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Rat Bite Fever

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Dear Dr. Songer, Dear Editor,

Thank you very much for sending us the comments by the referees on our manuscript “Rat Bite Fever” which was submitted to your journal. We have carefully read the comments and remarks of all three referees. We have reacted to them in the following way:

First we have corrected all grammatical errors and mistakes in syntax

We have added and/or removed text as requested at various positions in the manuscript. We have not removed the Figs for which deletion was requested by referee#1, since it is our opinion that these Figs. add significantly to the manuscript. The same is true for the “historical” description of Rat Bite Fever in animals.

We have rewritten the manuscript with the aim to obtain a better structured and less rambling manuscript. During rewriting we have given extra attention to Rat Bite Fever with respect to Laboratory Animal and we have also inserted a section on future research.

All these changes have lead to a completely revised and changed manuscript and make it impossible to give a point by point account of how we have dealt with the comments of the referees.

It is our opinion that the manuscript is considerably improved and we hope that you will find the manuscript acceptable for publication in Veterinary Microbiology.

Sincerely Yours

Wim Gaastra

1 **Title: RAT BITE FEVER**

2

3 **Type of article:** Review

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19

20

21 *Burning in the patches. Nodular and urticarial eruption: petichial and even haemorrhagic*
22 *patches on the body: oedematous condition, discoloration and even ulceration of the nodules:*
23 *lividity of the mucous membranes and haemorrhagus.*

24 *Yogaratanakarone, Wagabhatt Shushrut, 300 BC*

25

26

27 **Keywords:**

28 *Streptobacillus moniliformis, Spirillum minus, zoonosis, rat bite fever, Haverhill fever.*

29 **Abstract**

30 Rat bite fever (RBF) is a bacterial zoonosis for which two causal bacterial species
31 have been identified: *Streptobacillus moniliformis* and *Spirillum minus*. Haverhill fever (HF)
32 is a form of *S. moniliformis* infection believed to develop after ingestion of contaminated
33 food or water.
34 Here the infectious agents, their host species, pathogenicity (virulence factors and host
35 susceptibility), diagnostic methods, therapy, epidemiology, transmission and prevention are
36 described. Special emphasis is given on information from the field of laboratory animal
37 microbiology and suggestions for future research.

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88 **EPIDEMIOLOGY**89 **TRANSMISSION**90 **Bites and scratches**91 **Ingestion**92 **Unknown**93 **PREVENTION**94 **FUTURE RESEARCH**

95

96 **INTRODUCTION**

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

101 Worldwide millions of people are bitten by animals each year. Ninety percent of these
102 bites are by dogs and cats (Griego et al., 1995). Rats are responsible for one percent of the
103 bites (Glaser et al., 2000). The relation between humans and animals is changing and many
104 animal species once regarded as pests, are now kept as pets, of which rodents are just
105 examples. Bites from rats and other rodents therefore probably occur in increasing numbers.
106 With an estimated number of 10 billion, rats make up one third of the mammalian population
107 of the world (Wincewicz, 2002). According to one report 40.000 rat bites are recorded
108 annually (Committee on Urban Pest Management, 1980). It is estimated that 2% of rat bites
109 lead to infection (Ordog, 1985).

110 People have known for long that rat bites may result in illness (Roughgarden, 1965).
111 Wagabhatt who lived in India 2.300 years ago already referred to the cutaneous lesions
112 produced by rat bites (Row, 1918) and many observers believe that RBF was first recognized
113 in that country. Among the bacteria detected in rat bite wounds are staphylococci, *Leptospira*
114 spp., *Pasteurella* spp., *Corynebacterium* and *Fusobacterium* spp. and the RBF agents *S.*
115 *moniliformis* and *S. minus* (Krauss et al., 2003). The disease was already reported in the US
116 in 1839 (Wilcox, 1839). For many years great confusion over the etiology of RBF existed.
117 Schottmüller, Blake, Tileston and others described the isolation of “*Streptothrix muris ratti*”
118 (*S. moniliformis*) from the blood of human patients with recurrent fever following rat bites
119 almost 100 years ago (Schottmüller, 1914; Blake, 1916; Tileston, 1916). A streptothrix-like
120 organism was recognized in the blood of RBF patients before the organism was isolated and
121 characterised in pure culture. Japanese scientists however, showed that RBF was also caused
122 by a spirochetal organism named “*Spirochaeta morsus muris*” or *Spirillum minus* (Futaki et
123 al., 1916). To date there is no question that RBF can be caused by either *S. moniliformis* or *S.*

