy with novarsenobenzene. Culture of the agent nor a bite of the pig by a rat was reported. It might be that the animal mouthed a rat.

3.1.3.3. Turkey. At least four reports have appeared on streptobacillosis in turkeys (Boyer et al., 1958; Yamamoto and Clark, 1966; Mohamed et al., 1969; Glűnder et al., 1982). Some authors attributed the infection to rat bites. Polyarthritis and synovitis were reported (Glűnder et al., 1982) as well as tendon sheath swelling and joint lesions (Yamamoto and Clark, 1966). Some turkeys died in the weeks before *S. moniliformis* was isolated from the exudate of one bird and from a rat trapped in the compound where the turkeys were held. The isolates were similar in

morphology, growth and biochemical characteristics and cross-reacted in double immune-diffusion tests (Yamamoto and Clark, 1966). The strains fermented arabinose but not salicin which is at variance to the characteristics listed for *S. moniliformis* but other biochemical properties tested agreed.

Both the turkey and rat *S. moniliformis* reproduced the disease via experimental foot pad or intravenous injection in turkeys but not in chickens. In contrast to the rat *S. moniliformis* strain the turkey strain was not lethal to mice upon intraperitoneal inoculation. Seven-days-old chicken embryos inoculated via the yolk sac died from both bacterial strains (Yamamoto and Clark, 1966). In an earlier study rat *S. moniliformis* inoculated into chicken embryo's showed an almost exclusive localization in the synovial lining of the joints and the infection appeared self-limiting (Buddigh, 1944).

3.1.3.4. Koala. Pleuritis due to *S. moniliformis* infection was reported (Russell and Straube, 1979) in a koala (*Phascolarctos cinereus*). The agent isolated from the animal appeared lethal in intraperitoneally or intravenously inoculated mice. How the agent was contracted by the koala is unknown.

3.1.3.5. Non-human primates. RBF by *S. moniliformis* has been reported in a rhesus monkey (*Macaca mulatta*) with valvular endocarditis (Valverde et al., 2002) and in a titi monkey (*Callicebus* spp.) with septic arthritis. Rat bites were not recorded in both cases and water or food contaminated with rodent faeces was suggested as a source of infection; if so this may indicate HF cases.

RBF after a monkey bite was reported from India in two humans. *S. minus* was indicated as the infectious agent without convincing proof (Iyer, 1936).

3.2. Human infection

Bacteria grow in one third of rat bite wounds. The risk of any type of infection following a rat bite has been estimated from 1 to 10% (Hagelskjaer et al., 1998; Van Hooste, 2005; Elliott, 2007) but the risk of RBF is unknown as is the infectious dose of both *S. moniliformis* and *S. minus* for humans.

3.2.1. Clinical symptoms

Two distinct clinical syndromes have been identified in association with *S. moniliformis* infection: rat bite fever and Haverhill fever.

3.2.1.1. Haverhill fever (erythema arthriticum epidemicum). Haverhill fever was initially recognized as an infection transmitted to humans via the consumption of water, milk or food that had been contaminated by rat excrements. The most well known outbreak occurred in Haverhill, Massachusetts in 1926. The source of the infection probably was contaminated milk and the outbreak affected 86 people (Parker and Hudson, 1926). A year before, a similar outbreak occurred in Chester, USA, involving more than 400 people (Place and Sutton, 1934). In 1983, 304 people became infected at a boarding school in Chelmsford, England, probably from spring water contaminated with rat excrements (Shanson et al., 1983; McEvoy et al., 1987). Both in Haverhill and in Chelmsford, no *S. moniliformis* could be isolated from captured rats and the contamination was suggested based on epidemiological data.

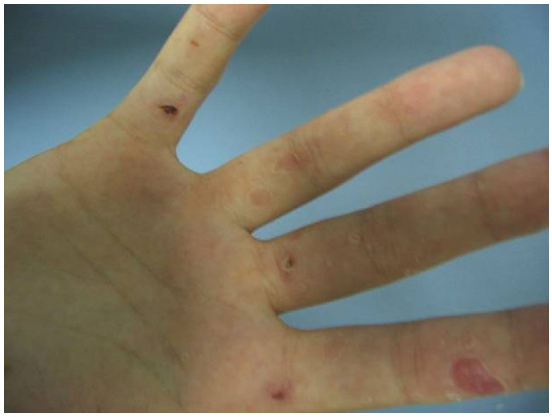

Fig. 4. Maculopapular rash on the hand of a patient with confirmed *S. moniliformis* rat bite fever. Courtesy of Dr. S.H.A. Peters (Flevo Ziekenhuis, Almere, The Netherlands).

Haverhill fever symptoms are fever, chills, pharyngitis and pronounced vomiting, which may be followed by skin rashes and polyarthralgia.

3.2.1.2. Rat bite fever.

3.2.1.2.1. Streptobacillus moniliformis RBF. This is the more common syndrome associated with rat bites and scratches. Since bite or scratch wounds heal well information about the incident often is absent from the anamnesis, which hampers the correct diagnosis.

The incubation period varies from 3 days to more then 3 weeks (on average 2–3 days).

Clinical symptoms (Table 1) include an abrupt onset of high fever, followed by headache, chills, vomiting and a rash. The petechial rash develops over the extremities, in particular the palms and the soles, but sometimes it is present all over the body (Fig. 4). In 20% of the cases the rash desquamates. Infants and children may experience severe diarrhoea resulting in loss of weight (Raffin and Freemark, 1979).

Later a symmetric polyarthritis develops in about 50–70% of patients. The joints most commonly associated with streptobacillary septic arthritis are the knees, followed by the ankles, wrists, joints of the hands, elbow and shoulders (Dendle et al., 2006; Wang and Wong, 2007) and swelling of the joints leads to both active and passive restrictions in movement. Monoarthritis of the hip and asymmetric oligoarthritis have also been reported (Hockman et al., 2000; Downing et al., 2001). Arthritis which can either be suppurative or non-suppurative rarely occurs without other RBF manifestations. The joint fluid is usually highly inflammatory with a predominance of polymorphonuclear leucocytes.

All symptoms do not occur at the same time, nor do they all occur in the same patient.

Rare complications are anaemia, endocarditis, pericarditis (Carbeck et al., 1967), pneumonia, meningitis, diarrhoea and abscess formation in organs including the brain (Oeding and Pedersen, 1950; Dijkmans et al., 1984), liver, spleen (Chulay and Lankerani, 1976), and skin (Vasseur et al., 1993; Hagelskjaer et al., 1998; Torres et al., 2001). Other complications comprise parotitis, amnionitis, tenosynovitis, prostatitis and pancreatitis (Delannoy et al., 1991).

In a review of 20 cases of *S. moniliformis* endocarditis 50% of the patients had previously damaged heart valves. Endocarditis mortality can be as high as 53% (McCormack et al., 1967; Rupp, 1992; Torres et al., 2003; Chen et al., 2007). In a review of 16 cases of endocarditis from 1915 to 1991 (Rupp, 1992) most patients had fever, cardiac murmurs and a history of being bitten by a rat. Ten of these 16 patients died. In four cases of endocarditis reported after 1992, all patients recovered after antimicrobial therapy combined with surgery in two cases (Rordorf et al., 2000; Balakrishnan et al., 2006; Chen et al., 2007; Kondruweit et al., 2007). Mortality has also been reported in a previously healthy young female (MMWR, 2005).

A unique case of amnionitis with intact amniotic membranes involving *S. moniliformis* was described (Faro et al., 1980). The patient stated that the basement of her home was infested with rats or mice. Three cases of abscesses in the female genital tract in which *S. moniliformis* infection was clearly demonstrated have been reported (Pins et al., 1996). The route of infection however was obscure as no contact with rats or ingestion of unpasteurised milk was mentioned.

Untreated RBF mortality ranges from 7 to 13% (Hagelskjaer et al., 1998; Graves and Janda, 2001; Washburn, 2005). Even without treatment patients can recover within several weeks, but the disease can also continue for months. Persistent damage sometimes occurs even after treatment with an antibiotic for which the isolate was sensitive (Tattersall and Bourne, 2003).

Treatment using antibiotics active on the bacterial cell wall might induce the formation of L-forms of the bacterium that persist in the human body (Domingue and Woody, 1997) and be the cause of relapses after stopping antibiotic therapy (Domingue et al., 1974). In the streptobacillary epizootic in C56Bl/6 mice the breeding nucleus was effectively treated via the drinking water with ampicillin and tetracycline given in succession to prevent the survival of penicillin resistant L-forms. After finishing therapy some mice however relapsed and died from septicaemia (Wullenweber et al., 1990). In vivo L-forms of *S. moniliformis* frequently revert to the bacillary form and regain their full pathogenic properties (Freundt, 1956a).

Depending on whether or not a rash or polyarthritis accompany febrile episodes the differential diagnosis of RBF comprises brucellosis, leptospirosis, Rocky Mountain spotted fever (by *Rickettsia rickettsii*), Lyme disease, viral exanthems, disseminated sexually transmitted diseases and a variety of other infective or vascular processes (Freels and Elliott, 2004; Elliott, 2007).

3.2.1.2.2. Spirillum minus RBF. This infection usually becomes manifest at a later stage than RBF by *S. moniliformis*. *S. minus* infections have an incubation period of 2–3 weeks, with a maximum of 4 months. The wound at the bite site at first heals spontaneously but reappears at the onset of clinical symptoms 1–4 weeks later, becomes painful, oedematous and purple and may ulcerate.

The first clinical symptoms are aspecific and consist mainly of fever, chills, headache and malaise. Lymph nodes in the proximity of the bite wound become swollen and tender. Rash is less common than in *S. moniliformis* infection, but if rash appears it is pinkish (Downing et al., 2001), accompanied by itching and apparent all over the body. Arthritis and muscle pain (myalgia) occur infrequently. There is regional lymphangitis and lymphadenopthy. Maculopapular and urticarial rashes can develop around the area of the bite. Asymmetric polyarthritis is less frequently observed than in *S. moniliformis* RBF.

Diarrhoea, vomiting, arthralgias, neuralgias and central nervous system symptoms may occur. Endo- and myocarditis, hepatitis and meningitis are possible complications.

Without treatment, the fever temporarily disappears but returns intermittently within a period of several days. Fever may last for 3–5 days. In some cases this can continue for a year, but normally the symptoms disappear within 2 months (Downing et al., 2001). After afebrile intervals of 3–7 days febrile episodes recur, but they subsequently lose their intensity. The illness may last for weeks to months. Mortality due to *S. minus* RBF (6.5%) is lower than for *S. moniliformis* infection (Freels and Elliott, 2004).

S. minus was demonstrated in a 14-year-old boy bitten in the finger by a wild field mouse (*M. musculus*) (Reitzel et al., 1936). An 11-year-old boy was bitten by a mouse on a farm in England, the infectious agent was not demonstrated by inoculation of mice or guinea pigs with the patient's blood, but *S. minus* was demonstrated in considerable numbers in mice captured on the farm (Farquhar et al., 1958).

3.2.2. Geographic distribution

Streptobacillary RBF has been reported worldwide. Reports until 1993 concerning *S. moniliformis* in humans and animals have been summarized by Wullenweber (1995). After 1993 further reports can be found in PubMed. RBF by *S. minus* was first described in Japan and although it occurs predominantly in Asia human infection has also been diagnosed in Europe and the United States. So there seem to be no geographic restrictions on the occurrence of both agents (Buranakitjaroen et al., 1994; Chen et al., 2007).

3.3. Pathogenicity

What happens after a RBF bacterium is introduced into the body will be determined by the pathogenic properties (virulence factors) of the bacterium and the susceptibility of the host.

3.3.1. Virulence factors

Very little is known about potential virulence factors of *S. moniliformis*. An alpha-hemolytic strain has been isolated from a rat with otitis media (Wullenweber et al., 1992).

S. moniliformis agglutinated red blood cells from various animal species. Reactions with turkey, human, guinea pig and pig red blood cells were stronger than reactions with rat and chicken cells. Hemagglutinating activity with cells from susceptible C57Bl/6 and resistant BALB/c mice did not differ. Hemagglutinating activity appeared mannose resistant (Hofmann, 1994) and the receptor(s) involved in adhesion remain to be elucidated (Beachey, 1981).

Bacillary forms of *S. moniliformis* are pathogenic to mice after parenteral inoculation. Growth on agar yields long streptobacillary forms whereas minute coccoidal cells result from growth in (serum-broth (Freundt, 1956a). The bacillary forms appeared more virulent than the coccoidal form (Savage, 1972), and L-forms have been found apathogenic to mice (Freundt, 1956b). L-forms lack at least one antigen present in the bacillary form (Klieneberger, 1942; Smith, 1998). Experimental vaccination of mice with inactivated preparations of *S. moniliformis* provokes incomplete protection against challenge (Savage, 1972; Smith, 1998).

Experimental infection of mice showed that macrophages that engulfed *S. moniliformis* cells died more rapidly than those in the absence of the bacteria (Savage, 1972).

Experimental infections in rats have been used as a model for the arthritis seen in streptobacillosis, but without much success. Adult rats are usually resistant to experimental parenteral inoculation but neonates may develop pneumonia (Strangeways, 1933; Bell and Elmes, 1969; Gay et al., 1972). The organism is a secondary invader in chronic murine pneumonia of conventional rats (Olson and McCune, 1968). Experimental oral and nasal infections of SPF rats of several inbred strains and random bred stocks did however not yield any indication for gross lesions in the respiratory tract (Boot et al., 1993b, 2002, 2006). The difference between conventional and SPF rats with respect to respiratory tract pathology is likely due to the presence of viral and other bacterial pathogens (including *Mycoplasma* spp.) in conventional animals which are usually absent from SPF animals (Boot et al., 2001). Mice injected with *S. moniliformis* get arthritis and may die (dependent on the mouse strain) whereas mice can have *S. minus* in their blood without showing any clinical signs (Haneveld, 1958).

3.3.2. Host susceptibility

Heritable variability in expression of disease has been observed among inbred and hybrid mouse strains (Wullenweber et al., 1990). C57Bl/6J mice inoculated intravenously or intraperitoneally with a suspension of *S. moniliformis* developed either acute septicaemia or a chronic disease with arthritis. Hepatitis and lymphadenitis were also observed. Oral infection of C57BL/6J mice led to cervical lymphadenitis and to *S. moniliformis* isolation from 55% and IgG production in 65% of the animals. *S. moniliformis* did with few exceptions not yield pathology nor could the bacterium be isolated from inbred BALB/cJ, C3H/He, DBA/2J and hybrid CB6F1 and B6D2F1 mice inoculated in the same way. Only 5% of the DBA/2J and B6D2F1 mice produced IgG. This different reaction against *S. moniliformis* infection might be related to differential recognition by Toll-like receptors. C57BL/6J mice produce higher levels of IL-12 in response to Toll-like receptor 2 agonists on the surface of bacteria like *E. coli* and *L. monocytogenes* than BALB/c mice (Liu et al., 2002). The more severe inflammatory reactions after infection with *S. moniliformis* could be explained by recognition of *S. moniliformis* by Toll-like receptors in C57BL/6J mice (Irvine and Wills, 2006).

Rat inbred strains differ in the degree of antibody development to *S. moniliformis* after experimental oral and nasal inoculation (Boot et al., unpublished). In studies in which random bred Wistar rats were exposed to *S. moniliformis* infected counterparts in the same cage for 6 weeks, clear differences in seroconversion between cage mates were observed (Boot et al., 2002).

The observations in mice and rats are in line with a vast amount of literature indicating that susceptibility of mammalian species to infection by many micro-organisms is genetically based (Kimman, 2001; Buer and Balling, 2003).

These observations extend to the human species. It has been observed that of two persons bitten by the same rat or a weasel (Dick and Tunnicliff, 1918) only one developed RBF. A brother and sister in contact with the same pet rat both contracted RBF (Freels and Elliott, 2004).

Dendle et al. (2006) postulated two mechanisms for the development of arthritis in streptobacillary infection. One is immunological in origin and occurs in cases where joint effusions are sterile. The other is due to direct infection of the joint and causes suppurative arthropathy.

A predisposition to rat bite and thus RBF was noted in rural patients with severe neuropathy and a poor glycaemic control (Kalra et al., 2006).

4. Diagnostic methods

4.1. Direct examination

S. minus may be detected by direct dark-field microscopy of serum exudate, tissue or from primary lesions (Bloch and Baldock, 1937; Hinrichsen et al., 1992). Only in a few reports a positive diagnosis by direct dark-field examination of the patient's blood was claimed (Bloch and Baldock, 1937; Bhatt and Mirza, 1992).

4.2. Culture

Isolation of *S. moniliformis* from blood culture is common, isolation from abscess aspirates, synovial fluid and wound cultures have likewise been successful (Freels and Elliott, 2004; Dendle et al., 2006) but cultures from affected joints are usually negative (Dendle et al., 2006).

S. moniliformis is fastidious and primary culture needs the use of agar media supplemented with ascitic fluid or serum (Von Gravenitz et al., 2003). The typical "puff-ball" or "bread crumb like" growth (Fig. 1) in liquid media with serum and the Gram-stain of *S. moniliformis* still are important for diagnostics.

4.3. Identification

Identification of *S. moniliformis* suspected growth may comprise biochemical characterisation and cell wall fatty acid profiling (Rowbotham, 1983; Clausen, 1987; Holroyd

et al., 1988; Lopez et al., 1992; Pins et al., 1996; Hockman et al., 2000; Frans et al., 2001; Torres et al., 2003). Serum agglutination reactions have been used in the past for the identification of *S. moniliformis* (Burke et al., 1959). Identification was also achieved by a direct fluorescent antibody test with a polyclonal antiserum to the bacterium (Graves and Janda, 2001).

PCR and DNA sequencing of amplicons are more modern methods used for identification (and diagnostic purposes). Sequencing of the 16S rDNA gene was used for the identification of *S. moniliformis* (Chen et al., 2007; Mignard et al., 2007).

4.4. PCR

Several PCR tests for *S. moniliformis* detection (and identification) have been described using different primer sets.

Bacterial DNA may be amplified by two sets of broad range bacterial 16S rRNA gene primers (Berger et al., 2001). The first set yielded an amplicon of 798 nucleotides which was reamplified to yield an amplicon of 425 nucleotides. The sequence of the latter was identical to that of *S. moniliformis*. The most closely related organism *Leptotrichia sanguinegens* appeared 94% related. A similar broad range 16S rRNA PCR (Wallet et al., 2003) generated a 473 bp amplicon with 99% sequence similarity to that of *S. moniliformis*.

Boot et al. (2002) designed primers based on the nucleotide sequence of the 16S rDNA gene of eleven *S. moniliformis* strains that yield an amplicon of 296 nucleotides. Similar sized amplicons were obtained with DNA from *Fusobacterium necrogenes* and *Sebaldella* (*Bacteroides*) *termitidis*, but these could be distinguished from the *S. moniliformis* amplicons by cleavage with the restriction endonuclease BfaI. The PCR detects *S. moniliformis* strains from mice, rats, human (Boot et al., 2002) and turkey (unpublished).

PCRs have been used both for screening and diagnostic purposes (Kadan et al., 2002; Andre et al., 2005; Mignard et al., 2007). False positive results for *S. moniliformis* PCR, due to the presence of *Leptotrichia* sp. were recently reported (Boot et al., 2008; Wouters et al., 2008) so sequencing of PCR amplicons may be necessary. Reversily a fluorescence in situ hybridization assay (FISH) for rapid identification of *Fusobacterium* spp. showed cross-reaction between *Leptotrichia* spp. and *S. moniliformis* (Sigge et al., 2007).

Theoretically also *S. minus* bacterial DNA may be amplified by broad range bacterial 16S rRNA gene primers.