124 *minus*. *S. moniliformis* is the more common cause of RBF occurring worldwide. *S. minus*
125 infection is reported less frequently and occurs mainly in Asia. In Japan the disease is known
126 as sodoku (so = rat, doku = poison).

127

128 **THE INFECTIOUS AGENTS**

129 **Historical names**

130 *Streptobacillus moniliformis*

131 In the older literature several names for this bacterium can be encountered like
132 “Streptothrix muris ratti”, “Nocardia muris”, “Actinomyces muris ratti” (Borgen and
133 Gaustad, 1948), “Haverhillia multiformis”, “Actinomyces muris”, “Asterococcus muris”
134 (Heilman, 1941), “Proactinomyces muris”, “Haverhillia moniliformis” (Parker and Hudson,
135 1926), *Actinobacillus muris* (Waterson and Wedgwood, 1953) and “Clostridium actinoides
136 var. muris”. In 1925, the organism obtained its present name *Streptobacillus moniliformis*
137 (Levaditi et al., 1925). It is the only species in the genus.

138 *Spirillum minus*

139 *S. minus* was first described by Futaki et al. (1916) as the cause of RBF. Almost 30
140 years earlier bacteria named “Spirillum minor” were described in wet mounts from the blood
141 of a wild rat (Carter, 1888). In older literature also several other names such as “Spirochaeta
142 morsis muris”, “Spirochaeta laverani”, “Spirochaeta minor”, “Leptospira morsus minor”,
143 “Spirochaeta muris” and “Spirochaeta petit” can be found. The organism was named *S. minus*
144 in 1924 (Robertson, 1924). It should be noted that the organism is not on the Approved List
145 of Bacterial Names (<http://www.bacteriocict.fr/>) since no type or reference strain for this
146 taxon have been identified.

147 **Cultural properties**

148 *S. moniliformis* is fastidious and requires media enriched with 10-20% blood, serum or
149 ascitic fluid for growth. *S. moniliformis* may appear an obligate anaerobe on first isolation,
150 but on subculture it is a facultative anaerobe except isolates from guinea pigs which are
151 obligate anaerobes (Fleming, 1976). In liquid media with serum, the bacterial growth shows a
152 typical “puff-ball” or “bread crumb like” appearance (Fig. 1). The ability to develop cell wall
153 deficient L-forms that are difficult to culture was demonstrated (Freundt, 1956a; Freundt,
154 1956b; Pins et al., 1996). They are readily formed, likely due to the low glucosamine and
155 muramic acid content of the bacterial cell wall (Smith, 1998). Colonies of L-forms have a
156 “fried egg” appearance, difficult to distinguish from *Mycoplasma* colonies. As for other

157 fastidiously growing bacteria like *Capnocytophaga canimorsus* (Sowden et al., 1995),
158 polyanethole-sulphonate, an anticoagulant frequently present in automatic blood culture
159 systems, inhibits the growth of *S. moniliformis* in concentrations as low as 0.0125% (Lambe
160 et al., 1973; Shanson et al., 1985; Andre et al., 2005). Nevertheless, several successful
161 isolations of *S. moniliformis* using these systems have been reported (Sens et al., 1989; Torres
162 et al., 2003).