4.5. Serology

For humans currently no validated serological tests are available but such assays are in use in the monitoring of SPF laboratory animals for *S. moniliformis*. Antibodies to the bacterium in rats, mice and guinea pigs have in the past been demonstrated by agglutination and complement fixation tests (Boot et al., 1993b). These assays have been replaced by the more sensitive enzyme-linked immunosorbent assay (ELISA) and the indirect immunofluorescence assay (IFA). ELISA seropositive SPF laboratory animals can be found rather frequently. Whereas in most cases infection can be ruled out by negative immunoblot (IB) and PCR findings, sometimes it can be confirmed by culture or PCR (Boot et al., 2006).

A partial serological relationship between *S. moniliformis* and *A. laidlawii* (a non-pathogenic *Mycoplasma* spp. from horses and cattle) has been found by ELISA (Boot et al., 1993b) and IFA (Wullenweber, 1995). IFA showed also cross reactivity with other *Acholeplasma* species but not with *Mycoplasma arthritidis* and *M. pulmonis* (Wullenweber, 1995). Rat antiserum against *A. laidlawii* is not reactive against *S. moniliformis* antigens by IB (Boot et al., 2006).

Immunoblots of whole cell antigens of a rat *S. moniliformis* strain and immune sera to various *S. moniliformis* isolates show a number of bands in the 32–55 kD range (Boot et al., 2006).

4.6. Experimental infection

The presence of good alternatives, notably PCR, implies that experimental inoculation of mice or other animals with blood or liquid from pustules to demonstrate *S. moniliformis* is now obsolete.

Unfortunately this is not so for *S. minus*. The failure to grow *S. minus* implies that serological or molecular (PCR) tests are not available for diagnostic efforts. In case of suspected infection, blood or wound aspirates are injected intraperitoneally into guinea pigs or mice for diagnostic purposes. After successful infection spirochetes may be detected after 5–15 days in their blood using dark-field

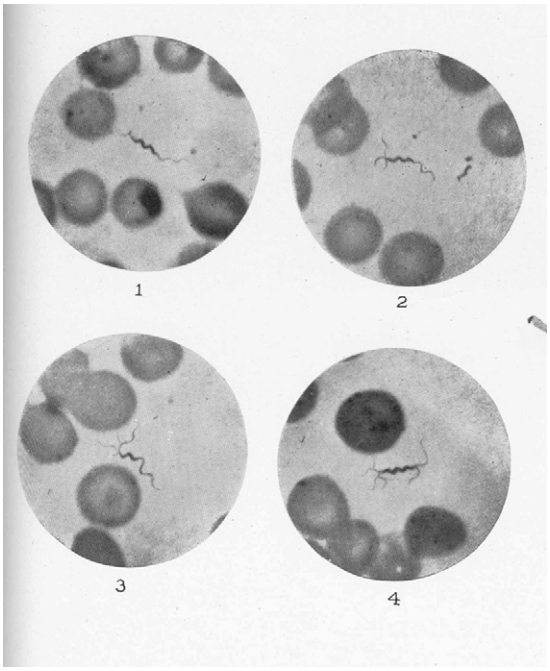

Fig. 5. Photograph of *Spirillum minus* in the blood of an experimentally infected mouse. The preparation was fixed with methanol and stained with Giemsa stain. Reproduced from Adachi (1921) with permission from the Journal of Experimental Medicine.

microscopy (Fig. 5) (Adachi, 1921; Hudemann and Mücke, 1951). Drawback of the technique are the time needed and the limited number of laboratories that perform it (Byington and Basow, 1998).

4.7. Infections are underdiagnosed

Although the number of reports on RBF is increasing, it is a still relatively rarely reported disease. Only three outbreaks of Haverhill fever have been reported. The relevant bacteria may be transmitted in various ways by close contact between pet rats and their owners. Transmission is not necessarily followed by multiplication of the bacteria in the human body (infection). Repeated introduction of bacteria into the human body will lead to the development of antibody activity as it does in immunized laboratory animals (Boot et al., 1993a, 2006). Infection does not necessarily lead to serious clinical symptoms and humans with subclinical infections will not report to the physician. If the incubation period extends to several weeks and clinical symptoms are aspecific, RBF is presumably not considered if contact with rats or other possible hosts is not explicitly mentioned in the anamnesis.

RBF suspected patients will be treated by antibiotics most of which will be active against the causative bacteria. The number of cases in which laboratory diagnostic examinations are carried out will therefore be limited to very severe cases and when antibiotic therapy fails.

S. moniliformis may be difficult to grow on primary culture after antibiotic therapy and detection by PCR is operational in a limited number of diagnostic laboratories only. Bacterial strains obtained may be misidentified despite the fact that the bacteriologic characteristics are rather typical. *S. minus* cannot be cultured at all.

RBF is probably under diagnosed and may occur more often than reported. RBF is not a reportable disease.

HF will is more likely to be diagnosed and reported when the disease reveals itself as an outbreak involving several patients within a short period of time.

5. Therapy

Antibiotic susceptibility of *S. moniliformis* was tested systematically by the agar diffusion and agar dilution methods (Edwards and Finch, 1986; Holroyd et al., 1988; Wullenweber, 1995) and empirically in a number of case reports (Elliott, 2007). Much less is known on the susceptibility of *S. minus* for antibiotics.

Susceptibility tests by the disk diffusion method performed with a single isolate showed that this isolate was susceptible to gentamicin, penicillin, chloramphenicol, erythromycin, clindamycin, tetracycline, cephalothin and vancomycin (Holroyd et al., 1988).

In a study with 13 *S. moniliformis* isolates from various origins tested for susceptibility for more than 30 antibiotics resistance of all isolates was observed against nalidixic acid, norfloxacin, polymyxin B and the combination of trimethoprim-sulfamethoxazol (Wullenweber, 1995). Polymixin B disrupts the structure of the membrane phospholipids and the other antibiotics are involved in inhibition of DNA synthesis. The 13 isolates were intermediate resistant against ciprofloxacin, another antibiotic that inhibits DNA synthesis. Resistance against cephalosporins and aminoglycosides has also been reported (Cunningham et al., 1998; Freunek et al., 1997).

The treatment of choice is penicillin for both forms of rat bite fever but penicillin resistant strains of *S. moniliformis* do occur (Toren, 1953; Freunek et al., 1997). Dendle et al., reported the use of penicillin in 56% of the cases of septic arthritis by *S. moniliformis* infection that were reviewed (Dendle et al., 2006). Tetracycline is considered the best alternative in penicillin-allergic patients. Other antibiotics used for treatment of human *S. moniliformis* RBF are ampicillin, streptomycin, tetracycline, chloramphenicol, gentamicin, cefuroxime, vancomycin and erythromycin (Wullenweber, 1995).

In case of *S. minus* endocarditis, the addition of streptomycin is advisable. Two unusual cases where both patients recovered completely without chemotherapy have been reported however (Burke et al., 1959).

6. Epidemiology

By one-dimensional SDS-PAGE analysis of 22 different strains of *S. moniliformis* from mouse, rat, the spinifex hopping mouse, turkey and humans 40–50 proteins ranging from 18 to 100 kDa were observed. Four major protein bands in the region 60–67 kDa accounting for 20–30% of the total protein were present in all strains (Costas and Owen, 1987). No clear differences were found among the strains that could be related to geographical origin or host species. The only exception was the unique position of the strain from the Australian spinifex hopping mouse. It cannot be decided whether this is a reflection of the geography or the host species. Geographically related differences have been observed among rodent pathogenic *Corynebacterium kutscheri* strains (Boot et al., 1995) and other rodent pathogens such as *Pasteurella pneumotropica* show host species related differences in bacterial properties (Boot et al., 1993a).

S. moniliformis isolates from guinea pigs are said to differ from those isolated from rats (Smith, 1941; Aldred et al., 1974). This is difficult to verify since isolates from guinea pigs have not been saved. Guinea pig *Streptobacillus* strains were reported to grow only under strict anaerobic conditions unlike isolates from rats and mice (Smith, 1941; Aldred et al., 1974) and special growth conditions for isolates from guinea pigs were confirmed by Fleming (1976) who recommended the addition of neutralised liver digest to the growth medium. Differences in the properties of rat and guinea pig *S. moniliformis* strains are paralleled by differences in the *Pasteurellaceae* species obtained from naturally infected conventional animals: whereas rat *Pasteurellaceae* belong to the so-called Rodent cluster of the bacterial family, guinea pig *Pasteurellaceae* belong to other phylogenetic clusters (Olsen et al., 2005). In conventional animals the bacterial flora will have evolved with the host and taxonomic studies indicated that guinea pigs do not belong to the Rodentia lineage (Adkins et al., 2001). Guinea pigs were not easily orally and nasally infected with a rat strain of *S. moniliformis* (Boot et al., 2007).

It is obvious that turkeys are phylogenetically remote from the human species. That based on SDS-PAGE protein profiling turkey *S. moniliformis* strains clustered with human RBF strains (Costas and Owen, 1987) might be just the coincidental result of computation of similarities and the clustering method used. It remains however possible that rats are the source of both turkey and human RBF strains. 16S rDNA sequencing data of turkey *S. moniliformis* strains are lacking. The hemagglutinating characteristics of turkey strains of *S. moniliformis* did not differ from the behaviour of strains isolated from other host species (Hofmann, 1994).

An interesting observation from the protein profiling study (Costas and Owen, 1987) was that the protein profiles of human HF strains were found to differ from profiles of RBF strains. This suggests the possibility that HF and RBF might be caused by different clones (strains) of the bacterium. Isolates of the same bacterial species can show significant genetic variability (Joyce et al., 2002; Binnewies et al., 2006) and different clones of a given species can be associated with different disease processes (Raskin et al., 2006). Data on strain diversity of close relatives of *S. moniliformis* is limited to a report describing the isolation of different clones of *Fusobacterium nucleatum* from different clinical conditions (Avila-Campos et al., 2006).