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

172 **Genetic characteristics**

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

183 The G+C content of *S. moniliformis* DNA is 25% (Savage, 1984). *S. moniliformis*
184 strains of rat, mouse and human origin have been submitted to 16S rDNA sequence analysis.
185 On the basis of these 16S rDNA sequences the genus *Streptobacillus* is now placed with the
186 genera *Fusobacterium*, *Ilyobacter*, *Leptotrichia*, *Propionigenium*, *Sebaldella* and *Sneathia*
187 within the *Fusobacteriaceae* family (Brenner et al., 2005) which is quite remote from the
188 Mycoplasmatales. A 90% 16S rDNA sequence similarity between an unclassified bacterial
189 fish pathogen and the type strain of *S. moniliformis* was noted (Maher et al., 1995). The 16S

190 rDNA based relationship of *S. moniliformis* with other *Fusobacteriaceae* genera is supported
191 by the outcome of a comparison of 16S-23S rRNA internal transcribed spacer sequences
192 (Conrads et al., 2002). *S. moniliformis* strains from guinea pig, turkey and “*S. actinoides*”
193 from calves have not been submitted to 16S rDNA sequencing. As these strains were not
194 stored their exact taxonomy is unknown.

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

199 *S. minus*

200 *S. minus* is a spiral shaped Gram-negative (sometimes Gram-variable) bacterium, 0.2-
201 0.5 μm wide and 1.7 to 5 μm long. The bacterium is actively motile by two to six spirals and
202 bipolar bundles of flagella (Adachi, 1921; see Shwartzman et al., 1951 for an electron
203 micrograph). The bacterium can not be cultured on artificial media in spite of reports on its
204 successful culture in fluid media, consisting of modified veal infusions incubated under CO₂
205 atmosphere (Joekes, 1925; Hitzig and Liebesman, 1944; Shwartzman et al., 1951). The
206 taxonomic position of *S. minus* will remain unclear until appropriate nucleic acid based
207 phylogenetic studies have been performed. The failure to grow *S. minus* implies a lack of data
208 with respect to growth requirements, phenotypic and genetic characteristics. Isolation of the
209 organism still requires animal inoculation.

210 **Phenotypic characteristics**

211 *S. moniliformis*

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

220 *S. moniliformis* studied by the API ZYM system consistently showed positive
221 reactions for alkaline phosphatase, butyrate esterase, caprylate esterase, myristate esterase,

222 leucine arylamidase, chymotrypsin and acid phosphatase (Edwards and Finch, 1986;
223 Hofmann, 1994).

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

227 **HOST SPECIES**

228 *S. moniliformis* was common in laboratory rats in the first half of the last century
229 (Strangeways, 1933). At that time laboratory animals were kept under poor hygienic
230 conditions and their microbiologic status is now termed “conventional” which is synonymous
231 with “infected by various pathogenic micro-organisms”. In 1962 the first publication
232 appeared on the breeding of so called “disease-free animals” (Foster, 1962). These animals
233 were obtained by hysterectomy shortly before natural delivery from conventional donor
234 animals. The germfree (GF) animals obtained have been used to constitute breeding colonies
235 free from devastating infections. Due to the absence of a wide variety of named (specified)
236 pathogenic micro-organisms these animals are described as specified pathogen free (SPF)
237 animals. Their SPF status is maintained by high animal care standards and all these
238 preventive hygienic measures taken are laid down in the term “SPF barrier measures” (Boot
239 et al., 2001). The success of the barrier (exclusion of pathogens) is periodically evaluated by
240 testing animals for the absence of unwanted micro-organisms (Nicklas et al., 2002).

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

254 To compensate the loss of the host specific indigenous flora and to normalize the
255 anatomical and physiological abnormalities, GF animals have deliberately been dosed a

256 complex colonization resistant enteric flora (Van der Waaij et al., 1971) or the so called
257 Schaedler flora which consists of eight bacterial strains (Dewhirst et al., 1999). Flora
258 associated animals are used to start SPF breeding colonies. Inherent to the direct contact with
259 animal caretakers SPF animals become spontaneously colonized by human and
260 environmental bacteria and have as a consequence a non standardised microbial ecology. SPF
261 animals are often susceptible to opportunistic infections by micro-organisms that are rarely
262 encountered as pathogens in conventional counterparts (Boot et al., 1989; ILAR, 1998).

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

266 **Non human hosts**

267 **Rodents**

268 **Rat**

269 It is generally assumed that conventional rats are the natural host and asymptomatic
270 carriers of *S. moniliformis*. This applies both to *Rattus rattus* (the black rat) and *R. norvegicus*
271 (the Norwegian rat) which is the species kept as laboratory rat and as pet. The non-
272 pathogenicity in its natural host insures its survival. Remarkably, in a number of RBF cases
273 caused by pet rats, the death of the rat shortly after the bite incident was mentioned explicitly
274 (Rygg and Bruun, 1992; Prager and Frenck, 1994; Ojukwu and Christy, 2002; Andre et al.,
275 2005; Clarke et al., 2005; Donker et al., 2005). A bite from a dying rat (Hudsmith et al.,
276 2001) and the death of a pet rat on the first day of illness of the human patient were likewise
277 noted (Freels and Elliott, 2004). Illness in these rats may have been the reason for the bite but
278 involvement of *S. moniliformis* in the death of the rats seems unlikely.

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

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

288 **Mouse**

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

302 Natural infection of pregnant mice resulted in arrested pregnancy and abortions
303 (Mackie et al., 1933; Sawicki et al., 1962). The chronic infection can last for six months. The
304 mobility of mice and their capacity to reproduce is reduced by streptobacillary arthritis.
305 Recently, mice were suggested as the cause of RBF in a retired microbiologist who
306 maintained mice to feed his pet snake (Irvine and Wills, 2006). *S. moniliformis* was isolated
307 from the patient but isolation from the mouse was not attempted.

308 Most cases of natural clinical infection in laboratory mice have been reported before
309 the introduction of SPF mice (Levaditi et al., 1932; Mackie et al., 1933; Freundt, 1956b;
310 Sawicki et al., 1962). Due to poor housing standards mice may occasionally have been
311 infected from laboratory rats held in the same room or vicinity via aerosols or handling by
312 animal caretakers (Freundt, 1956b). The most recent report on streptobacillosis in laboratory
313 mice explicitly mentioned that wild rats were trapped in the farm shed (Glastonbury et al.,
314 1996).

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

322 **Spinifex hopping mouse**

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

328 **Gerbil**

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

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

338 **Squirrel**

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

350 **Guinea pig**

351 Guinea pigs (*Cavia aperea porcellus*) are susceptible to natural *S. moniliformis*
352 infection. Fleming (1976) reported a high incidence of cervical lymphadenitis in stocks of
353 conventional guinea pigs at several research laboratories. The bacterium was isolated from
354 cervical lymphnodes and cervical abscesses (Smith, 1941; Aldred et al., 1974; Fleming,
355 1976). The isolation of *S. moniliformis* from a guinea pig with granulomatous

356 bronchopneumonia has been reported (Kirchner et al., 1992); it cannot be decided whether
357 the animal came from a conventional or an SPF colony. Most contemporary guinea pigs
358 come from SPF breeding colonies and these colonies are periodically monitored for absence
359 of the bacterium (Nicklas et al., 2002).

360 **Carnivores**

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

365 **Cat**

366 RBF was reported in a previously healthy male bitten by a cat (Mock and Morrow,
367 1932). The etiological agent was not directly isolated from the patient but a spirillum was
368 isolated in very low numbers from the blood of a guinea pig inoculated with material from
369 the patient. This combined with laboratory tests lead to the RBF diagnosis.

370 **Dog**

371 Approximately one in twenty dogs will bite a human being during the dogs lifetime
372 (Griego et al., 1995). The number of proven cases of *S. moniliformis* infection after a dog bite
373 is however limited to three Australian reports (Gilbert et al., 1971; Maynard et al., 1986; Peel,
374 1993) of which the latter two were possibly on the same case. The involvement of a
375 greyhound, a breed that eats rats, was explicitly mentioned (Peel, 1993).