Another possibility is that the difference in protein profiles of the HF and RBF strains results from the differing routes of infection: oral and parenteral, respectively. The infected host is a complex and dynamic environment and various bacterial genes are induced in vivo (Buer and Balling, 2003). Which bacterial genes are induced might be different after oral and parenteral infection (Khan and Isaacson, 2002; Marco et al., 2007). It remains to be elucidated which *S. moniliformis* genes are induced after experimental oral or parenteral infection and if this results in the formation of stable clones of the bacterium. Differences in the hemagglutinating behaviour between RBF and HF strains of the bacterium were not found (Hofmann, 1994).

7. Transmission

S. minus is transmitted to humans by a bite. *S. moniliformis* can also be transmitted via ingestion. Several human RBF cases have an unknown origin. Human to human transmission of *S. moniliformis* or *S. minus* has not been documented.

7.1. Bites or scratches

Rats have been most frequently implicated as host species involved in human RBF both by *S. moniliformis* and *S. minus*. Other rodent species such as mouse, squirrel and gerbil and non-rodent species have occasionally been identified as possible sources of infection.

The main reservoir for *S. moniliformis* is the pharynx of rats. Scratch incidents by rats were reported in a few cases (Cunningham et al., 1998; Van Nood and Peters, 2005; Dendle et al., 2006), as well as a scratch incident in a rat infested pig pen (Fordham et al., 1992). A scratch from a contaminated rat cage ended in fatal RBF in a pet shop employee (Shartsblat et al., 2004) and also handling dead rats as a cause of *S. moniliformis* infection has been reported (Lambe et al., 1973).

It is assumed that *S. minus* does not occur in rat saliva but rather in the blood and perhaps in the conjunctiva. Only if there are lesions in the oral mucosa is *S. minus* transferred to the animal's saliva. *S. minus* has been reported to be present in considerable numbers in the muscles of the tongue (Manouélian, 1940). In the mouse the salivary glands of the ear contained higher numbers of spirillae than the peripheral blood suggesting that saliva is indeed important in transmission of *S. minus* through a mouse bite (Bok, 1940).

7.2. Ingestion

S. moniliformis can also be transmitted via food or drinking water contaminated by rats. HF in a 7-year-old boy was probably due to the ingestion of rat faeces as was admitted by the patient. *S. moniliformis* was cultured from blister fluid and detected in one of his pet rats by PCR (Andre et al., 2005) but rat faeces was not tested. It is unclear if *S. moniliformis* is shed in rat faeces. There are two reports on vainly efforts to grow *S. moniliformis* in milk (Schottmüller, 1914; Smith, 1998). In some human streptobacillary infections close contact with the oral flora of pet rats through kissing and sharing food may have been the route of transmission (Vasseur et al., 1993; Hockman et al., 2000; Frisk and Patterson, 2002; Ojukwu and Christy, 2002; Abdulaziz et al., 2006; Dendle et al., 2006; Schachter et al., 2006).

7.3. Unknown

Several cases of human RBF without a history of bite or scratch incidents have been reported (Rumley et al., 1987; Holroyd et al., 1988, Fordham et al., 1992, Rygg and Bruun, 1992; Pins et al., 1996). In some cases contact with rats or other rodents could be excluded completely (Clausen, 1987; Pins et al., 1996; Torres et al., 2003; Kondruweit et al., 2007).

8. Prevention

RBF has been identified in various groups of people who have increased contact with animals, notably with rats. Exposure may be accidental, occupational and recreational. The greatest risk comes from exposure to wild rats (homeless people, farmers, sewage workers, hunters and trappers, tourists) and pet rats that are descendants from conventional laboratory *R. norvegicus* (pet shop personnel, pet owners, veterinarians).

Children handling pet rats may be a special risk group. In a series of RBF cases children were exposed to a rat at school in 14% of the cases and the relative prevalence among children seems to be much higher than among adults (Roughgarden, 1965; Hirschhorn and Hodge, 1999; Graves and Janda, 2001). *S. moniliformis* infection has been suggested to be a pediatric problem (Raffin and Freemark, 1979). More than half of the reported cases of rat bite fever occurred in children (Freels and Elliott, 2004). Children

presumably tend to have closer contact with pet rats than adults but they may also be more susceptible to clinical infection. Infection may also be contracted via small wounds when rat cages are cleaned.

Obviously avoiding direct and indirect contact with infected animals is the best way of prevention. It must be realised that many species of laboratory animals, of which several may be kept as pets, have never been examined for the presence of the RBF agents: ferrets (*M. putorius furo*), rodents other than mice and rats such as hamsters (*Mesocricetus auratus*), cotton rats (*Sigmodon hispidus*), voles (*Microtus* spp.), chinchillas (*Chinchilla chinchilla*), etc.

Contact with rats is inherent to and hence unavoidable in some occupations such as sewage workers, laboratory technicians and veterinarians working with laboratory animals.

Probably the first report of a laboratory worker suffering from RBF was by Levaditi et al. (1925). The reported incidence of *S. moniliformis* RBF in laboratory personnel is low. Thirteen cases have been documented between 1958 and 1983 (Anderson et al., 1983). References to various other cases can be found (Wullenweber, 1995).

Where possible conventional laboratory animals should be replaced by SPF animals. Facilities housing experimental animals should be inaccessible to wild rodents. If this cannot be fully excluded populations of wild animals must be controlled.

Workers professionally occupied with wild rodent control, sewage workers and pet shop staff is continuously at risk of exposure. This risk can obviously be diminished by wearing personal protective working clothes, shoes and gloves that are impermeable to rodent bites and scratches. The use of good equipment needed for the work will further minimise the risk of exposure.

In case animal bites and scratches occur, meticulous wound treatment is necessary (Smith and Meadowcroft, 2002). After an animal bite or scratch the wound should be cleaned thoroughly and tetanus prophylaxis might be advisable.

RBF remains an occasional hazard for the general public and professionals having contact with pet or wild rats.

9. Future research

Various aspects of infections caused by *S. moniliformis* and *S. minus* have not been elucidated and might be the subject of further studies.

Efforts to culture *S. minus* do not seem very promising given all unsuccessful attempts. In clinical disease suggestive of *S. minus* infection the detection of causative bacteria might be attempted by culture free methods (Dong et al., 2008; Lynch et al., 2008). Also for *S. moniliformis* each paragraph of this review shows a lack of basic information. More insight into the *genetic properties* of the bacterium is basic to understanding most if not all other aspects of the RBF and HF. Some issues that might be relevant here comprise:

- whole-genome sequencing of strains from different host species;
- the existence of extra chromosomal genetic elements such as plasmids;
- genome plasticity;
- intraspecies genetic variability and
- identification of the genetic basis of virulence factors.

The *host species* of the bacterium might be further delineated by molecular detection using 16S rDNA primers in samples from species kept as pets or new animal models in biomedical research with a special focus on relatives of *Rattus* in the Rodent lineage.

Whether *human infection* is genetically determined might be explored via identification of susceptibility loci in rodents and their human orthologs by comparative genomic analysis.

The possible persistence of L-forms in the human body after antibiotic treatment and relapsing fever after stopping treatment might be studied in experimental animal models and in human patients. Real-time quantitative reverse transcription PCR can be used to detect bacterial messenger RNA as a way to distinguish live and dead bacteria as an indicator of active infection.

Pathogenicity of the bacterium will be determined by factors involved in colonization via adhesion–receptor interaction, subsequent invasion into the body, development of cellular and humoral immune activity, and escape from the immune response. None of the issues can be elucidated without insight in the molecular biology of the bacterium and genetic determinants of host susceptibility.

Regarding *diagnostic methods* the use of serology in RBF and HF suspected human patients seems possible although interpretation of IgM and IgG antibody activity levels will be difficult when paired sera are not available. It is obvious that molecular detection of the causative bacterium would give a more clear answer.

Epidemiological issues comprise the possible existence of clones of the bacterium which might show a relationship with host species, geographic origin, disease pattern and route of infection (RBF and HF). Differences between bacteria might be studied by genetic as well as phenotypic methods.

Relevant to *transmission* and the origin of HF are the possible faecal shedding of *S. moniliformis* by rats and the survival or the bacterium in milk and water.

Acknowledgements

The authors are indebted to Anky Schoormans and Carolien Flemming (Veterinary Microbiological Diagnostics Centre, Veterinary Faculty, Utrecht University) for growing *Streptobacillus moniliformis* strains and for Figs. 1 and 2. Dr. S.H.A. Peters (Flevoziekenhuis, Almere, The Netherlands) kindly provided Fig. 4; Thieme Verlag is acknowledged for the permission to reproduce Fig. 3. The librarians of the Veterinary Faculty of Utrecht University are acknowledged for making even the most exotic manuscripts available.

References

Abdulaziz, H., Touchie, C., Toye, B., Karsh, J., 2006. Haverhill fever with spine involvement. J. Rheumatol. 33, 1409–1410.

Adachi, K., 1921. Flagellum of the microorganism of rat bite fever. J. Exp. Med. 33, 647–654.

Adkins, R.M., Gelke, E.L., Rowe, D., Honeycutt, R.L., 2001. Molecular phylogeny and divergence time estimates for major rodent groups: evidence from multiple genes. Molecul. Biol. Evol. 18, 777–791.

Adler, H.E., Shirfrine, M., 1960. Nutrition, metabolism and pathogenicity of Mycoplasmas. Ann. Rev. Microbiol. 14, 141–160.

Aldred, P., Hill, A.C., Young, C., 1974. The isolation of *Streptobacillus moniliformis* from cervical abscesses of guinea-pigs. Lab. Animals 8, 275–277.

Anderson, L.C., Leary, S.L., Manning, P.J., 1983. Rat bite fever in animal research laboratory personnel. Lab. Anim. Sci. 33, 292–294.

Andre, J.M., Freydiere, A.M., Benito, Y., Rousson, A., Lansiaux, S., Kodjo, A., Mazzocchi, C., Berthier, J.C., Vandenesch, F., Floret, D., 2005. Rat bite fever caused by *Streptobacillus moniliformis* in a child: human infection and rat carriage diagnosed by PCR. J. Clin. Pathol. 58, 1215–1216.

Arkless, H.A., 1970. Rat bite fever at Albert Einstein Medical Center. Pa. Med. 73, 49.

Avila-Campos, M.J., Rivera, I.N., Nakano, V., 2006. Genetic diversity of oral *Fusobacterium nucleatum* isolated from patients with different clinical conditions. Revista Inst. Med. Tropical de Sao Paulo 48, 59–63.

Balakrishnan, N., Menon, T., Shanmugasundaram, S., Alagesan, R., 2006. *Streptobacillus moniliformis* endocarditis. Emerg. Infect. Dis. 12, 1037–1038.

Beachey, E.H., 1981. Bacterial adherence: adhesin-receptor interactions mediating the attachment of bacteria to mucosal surfaces. J. Infect. Dis. 143, 325–345.

Bell, D.O., Elmes, P.C., 1969. Effects of certain organisms associated with chronic respiratory disease on SPF and conventional rats. Med. Microbiol. 2, 511–519.

Berger, C., Altwegg, M., Meyer, A., Nadal, D., 2001. Broad range polymerase chain reaction for diagnosis of rat bite fever caused by *Streptobacillus moniliformis*. Pediatr. Infect. Dis. J. 20, 1181–1182.

Holt, J.G., Krieg, N.R., Sneath, P.H.A., Staley, J.T., Williams, S.T. (Eds.), 1994. Bergey's Manual of Determinative Bacteriology. Williams & Wilkins, Baltimore Md.

Bhatt, K.M., Mirza, N.B., 1992. Rat bite fever: a case report of a Kenyan. East Afr. Med. J. 69, 542–543.

Binnewies, T.T., Motro, Y., Hallin, P.F., Lund, O., Dunn, D., La, T., Hampson, D.J., Bellgard, M., Wassenaar, T.M., Ussery, D.W., 2006. Ten years of bacterial genome sequencing: comparative-genomics-based discoveries. Funct. Integr. Genomics 6, 165–185.

Blake, F.G., 1916. The etiology of ratbite fever. J. Exp. Med. 23, 39–60.

Bloch, O., Baldock, H., 1937. A case of rat bite fever with demonstration of *Spirillum minus*. J. Ped. 10, 358–360.

Bok, R., 1940. Het voorkomen van de rattebeetspiril in de oorspeekselklier van de muis. Acta Leidensia 15–16, 143–151 (in Dutch).

Bolstad, A.I., 1994. Sizing the *Fusobacterium nucleatum* genome size by pulsed-field gel electrophoresis. FEMS Microbiol. Lett. 123, 145–151.

Boot, R., Koopman, J.P., Kruijt, B.C., Lammers, R.M., Kennis, H.M., Lankhorst, A., Mullink, J.W.M.A., Stadhouders, A.M, de Boer, H., Welling, G.W., Hectors, M.P.C., 1985. The "normalization" of germ-free rabbits with host-specific caecal microflora. Lab. Anim. 19, 344–352.

Boot, R., Angulo, A.F., Walvoort, H.C., 1989. *Clostridium difficile*-associated typhlitis in specific pathogen free guinea pigs in the absence of antimicrobial treatment. Lab. Animals 23, 203–207.

Boot, R., Koopman, J.P., Kunstyr, I., 2001. Microbiological standardization. In: Van Zutphen, L.F.M., Baumans, V., Beynen, A.C. (Eds.), Principles of Laboratory Animal Science. Elsevier, Amsterdam, pp. 143–165.

Boot, R., Thuis, H., Teppema, J.S., 1993a. Hemagglutination by *Pasteurellaceae* from rodents. Zentralblatt für Bakteriologie 279, 259–273.

Boot, R., Bakker, R.H., Thuis, H., Veenema, J.L., De Hoog, H., 1993b. An enzyme-linked immunosorbent assay (ELISA) for monitoring rodent colonies for *Streptobacillus moniliformis* antibodies. Lab. Anim. 27, 350–357.

Boot, R., Thuis, H., Bakker, R.H.G., Veenema, J.L., 1995. Serological studies of *Corynebacterium kutscheri* and coryneform bacteria using an enzyme-linked immunosorbent assay (ELISA). Lab. Anim. 29, 294–299.

Boot, R., Oosterhuis, A., Thuis, H.C., 2002. PCR for the detection of *Streptobacillus moniliformis*. Lab. Anim. 36, 200–208.

Boot, R., van de Berg, L., Vlemminx, M.J., 2006. Detection of antibodies to *Streptobacillus moniliformis* in rats by an immunoblot procedure. Lab. Anim. 40, 447–455.

Boot, R., van de Berg, L., Koedam, M.A., Veenema, J.L., Vlemminx, M.J., 2007. Resistance to infection of guinea pigs with a rat *Streptobacillus moniliformis*. Scand. J. Lab. Anim. Sci. 34, 1–5.

Boot, R., van de Berg, L., Reubsaet, F.A.G., Vlemminx, M.J., 2008. Positive *Streptobacillus moniliformis* PCR in guinea pigs likely due to *Leptotrichia* spp. Vet. Microbiol. 128, 395–399.

Borgen, L.O., Gaustad, V., 1948. Infection with *Actinomyces muris ratti* (*Streptobacillus moniliformis*) after bite of laboratory rat. Acta Med. Scand. 130, 189–198.

Boyer, C.I.J., Bruner, D.W., Brown, J.A., 1958. A *Streptobacillus*, the cause of tendon-sheath infection in turkeys. Avian Dis. 2, 418–427.

Brenner, D.J., Krieg, N.R., Staley, J.T., 2005. Taxonomic outline of the Archea and Bacteria. In: Brenner, D.J., Krieg, N.R., Staley, J.T. (Eds.), Bergey's Manual of Systematic Bacteriology, 2nd ed., vol.2, Part A. Springer, New York, Appendix 2.

Buddigh, G.J., 1944. Experimental *Streptobacillus moniliformis* arthritis in the chick embryo. J. Exp. Med. 80, 59–64.

Buer, J., Balling, R., 2003. Mice, microbes and models of infection. Nat. Rev. Genet. 4, 195–205.

Buranakitjaroen, P., Nilganuwong, S., Gherunpong, V., 1994. Rat bite fever caused by *Streptobacillus moniliformis*. Southeast Asian J. Trop. Med. Public Health 25, 778–781.

Burke, W.A., Kwong, O., Halpern, R., 1959. Rat bite fever due to *Streptobacillus moniliformis*: a report of two cases. Calif. Med. 91, 356–358.

Byington, C., Basow, R., 1998. *Spirillum minus* (rat bite fever). In: Feigen, R., Cherry, J.D. (Eds.), Textbook of Pediatric Infectious Diseases. W.B. Saunders Company, Philadelphia, pp. 1542–1543.

Carbeck, R.B., Murphy, J.F., Britt, E.M., 1967. Streptobacillary rat bite fever with massive pericardial effusion. J. Am. Med. Ass. 201, 703–704.

Carter, H.V., 1888. Notes on the occurrence of a minute blood spirillum in an Indian rat. Sci. Mem. Med. Officers India 3, 45–48.

Chen, P.-L., Lee, N.-Y., Yan, J.-J., Yang, Y.-j., Chen, H.-M., Chang, C.-M., Ko, N.-Y., Lai, C.-H., Ko, W.-C., 2007. Prosthetic valve endocarditis caused by *Streptobacillus moniliformis*: a case of rat bite fever. J. Clin. Microbiol. 45, 3125–3126.

Chulay, J.D., Lankerani, M.R., 1976. Splenic abcesses: report of 10 cases and review of the literature. Am. J. Med. 61, 513–522.

Clarke, A.M., Virgincar, N., Lankester, B.J.A., Raza, M.M., Robertson, L., Gargan, M.F., 2005. Rat bite fever-a rare cause of septic arthritis. Injury Extra 36.

Clausen, C., 1987. Septic arthritis due to *Streptobacillus moniliformis*. Clin. Microbiol. Newslett. 9, 123–124.

Coates, M.E., Gustafsson, B.E. (Eds.), 1984. The Germ-Free Animal in Biomedical Research, vol. 9. Laboratory Animals (Laboratory Animal Handbooks, London.

Cohen, R.L., Wittler, R.G., Faber, J.E., 1968. Modified biochemical tests for characterization of L-phase variants of bacteria. Appl. Microbiol. 16, 1655–1662.

Committee on Urban Pest Management, 1980. Urban pest management. National Acadamy Press, Washinton.

Conrads, G., Claros, M.C., Citron, D.M., Tyrrell, K.L., Merriam, V., Goldstein, E.J.C., 2002. 16S-23S rDNA internal transcribed spacer sequences for analysis of the phylogenetic relationships among species of the genus *Fusobacterium*. Int. J. Sys. Evol. Microbiol. 52, 493–499.

Costas, M., Owen, R.J., 1987. Numerical analysis of electrophoretic protein patterns of *Streptobacillus moniliformis* strains from human, murine and avian infections. J. Med. Microbiol. 23, 303–311.

Cunningham, B.B., Paller, A.S., Katz, B.Z., 1998. Rat bite fever in a pet lover. J. Am. Acad. Dermatol. 38, 330–332.

Das, A.M., 1986. *Streptobacillus moniliformis* isolated from an abcess of a dog. Ind. J. Comp. Microbiol. Immunol. Infect. Dis. 7, 115.

Delannoy, D., Savinel, P., Balquet, M.H., Canonne, J.P., Amourette, J., Bugnon, P.Y., 1991. Manifestations digestives et pulmonaires rélévant une septicémie à *Streptobacillus moniliformis*: présantation atypique d'une pathologie rare et méconnue. Revue de Med. Interne 3, S158 (in French).

Dendle, C., Woolley, I.J., Korman, T.M., 2006. Rat bite fever septic arthritis: illustrative case and literature review. Eur. J. Clin. Microbiol. Infect. Dis. 25, 791–797.

Dewhirst, F.E., Chien, C.C., Paster, B.J., Ericson, R.L., Orcutt, R.P., Schauer, D.B., Fox, J.G., 1999. Phylogeny of the defined murine microbiota: altered Schaedler flora. Appl. Environm. Microbiol. 65, 3287–3292.