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

383 In a first case of clinical *S. moniliformis* infection in a dog (Ditchfield et al., 1961) the
384 animal suffered from diarrhoea, vomiting, anorexia and arthritis in the hind legs and died
385 after ten days of hospitalisation, despite antimicrobial therapy with penicillin and
386 chloramphenicol. Post mortem examination showed purulent polyarthritis, endocarditis and
387 pneumonia. Gram-negative highly pleomorphic bacilli with numerous pear shaped swellings
388 were isolated on blood agar from blood samples and taken as an indication of *S. moniliformis*
389 infection. No history of exposure to rats was known, nor were there any apparent bite

390 wounds. Since the dog ate garbage and illness started with acute gastroenteritis, this may
391 indicate a HF case in this particular dog but other causes of infection are imaginable. In a
392 second case *S. moniliformis* was claimed to be isolated from the aspirate of an abscess in a
393 dog (Das, 1986). The growth characteristics and antibiotic susceptibility of the dog isolate
394 were however not fully in accordance with those of *S. moniliformis* (see Wullenweber, 1995).

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

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

403 **Ferret**

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

406 **Weasel**

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

414 **Other non-human hosts**

415 **Calve**

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

424 **Pig**

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

430 **Turkey**

431 At least four reports have appeared on streptobacillosis in turkeys (Boyer et al., 1958;
432 Yamamoto and Clark, 1966; Mohamed et al., 1969; Glünder et al., 1982). Some authors
433 attributed the infection to rat bites. Polyarthrititis and synovitis were reported (Glünder et al.,
434 1982) as well as tendon sheath swelling and joint lesions (Yamamoto and Clark, 1966). Some
435 turkeys died in the weeks before *S. moniliformis* was isolated from the exudate of one bird
436 and from a rat trapped in the compound where the turkeys were held. The isolates were
437 similar in morphology, growth and biochemical characteristics and cross-reacted in double
438 immune-diffusion tests (Yamamoto and Clark, 1966). The strains fermented arabinose but
439 not salicin which is at variance to the characteristics listed for *S. moniliformis* but other
440 biochemical properties tested agreed.

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

448 **Koala**

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

453 **Non-human primates**

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

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

460 **Human infection**

461 Bacteria grow in one third of rat bite wounds. The risk of any type of infection
462 following a rat bite has been estimated from 1-10% (Hagelskjaer et al., 1998; Van Hooste,
463 2005; Elliott, 2007) but the risk of RBF is unknown as is the infectious dose of both *S.*
464 *moniliformis* and *S. minus* for humans.

465 **Clinical symptoms**

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

468 **Haverhill fever** (erythema arthriticum epidemicum)

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

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

481 **Rat bite fever**

482 *Streptobacillus moniliformis* RBF

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

486 The incubation period varies from 3 days to more than 3 weeks (on average 2-3 days).
487 Clinical symptoms (Table 1) include an abrupt onset of high fever, followed by headache,
488 chills, vomiting and a rash. The petechial rash develops over the extremities, in particular the
489 palms and the soles, but sometimes it is present all over the body (Fig. 4). In 20% of the cases

490 the rash desquamates. Infants and children may experience severe diarrhoea resulting in loss
491 of weight (Raffin et al., 1979).

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

500 All symptoms do not occur at the same time, nor do they all occur in the same patient.
501 Rare complications are anaemia, endocarditis, pericarditis (Carbeck et al., 1967), pneumonia,
502 meningitis, diarrhoea and abscess formation in organs including the brain (Oeding and
503 Pedersen, 1950; Dijkmans et al., 1984), liver, spleen (Chulay and Lankerani, 1976), and skin
504 (Vasseur et al., 1993; Hagelskjær et al., 1998; Torres et al., 2001). Other complications
505 comprise parotitis, amnionitis, tenosynovitis, prostatitis and pancreatitis (Delannoy et al.,
506 1991).

507 In a review of 20 cases of *S. moniliformis* endocarditis 50% of the patients had
508 previously damaged heart valves. Endocarditis mortality can be as high as 53% (McCormack
509 et al., 1967; Rupp, 1992; Torres et al., 2003; Chen et al., 2007). In a review of 16 cases of
510 endocarditis from 1915-1991 (Rupp, 1992) most patients had fever, cardiac murmurs and a
511 history of being bitten by a rat. Ten of these 16 patients died. In four cases of endocarditis
512 reported after 1992, all patients recovered after antimicrobial therapy combined with surgery
513 in two cases (Rordorf et al., 2000; Balankrishnan et al., 2006; Chen et al., 2007; Kondruweit
514 et al., 2007). Mortality has also been reported in a previously healthy young female (MMWR,
515 2005).

516 A unique case of amnionitis with intact amniotic membranes involving *S.*
517 *moniliformis* was described (Faro et al., 1980). The patient stated that the basement of her
518 home was infested with rats or mice. Three cases of abscesses in the female genital tract in
519 which *S. moniliformis* infection was clearly demonstrated have been reported (Pins et al.,
520 1996). The route of infection however was obscure as no contact with rats or ingestion of
521 unpasteurised milk was mentioned.

522 Untreated RBF mortality ranges from 7-13% (Hagelskjær et al., 1998; Graves and
523 Janda, 2001; Washburn, 2005). Even without treatment patients can recover within several

524 weeks, but the disease can also continue for months. Persistent damage sometimes occurs
525 even after treatment with an antibiotic for which the isolate was sensitive (Tattersall and
526 Bourne, 2003).

527 Treatment using antibiotics active on the bacterial cell wall might induce the
528 formation of L-forms of the bacterium that persist in the human body (Domingue and
529 Woody, 1997) and be the cause of relapses after stopping antibiotic therapy (Domingue et al.,
530 1974). In the streptobacillary epizootic in C56Bl/6 mice the breeding nucleus was effectively
531 treated via the drinking water with ampicillin and tetracycline given in succession to prevent
532 the survival of penicillin resistant L-forms. After finishing therapy some mice however
533 relapsed and died from septicaemia (Wullenweber et al., 1990). In vivo L-forms of *S.*
534 *moniliformis* frequently revert to the bacillary form and regain their full pathogenic properties
535 (Freundt, 1956a).

536 Depending on whether or not a rash or polyarthritis accompany febrile episodes the
537 differential diagnosis of RBF comprises brucellosis, leptospirosis, Rocky Mountain spotted
538 fever (by *Rickettsia rickettsii*), Lyme disease, viral exanthems, disseminated sexually
539 transmitted diseases and a variety of other infective or vascular processes (Freels and Elliott,
540 2004; Elliott, 2007).

541 *Spirillum minus* RBF

542 This infection usually becomes manifest at a later stage than RBF by *S. moniliformis*.
543 *S. minus* infections have an incubation period of two to three weeks, with a maximum of four
544 months. The wound at the bite site at first heals spontaneously but reappears at the onset of
545 clinical symptoms one to four weeks later, becomes painful, oedematous and purple and may
546 ulcerate.

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

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

556 Without treatment, the fever temporarily disappears but returns intermittently within a
557 period of several days. Fever may last for three to five days. In some cases this can continue

558 for a year, but normally the symptoms disappear within two months (Downing et al., 2001).
559 After afebrile intervals of three to seven days febrile episodes recur, but they subsequently
560 lose their intensity. The illness may last for weeks to months. Mortality due to *S. minus* RBF
561 (6.5%) is lower than for *S. moniliformis* infection (Freels and Elliott, 2004).

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

567 **Geographic distribution**

568 Streptobacillary RBF has been reported worldwide. Reports until 1993 concerning *S.*
569 *moniliformis* in humans and animals have been summarised by Wullenweber (1995). After
570 1993 further reports can be found in PubMed. RBF by *S. minus* was first described in Japan
571 and although it occurs predominantly in Asia human infection has also been diagnosed in
572 Europe and the United States. So there seem to be no geographic restrictions on the
573 occurrence of both agents (Buranakitjaroen et al., 1994; Chen et al., 2007).

574 **Pathogenicity**

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

578 **Virulence factors**

579 Very little is known about potential virulence factors of *S. moniliformis*. An alpha-
580 hemolytic strain has been isolated from a rat with otitis media (Wullenweber et al., 1992).
581 *S. moniliformis* agglutinated red blood cells from various animal species. Reactions with
582 turkey, human, guinea pig and pig red blood cells were stronger than reactions with rat and
583 chicken cells. Hemagglutinating activity with cells from susceptible C57Bl/6 and resistant
584 BALB/c mice did not differ. Hemagglutinating activity appeared mannose resistant
585 (Hofmann, 1994) and the receptor(s) involved in adhesion remain to be elucidated (Beachey,
586 1981).