Dick, G.E., Tunnicliff, R., 1918. *Streptothrix* isolated from blood of a patient bitten by weasel. J. Infect. Dis. 23, 183–187.

Dijkmans, B.A., Thomeer, R.T., Vielvoye, G.J., Lampe, A.S., Mattie, H., 1984. Brain abscess due to *Streptobacillus moniliformis* and *Actinobacterium meyerii*. Infection 12, 262–264.

Ditchfield, J., Lord, L.H., McKay, K.A., 1961. *Streptobacillus moniliformis* infection in a dog. Can. Vet. J. 2, 457–459.

Domingue, G., Turner, B., Schlegel, J.U., 1974. Cell-wall deficient bacterial variants in kidney tissue. Urology 111, 288–292.
Domingue, G.J., Woody, H.B., 1997. Bacterial persistence and expression of disease. Clin. Microbiol. Rev. 10, 320–344.
Dong, J., Olano, J.P., McBride, J.W., Walker, D.H., 2008. Emerging pathogens: challenges and successes of molecular diagnostics. J. Mol. Diagn. 20, 185–197.
Donker, A.E., Mutsaers, J.A.E.M., van Ommen-Koolmees, R.G., Jansen, C.L., 2005. Rattenbeetziekte na een beet van een huisrat (Rat bite fever after a finger bite by a domestic rat). Tijdschr. Kindergeneesk. 73, 78–80 (in Dutch).
Downing, N.D., Dewnany, G.D., Radford, P.J., 2001. A rare and serious consequence of a rat bite. Ann. R. Coll. Surg. Engl. 83, 279–280.
Edwards, R., Finch, R.G., 1986. Characterisation and antibiotic susceptibilities of *Streptobacillus moniliformis*. J. Med. Microbiol. 21, 39–42.
Elliott, S.P., 2007. Rat bite fever and *Streptobacillus moniliformis*. Clin. Microbiol. Rev. 20, 13–22.
Fadiel, A., Eichenbaum, K.D., El Semary, N., Epperson, B., 2007. Mycoplasma genomics: tailoring the genome for minimal life requirements through reductive evolution. Front. Biosci. 12, 2020–2028.
Faro, S., Walker, C., Pierson, R.L., 1980. Amnionitis with intact amniotic membranes involving *Streptobacillus moniliformis*. Obstet. Gynecol. 55, 9S–11S.
Farquhar, J.W., Edmunds, P.N., Tillby, J.B., 1958. Soduku in a child: the result of a mouse bite. Lancet 6, 1211–1212.
Fleming, M.P., 1976. *Streptobacillus moniliformis* isolations from cervical abscesses of guinea pigs. Vet. Rec. 99, 256.
Fordham, J.N., McKay-Ferguson, E., Davies, A., Blyth, T., 1992. Rat bite fever without the bite. Ann. Rheum. Dis. 51, 411–412.
Foster, H.L., 1962. Establishment and operation of S.P.F. colonies. In: Harris, R.J.C. (Ed.), The Problems of Laboratory Animal Disease. Academic Press, London, pp. 249–259.
Frans, J., Verhaegen, J., Van Noyen, R., 2001. *Streptobacillus moniliformis*: case report and review of the literature. Acta Clin. Belg. 56, 187–190.
Freels, L.K., Elliott, S.P., 2004. Rat bite fever: three case reports and a literature review. Clin. Pediatr. 43, 291–295.
Freundt, E.A., 1956a. Experimental investigations into the pathogenicity of the L-phase variant of *Streptobacillus moniliformis*. Acta Pathol. Microbiol. Scand. 38, 246–258.
Freundt, E.A., 1956b. *Streptobacillus moniliformis* infection in mice. Acta Pathol. Microbiol. Scand. 38, 231–245.
Freunek, K., Turnwald-Maschler, A., Pannenbecker, J., 1997. Rattenbissfieber: Infektion mit *Streptobacillus moniliformis* (caused rat bite fever by *Streptobacillus moniliformis* infection). Monatsschr. Kinderheilkd. 145, 473–476 (in German).
Frisk, J., Patterson, R.H., 2002. Our case of rat bite fever could be termed Rat-lick fever! CMPT (Clin. Microbiol. Proficiency Testing) Connections (CMPT) 6, 1–4.
Futaki, K., Takaki, F., Taniguchi, T., Osumi, S., 1916. The cause of Rat bite fever. J. Exp. Med. 23, 249–250.
Gay, F.W., Macuire, M.E., Baskerville, A., 1972. Etiology of chronic pneumonia in rats and a study on experimental infection in mice. Infect. Immum. 6, 83–91.
Gilbert, G.L., Cassidy, J.F., Bennett, N.M., 1971. Rat bite fever. Med. J. Aust. 2, 1131–1134.
Glaser, C.P., Lewis, P., Wong, S., 2000. Pet, animal and vector-borne infections. Pediatr. Rev. 21, 219–295.
Glastonbury, J.R., Morton, J.G., Matthews, L.M., 1996. *Streptobacillus moniliformis* infection in Swiss white mice. J. Vet. Diagn. Invest. 8, 202–209.
Glűnder, G., Hinz, K.H., Stiburek, B., 1982. Joint disease in turkeys caused by *Streptobacillus moniliformis*. Dtsch. Tierarztl. Wochenschr. 89, 367–370 (in German).
Gourlay, R.N., Flanagan, B.F., Wyld, S.G., 1982. *Streptobacillus actinoides* (*Bacillus actinoides*): isolation from pneumonic lungs of calves and pathogenicity studies in gnotobiotic calves. Res. Vet. Sci. 32, 27–34.
Graves, M.H., Janda, J.M., 2001. Rat bite fever (*Streptobacillus moniliformis*): a potential emerging disease. Int. J. Infect. Dis. 5, 151–155.
Gray, H.H., 1967. Squirrel bite fever. Trans. R. Soc. Trop. Med. Hyg. 61, 857.
Griego, R.D., Rosen, T., Orengo, I.F., Wolf, J.E., 1995. Dog, cat, and human bites: a review. J. Am. Acad. Dermatol. 33, 1019–1029.
Hagelskjaer, L., Sorensen, I., Randers, E., 1998. *Streptobacillus moniliformis* infection: 2 cases and a literature review. Scand. J. Infect. Dis. 30, 309–311.
Haneveld, G.T., 1958. Sodoku caused by a mouse. Ned. T. Geneeskunde 102, 1030–1032 (in Dutch).
Heilman, F.R., 1941. A study of *Asterococcus muris* (*Str. moniliformis*). 1. Morphologic aspects and nomenclature. J. Infect. Dis. 69, 32–44.
Hinrichsen, S.L., Ferraz, S., Romeiro, M., Muniz-Filho, M., Abath, A.H., Magelhaes, C., Damasceno, F., Araujo, C.M., Campos, C.M., Lamprea, D.P., 1992. Sodoku-a case report. Rev. Soc. Bras. Med. Trop. 25, 135–138 (in Portuguese).
Hirschhorn, R., Hodge, R., 1999. Identification of risk factors in rat bite incidents involving humans. Pediatrics 104, e35.
Hitzig, W.M., Liebesman, A., 1944. Subacute endocarditis associated with a spirillum: report of a case with repeated isolation of the organism from the blood. Arch. Int. Med. 73, 415–424.
Hofmann, N., 1994, Phänotypische und molekulartaxonomische Untersuchungen zur systematischen Stellung von *Streptobacillus moniliformis* dem Erreger des Rattenbiβfiebers. Dissertation Hannover (in German).
Hockman, D.E., Pence, C.D., Whittler, R.R., Smith, L.E., 2000. Septic arthritis of the hip secondary to rat bite fever: a case report. Clin. Orthop. Relat. Res. 173–176.
Holroyd, K.J., Reiner, A.P., Dick, J.D., 1988. *Streptobacillus moniliformis* polyarthritis mimicking rheumatoid arthritis: an urban case of rat bite fever. Am. J. Med. Technol. 85, 711–714.
Hopkinson, W.I., Lloyd, J.M., 1981. *Streptobacillus moniliformis* septicaemia in spinifex hopping mice (*Notomys alexis*). Aust. Vet. J. 57, 533–534.
Hudemann, H., Mücke, D., 1951. Zur bakteriologischen Diagnostiek des Sodoku. Arch. Klin. Exp. Dermatol. 192, 530–534 (in German).
Hudsmith, L., Weston, V., Szram, J., Allison, S., 2001. Clinical picture, rat bite fever. Lancet Infect. Dis. 1, 91.
ILAR, 1998. Opportunistic infections in laboratory rats and mice. ILAR J. 39 (4).
Irvine, L., Wills, T., 2006. *Streptobacillus moniliformis*: a mouse trying to become a rat. Clin. Microbiol. Newslett. 28, 118–120.
Iyer, M.A.K., 1936. Spirillum fever caused by a monkey bite. Indian. Med. Gaz. 71, 462.
Joekes, T., 1925. Cultivation of the spirillum of rat bite fever. Lancet 1, 1225–1226.
Joyce, E.A., Chan, K., Salama, N.R., Falkow, S., 2002. Redefining bacterial populations: a post-genomic reformation. Nat. Rev. Genet. 3, 462–473.
Kadan, D., Chih, D., Brett, A., Segasothy, M., 2002. A case of rat bite fever. Intern. Med. J. 32, 193–194.
Kalra, B., Kalra, S., Chatley, G., Singh, H., 2006. Rat bite as a cause of diabetic foot ulcer—a series of eight cases. Diabetologia 49, 1452–1453.
Khan, M.A., Isaacson, R.E., 2002. Identification of *Escherichia coli* genes that are specifically expressed in a murine model of septicemic infection. Infect. Immun. 70, 3404–3412.
Kaspareit-Rittinghausen, J., Wullenweber, M., Deerberg, F., Farouq, M., 1990. Pathologische Veränderungen bei *Streptobacillus moniliformis* Infektion von C7Bl/6J Mäusen. Berl. Münch. Tierärtzl. Wschr. 103, 84–87 (in German).
Kimman, T.G., 2001. Genetics of Infectious Disease Susceptibility. Kluwer Academic Publishers, Boston-Dordrecht-London.
Kirchner, B.K., Lake, S.G., Wightman, S.R., 1992. Isolation of *Streptobacillus moniliformis* from a guinea pig with granulomatous pneumonia. Lab. Anim. Sci. 42, 519–521.
Klieneberger, E., 1942. Some new observations bearing on the nature of the pleuropneumonia-like organism known as L1 associated with *Streptobacillus moniliformis*. J. Hyg. 42, 485–497.
Kondruweit, M., Weyand, M., Mahmoud, F.O., Geisdoerfer, W., Schoerner, C., Ropers, D., Achenbach, S., Strecker, T., 2007. Fulminant endocarditis caused by *Streptobacillus moniliformis* in a young man. J. Thorac. Cardiovasc. Surg. 134, 1579–1580.
Koopman, J.P., Van den Brink, M.E., Vennix, P.P., Kuypers, W., Boot, R., Bakker, R.H., 1991. Isolation of *Streptobacillus moniliformis* from the middle ear of rats. Lab. Anim. 25, 35–39.
Krauss, H., Weber, A., Appel, M., Enders, B., Isenberg, H.D., Schiefer, H.G., Slenczka, W., von Graevenitz, A., Zahner, H., 2003. Zoonoses: Infectious Diseases Transmissible from Animals to Humans, 3rd ed. ASM Press, ISBN: 1555812368.
Lambe Jr., D.W., McPhedran, A.M., Mertz, J.A., Stewart, P., 1973. *Streptobacillus moniliformis* isolated from a case of Haverhill fever: biochemical characterization and inhibitory effect of sodium polyanethol sulfonate. Am. J. Clin. Pathol. 60, 854–860.
Levaditi, C., Nicolau, S., Poincloux, P., 1925. Sur le role etiologique de *Streptobacillus moniliformis* (nov. spec.) dans l'erytheme polymorphe aigu septicemique. C. R. Acad. Sci. 180, 1188 (in French).
Levaditi, C., Selbie, R.F., Schoen, R., 1932. Le rheumatisme infectieux spontané la souris provoqué par le *Streptobacillus moniliformis*. Ann. Inst. Pasteur (Paris) 48, 308–343 (in French).
Liu, T., Matsuguchi, T., Tsuboi, N., Yajima, T., Yoshikai, Y., 2002. Differences in expression of Toll-like receptors and their reactivities in dendritic cells in BALB/c and C57BL/6 mice. Infect. Immum. 70, 6638–6645.