587 Bacillary forms of *S. moniliformis* are pathogenic to mice after parenteral inoculation.
588 Growth on agar yields long streptobacillary forms whereas minute coccoidal cells result from
589 growth in serum-broth (Freundt, 1956a). The bacillary forms appeared more virulent than the
590 coccoidal form (Savage, 1972), and L-forms have been found apathogenic to mice (Freundt,

591 1956b). L-forms lack at least one antigen present in the bacillary form (Klieneberger, 1942;
592 Smith, 1998). Experimental vaccination of mice with inactivated preparations of *S.*
593 *moniliformis* provokes incomplete protection against challenge (Savage, 1972; Smith, 1998).
594 Experimental infection of mice showed that macrophages that engulfed *S. moniliformis* cells
595 died more rapidly than those in the absence of the bacteria (Savage, 1972).

596 Experimental infections in rats have been used as a model for the arthritis seen in
597 streptobacillosis, but without much success. Adult rats are usually resistant to experimental
598 parenteral inoculation but neonates may develop pneumonia (Strangeways, 1933; Bell and
599 Elmes, 1969; Gay et al., 1972). The organism is a secondary invader in chronic murine
600 pneumonia of conventional rats (Olson and McCune, 1968). Experimental oral and nasal
601 infections of SPF rats of several inbred strains and random bred stocks did however not yield
602 any indication for gross lesions in the respiratory tract (Boot et al., 1993b; 2002; 2006). The
603 difference between conventional and SPF rats with respect to respiratory tract pathology is
604 likely due to the presence of viral and other bacterial pathogens (including *Mycoplasma* spp.)
605 in conventional animals which are usually absent from SPF animals (Boot et al., 2001). Mice
606 injected with *S. moniliformis* get arthritis and may die (dependent on the mouse strain)
607 whereas mice can have *S. minus* in their blood without showing any clinical signs (Haneveld,
608 1958).

609 **Host susceptibility**

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

624 Rat inbred strains differ in the degree of antibody development to *S. moniliformis* after
625 experimental oral and nasal inoculation (Boot et al., unpublished). In studies in which random
626 bred Wistar rats were exposed to *S. moniliformis* infected counterparts in the same cage for 6
627 weeks, clear differences in seroconversion between cage mates were observed (Boot et al.,
628 2002).

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

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

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

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

642 **DIAGNOSTIC METHODS**

643 **Direct examination**

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

648 **Culture**

649 Isolation of *S. moniliformis* from blood culture is common, isolation from abscess
650 aspirates, synovial fluid and wound cultures have likewise been successful (Freels and Elliott,
651 2004; Dendle et al., 2006) but cultures from affected joints are usually negative (Dendle et
652 al., 2006).

653 *S. moniliformis* is fastidious and primary culture needs the use of agar media
654 supplemented with ascitic fluid or serum (Von Graevenitz et al., 2003). The typical "puff-

655 ball” or “bread crumb like” growth (Fig. 1) in liquid media with serum and the Gram-stain of
656 *S. moniliformis* still are important for diagnostics.

657 **Identification**

658 Identification of *S. moniliformis* suspected growth may comprise biochemical
659 characterisation and cell wall fatty acid profiling (Rowbotham, 1983; Clausen, 1987; Holroyd
660 et al., 1988; Lopez et al., 1992; Pins et al., 1996; Hockman et al., 2000; Frans et al., 2001;
661 Torres et al., 2003). Serum agglutination reactions have been used in the past for the
662 identification of *S. moniliformis* (Burke et al., 1959). Identification was also achieved by a
663 direct fluorescent antibody test with a polyclonal antiserum to the bacterium (Graves and
664 Janda, 2001).