Lopez, P., Euras, J., Anglada, A., Garcia, M., Prats, G., 1992. Infection due to *Streptobacillus moniliformis*. Clin. Microbiol. Newslett. 14, 38–40.

Lynch, S.V., Yang, K., Brodie, E.L., MacDougall, C., Anderson, G.L., Wiener-Kronish, J.P., 2008. Culture independent bacterial population analysis, clinical implications for respiratory and other infections. Curr. Resp. Med. Rev. 4, 35–39.

Mackie, T.G., van Rooyen, C.E., Gilroy, E., 1933. An epizootic disease occurring in a breeding stock of mice: bacteriological and experimental observations. Br. J. Exp. Pathol. 14, 32–136.

MacLean, R.A., 1979. Rat bite fever. In: Stoenner, H., Kaplan, W., Torten, M. (Eds.), Handbook in Zoonoses; Section A: Bacterial, Rickettsial and Mycotic Diseases, vol. II. CRC Press Inc., Boca Raton, Florida, pp. 7–11.

Maher, M., Palmer, R., Gannon, F., Smith, T., 1995. Relationship of a novel bacterial fish pathogen to *Streptobacillus moniliformis* and the fusobacteria group, based on 16S ribosomal RNA analysis. Syst. Appl. Microbiol. 18, 79–84.

Manouélian, Y., 1940. Etude morphologique du *Spirochaeta pallida*. Modes de division Spirochétogè syphilitique. Ann. Inst. Pasteur 64, 439–455 (in French).

Marco, M.J., Bongers, R.S., De Vos, W.M., Kleerebezem, M., 2007. Spatial and temporal expression of *Lactobacillus plantarum* genes in the gastrointestinal tracts of mice. Appl. Environm. Microbiol. 73 134-132.

Maynard, J.H., McNaughton, W.M., Travis, T., 1986. *Streptobacillus moniliformis* cellulitis and bacteraemia following a dog bite. Commun. Dis. Intell. 10.

McCormack, R.C., Kaye, D., Hook, E.W., 1967. Endocarditis due to *Streptobacillus moniliformis*. J. Am. Med. Ass. 200, 77–79.

McEvoy, M.B., Noah, N.D., Pilsworth, R., 1987. Outbreak of fever caused by *Streptobacillus moniliformis*. Lancet 2, 1361–1363.

Mignard, S., Aubry-Rozier, B., de Montclos, M., Llorca, G., Carret, G., 2007. Pet-rat bite fever and septic arthritis: molecular identification of *Streptobacillus moniliformis*. Med. Mal. Infect. 37, 293–294.

MMWR, 1998. Rat bite fever-New Mexico, 1996. Morb. Mortal. Wkly. Rep. 47, 89–91.

MMWR, 2005. Fatal rat bite fever—Florida and Washington, 2003. Morb. Mortal. Wkly. Rep. 53, 1198–1202.

Mock, H.E., Morrow, A.R., 1932. Rat bite fever transmitted by cat. Ill. Med. J. 61, 67–70.

Mohamed, Y.S., Moorhead, P.D., Bohl, E.H., 1969. Natural *Streptobacillus moniliformis* infection of turkeys, and attempts to infect turkeys, sheep, and pigs. Avian Dis. 13, 379–385.

Nicklas, W., Baneux, P., Boot, R., Decelle, T., Deeny, A.A., Illgen-Wilke, B., Fumanelli, M., 2002. Recommendations for the health monitoring of rodent and rabbit colonies in breeding and experimental units. Lab. Anim. 36, 20–42.

Nixon, J.H., 1914. "Rat bite fever" caused by a ferret. Bri. Med. J. 2, 629.

Oeding, P., Pedersen, H., 1950. *Streptothrix muris ratti* (*Streptobacillus moniliformis*) isolated from a brain abcess. Arch. Pathol. Microbiol. Scand. 27, 436–442.

Ojukwu, I.C., Christy, C., 2002. Rat bite fever in children: case report and review. Scand. J. Infect. Dis. 34, 474–477.

Olson, L.D., McCune, E.L., 1968. Histopathology of chronic otitis media in the rat. Lab. Anim. Care 18, 478–485.

Olsen, I., Dewhirst, F.E., Paster, B.J., Busse, H.J., 2005. Pasteurellaceae. In: Brenner, D.J., Krieg, N.R., Staley, J.T. (Eds.), Bergey's Manual of Systematic Bacteriology, 2nd ed., vol. 2Springer, New York, pp. 851–912, Part B.

Ordog, G.J., Balasubramanium, S., Wasserberger, J., 1985. Rat bites: fifty cases. Ann. Emer. Med. 14, 126–130.

Parker, F., Hudson, N.P., 1926. The etiology of Haverhill fever (erythrema arthriticum epidemicum). Am. J. Pathol. 2, 357–379.

Peel, M.M., 1993. Dog-associated bacterial infections in humans: isolates submitted to an Australian reference laboratory, 1981–1992. Pathology 25, 379–384.

Pins, M.R., Holden, J.M., Yang, J.M., Madoff, S., Ferraro, M.J., 1996. Isolation of presumptive *Streptobacillus moniliformis* from abscesses associated with the female genital tract. Clin. Infect. Dis. 22, 471–476.

Place, E.H., Sutton, L.E., 1934. Erythema arthrticum epidemicum (Haverhill fever). Arch. Intern. Med. 54, 659–684.

Prager, L., Frenck, R.W.J., 1994. *Streptobacillus moniliformis* infection in a child with chickenpox. Pediatr. Infect. Dis. J. 13, 417–418.

Raffin, B.J., Freemark, M., 1979. Streptobacillary rat bite fever: a pediatric problem. Pediatrics 64, 214–217.

Raskin, D.M., Seshadri, R., Pukatzki, S.U., Mekalanos, J.J., 2006. Bacterial genomics and pathogen evolution. Cell 124, 703–714.

Reitzel, R.J., Haim, A., Prindle, K., 1936. Rat bite fever from field mouse. J. Am. Med. Ass. 106, 1090–1091.

Ripley, H.S., van Sant, H.M., 1934. Rat bite fever acquired from a dog. J. Am. Med. Assoc. 102, 1917–1921.

Robertson, A., 1924. Observations on the causal organism of rat bite fever in man. Ann. Trop. Med. Parasitol. 18, 157–175.

Rordorf, T., Zuger, C., Zbinden, R., von Graevenitz, A., Pirovino, M., 2000. *Streptobacillus moniliformis* endocarditis in an HIV-positive patient. Infection 28, 393–394.

Roughgarden, J.W., 1965. Antimicrobial therapy of rat bite fever. A review. Arch. Intern. Med. 116, 39–54.

Row, R., 1918. Cutaneous spirochetosis produced by rat bite in Bombay. Bulletin de la Societé de Pathologie Exotique 11, 188–195.

Rowbotham, T.J., 1983. Rapid identification of *Streptobacillus moniliformis*. Lancet 2, 567.

Rumley, R.L., Patrone, N.A., White, L., 1987. Rat bite fever as a cause of septic arthritis: a diagnostic dilemma. Ann. Rheum. Dis. 46, 793–795.

Rupp, M.E., 1992. *Streptobacillus moniliformis* endocarditis: case report and review. Clin. Infect. Dis. 14, 769–772.

Russell, E.G., Straube, E.F., 1979. Streptobacillary pleuritis in a koala (*Phascolarctos cinereus*). J. Wildl. Dis. 15, 391–394.

Rygg, M., Bruun, C.F., 1992. Rat bite fever (*Streptobacillus moniliformis*) with septicemia in a child. Scand. J. Infect. Dis. 24, 535–540.

Savage, N.L., 1972. Host-parasite relationships in experimental *Streptobacillus moniliformis* arthritis in mice. Infect. Immun. 5, 183–190.

Savage, N.L., Joiner, G.N., Florey, D.W., 1981. Clinical, microbiological and histopathological manifestations of *Streptobacillus moniliformis*-induced arthritis in mice. Infect. Immun. 34, 605–609.

Savage, N.L., 1984. Genus streptobacillus.In: vol. 1. 9th ed. In: Krieg, N.R., Holt, J.G. (Eds.), Bergey's Manual of Systematic Bacteriology, Williams & Wilkins, Baltimore, pp. 598–600.

Sawicki, L., Bruce, H.M., Andrews, C.H., 1962. *Streptobacillus moniliformis* infection as a probable cause of arrested pregnancy and abortion in laboratory mice. Br. J. Exp. Pathol. 43, 194–197.

Schachter, M.E., Wilcox, L., Rau, N., Yamamura, D., Brown, S., Lee, C.H., 2006. Rat bite fever, Canada. Emerg. Infect. Dis. 12, 1301–1302.

Schottmüller, H., 1914. Zur Atiologie und Klinik der Bisskrankheit (Ratten-, Katzen-Eichhornchen-Bisskrankheit). Dermatol. Wochenschr. Erganzungsh 58, 77–103.

Sens, M.A., Brown, E.W., Wilson, L.R., Crocker, T.P., 1989. Fatal *Streptobacillus moniliformis* infection in a two-month-old infant. Am. J. Clin. Pathol. 91, 612–616.

Shanson, D.C., Gazzard, B.G., Midgley, J., Dixey, J., Gibson, G.L., Stevenson, J., Finch, R.G., Cheesbrough, J., 1983. *Streptobacillus moniliformis* isolated from blood in four cases of Haverhill fever. Lancet 2, 92–94.

Shanson, D.C., Pratt, J., Greene, P., 1985. Comparison of media with and without 'Panmede' for the isolation of *Streptobacillus moniliformis* from blood cultures and observations on the inhibitory effect of sodium polyanethol sulphonate. J. Med. Microbiol. 19, 181–186.

Shwartzman, G., Florman, A.L., Bass, M.H., Karelitz, S., Richtberg, D., 1951. Repeated recovery of a spirillum by blood culture from two children with prolonged and recurrent fevers. Pediatrics 8, 227–236.

Shartsblat, S., Kochie, M., Harber, P., Howard, J., 2004. Fatal rat bite fever in a pet shop employee. Am. J. Indust. Med. 45, 357–360.

Sigge, A., Essig, A., Wirths, B., Fickweiler, K., Kaestner, N., Wellinghausen, N., Poppert, S., 2007. Rapid identification of *Fusobacterium nucleatum* and *Fusobacterium necrophorum* by fluorescence *in situ* hybridisation. Diagn. Microbiol. Infect. Dis. 58, 255–259.

Signorini, L., Colombini, P., Cristini, F., Matteelli, A., Cadeo, P., Casalini, C., Viale, P., 2002. Inappropriate footwear and rat bite fever in an international traveler. J. Travel Med. 9, 275–276.

Smallwood, R.P., 1929. Ratbite fever from the bite of a pig. Brit. Med. J. 29, 1159.

Smith, I.K.M., 1998. *Streptobacillus moniliformis*, infection and immunity. In: Roit, I., Delves, P. (Eds.), Encyclopedia of Immunology. Academic Press, NY, pp. 2215–2217.

Smith, W., 1941. Cervical abscesses in guinea pigs. J. Pathol. Bacteriol. 3, 29–37.

Smith, P.F., Meadowcroft, A.M., 2002. Treating mammalian bite wounds. J. Clin. Pharmacy Therap. 25, 85–99.

Sowden, D., Allworth, A., Davis, L.B., 1995. *Capnocytophaga canimorsus* sepsis: poor growth using an automated blood culture system. Clin. Microbiol. Newslett. 17, 94–96.

Strangeways, W.I., 1933. Rats and carriers of *Streptobacillus moniliformis*. J. Pathol. Bacteriol. 37, 45–51.

Tannock, G.W., 1999. A fresh look at the intestinal microflora. In: Tanock, G.W. (Ed.), Probiotics, a Critical Review. Horizon Scientific Press, Portland Ore, pp. 5–14.

Tattersall, R.S., Bourne, J.T., 2003. Systemic vasculitis following an unreported rat bite. Ann. Rheum. Dis. 62, 605–606.

Taylor, J.D., Stephens, C.P., Duncan, R.G., Singleton, G.R., 1994. Polyarthritis in wild mice (*Mus musculus*) caused by *Streptobacillus moniliformis*. Aust. Vet. J. 71, 143–145.

Tileston, W., 1916. The etiology and treatment of rat bite fever. J. Am. Med. Assoc. 66, 995–998.

Toren, D.A., 1953. Mycotic ratbite fever: report of case. Del. Med. J. 25, 334.

Torres, A., Cuende, E., De Pablos, M., Lezaun, M.J., Michaus, L., Vesga, J.C., 2001. Remitting seronegative symmetrical synovitis with pitting edema associated with subcutaneous *Streptobacillus moniliformis* abscess. J. Rheumatol. 28, 1696–1698.

Torres, L., Lopez, A.I., Escobar, S., Marne, C., Marco, M.L., Perez, M., Verhaegen, J., 2003. Bacteremia by *Streptobacillus moniliformis*: first case described in Spain. Eur. J. Clin. Microbiol. Infect. Dis. 22, 258–260.

Valverde, C.R., Lowenstine, L.J., Young, C.E., Tarara, R.P., Roberts, J.A., 2002. Spontaneous rat bite fever in non-human primates: a review of two cases. J. Med. Primatol. 31, 345–349.

Vasseur, E., Joly, P., Nouvellon, M., Laplagne, A., Lauret, P., 1993. Cutaneous abscess: a rare complication of *Streptobacillus moniliformis* infection. Br. J. Dermatol. 129, 95–96.

Van Hooste, W.L.C., 2005. Rattenbeet en rattenbeetkoorts. Tijdschrift voor Geneeskunde (Belgium) 61, 1693–1703 (in Dutch).

Van Nood, E., Peters, S.H., 2005. Rat bite fever; case report. Neth. J Med. 63, 319–321.

Van der Waaij, D., 1989. The ecology of the human intestine and its consequences for overgrowth by pathogens such as *Clostridium difficile*. Ann. Rev. Microbiol. 43, 69–87.

Van der Waaij, D., Berghuis-de Vries, J.M., Lekkerkerker-Van der Wees, A.H., 1971. Colonization resistance of the digestive tract in conventional and antibiotic treated mice. J. Hyg. Cambridge 69, 405–411.

Von Gravenitz, A., Zbinden, R., Mutters, R., 2003. Actinobacillus, Capnocytophaga, Eikenella, Kingella, Pasteurella and other fastidious or rarely encountered Gram-negative rods. In: Baron, E.J., Jorgensen, J.H., Pfaller, M.A., Yolken, R.H. (Eds.), Manual of Clinical Microbiology. 8th ed. ASM Press, Washington DC, pp. 609–622.

Wallet, F., Savage, C., Loiez, C., Renaux, E., Pischedda, P., Courcol, R.J., 2003. Molecular diagnosis of arthritis due to *Streptobacillus moniliformis*. Diagn. Microbiol. Infect. Dis. 47, 623–624.

Wang, T.K.F., Wong, S.S.Y., 2007. *Streptobacillus moniliformis* septic arthritis: a clinical entity distinct from rat bite fever? BMC Infect. Dis. 7, 56.

Washburn, R.G., 2005. *Spirillum minus* (rat bite fever). In: , G.L., Bennett, J.E., Dolin, R. (Eds.), Principles and Practice of Infectious Diseases. Elsevier Churchill Livingstone, Philadelphia, PA, p. 2810.

Waterson, A.P., Wedgwood, J., 1953. Rat bite fever: report of a case due to *Actinomyces muris*. Lancet 1, 472–473.

Weisbroth, S.H., Kohn, D.F., Boot, R., 2006. Bacterial, mycoplasmal and mycotic infections. In: Suckow, M.A., Weisbroth, S.H., Franklin, C.L. (Eds.), The Laboratory Rat. Elsevier, Amsterdam, pp. 340–441.

Wilcox, W., 1839. Violent symptoms from bite of a rat. Am. J. Med. Sci. 26, 245.

Wilkins, E.G., Millar, J.G., Cockcroft, P.M., Okubadejo, O.A., 1988. Rat bite fever in a gerbil breeder. J. Infect. 16, 177–180.

Wincewicz, E., 2002. Microbiological examination of wild rats living in various environments in the epizootic aspect. Electronic J. Pol. Agric. Universities (EJPAU), http://www.ejpau.media.pl/volume5/issue1/veterinary/art-04.html.

Wouters, E., Ho, H.T.K., Lipman, L., Gaastra, W., 2008. Dogs as vectors of *Streptobacillus moniliformis* infection? Vet. Microbiol. 128, 419–422.

Wullenweber, M., 1995. *Streptobacillus moniliformis*—a zoonotic pathogen. Taxonomic considerations, host species, diagnosis, therapy, geographical distribution. Lab. Anim. 29, 1–15.

Wullenweber, M., Jonas, C., Kunstyr, I., 1992. *Streptobacillus moniliformis* isolated from otitis media of conventionally kept laboratory rats. J. Exp. Anim. Sci. 35, 49–57.

Wullenweber, M., Kaspareit-Rittinghausen, J., Farouq, M., 1990. *Streptobacillus moniliformis* epizootic in barrier-maintained C57BL/6J mice and susceptibility to infection of different strains of mice. Lab. Anim. Sci. 40, 608–612.

Yamamoto, R., Clark, G.T., 1966. *Streptobacillus moniliformis* infection in turkeys. Vet. Rec. 79, 95–100.