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

668 **PCR**

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

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

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

683 PCRs have been used both for screening and diagnostic purposes (Kadan et al., 2002;
684 Andre et al., 2005; Mignard et al., 2007). False positive results for *S. moniliformis* PCR, due
685 to the presence of *Leptotrichia* sp. were recently reported (Boot et al., 2008; Wouters et al.,
686 2008) so sequencing of PCR amplicons may be necessary. Reversibly a fluorescence in situ

687 hybridization assay (FISH) for rapid identification of *Fusobacterium* spp. showed cross-
688 reaction between *Leptotrichia* spp. and *S. moniliformis* (Sigge et al., 2007).

689 Theoretically also *S. minus* bacterial DNA may be amplified by broad range bacterial
690 16S rRNA gene primers.

691 **Serology**

692 For humans currently no validated serological tests are available but such assays are
693 in use in the monitoring of SPF laboratory animals for *S. moniliformis*. Antibodies to the
694 bacterium in rats, mice and guinea pigs have in the past been demonstrated by agglutination
695 and complement fixation tests (Boot et al., 1993b). These assays have been replaced by the
696 more sensitive enzyme-linked immunosorbent assay (ELISA) and the indirect
697 immunofluorescence assay (IFA). ELISA seropositive SPF laboratory animals can be found
698 rather frequently. Whereas in most cases infection can be ruled out by negative immunoblot
699 (IB) and PCR findings, sometimes it can be confirmed by culture or PCR (Boot et al. 2006).
700 A partial serological relationship between *S. moniliformis* and *A. laidlawii* (a non-pathogenic
701 *Mycoplasma* spp. from horses and cattle) has been found by ELISA (Boot et al., 1993b) and
702 IFA (Wullenweber, 1995). IFA showed also cross reactivity with other *Acholeplasma* species
703 but not with *Mycoplasma arthritidis* and *M. pulmonis* (Wullenweber, 1995). Rat antiserum
704 against *A. laidlawii* is not reactive against *S. moniliformis* antigens by IB (Boot et al., 2006).
705 Immunoblots of whole cell antigens of a rat *S. moniliformis* strain and immune sera to various
706 *S. moniliformis* isolates show a number of bands in the 32-55 kD range (Boot et al., 2006).

707 **Experimental infection**

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

711 Unfortunately this is not so for *S. minus*. The failure to grow *S. minus* implies that
712 serological or molecular (PCR) tests are not available for diagnostic efforts. In case of
713 suspected infection, blood or wound aspirates are injected intraperitoneally into guinea pigs
714 or mice for diagnostic purposes. After successful infection spirochetes may be detected after
715 5-15 days in their blood using dark-field microscopy (Fig. 5) (Adachi, 1921; Hudemann and
716 Mücke, 1951). Drawback of the technique are the time needed and the limited number of
717 laboratories that perform it (Byington and Basow, 1998).

718 Infections are underdiagnosed

719 Although the number of reports on RBF is increasing, it is still relatively rarely
720 reported disease. Only three outbreaks of Haverhill fever have been reported. The relevant
721 bacteria may be transmitted in various ways by close contact between pet rats and their
722 owners. Transmission is not necessarily followed by multiplication of the bacteria in the
723 human body (infection). Repeated introduction of bacteria into the human body will lead to
724 the development of antibody activity as it does in immunized laboratory animals (Boot et al.,
725 1993a; 2006). Infection does not necessarily lead to serious clinical symptoms and humans
726 with subclinical infections will not report to the physician. If the incubation period extends to
727 several weeks and clinical symptoms are aspecific, RBF is presumably not considered if
728 contact with rats or other possible hosts is not explicitly mentioned in the anamnesis.

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

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

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

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

741 THERAPY

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

746 Susceptibility tests by the disk diffusion method performed with a single isolate
747 showed that this isolate was susceptible to gentamicin, penicillin, chloramphenicol,
748 erythromycin, clindamycin, tetracycline, cephalothin and vancomycin (Holroyd et al., 1988).
749 In a study with 13 *S. moniliformis* isolates from various origins tested for susceptibility for
750 more than 30 antibiotics resistance of all isolates was observed against nalidixic acid,

751 norfloxacin, polymyxin B and the combination of trimethoprim-sulfamethoxazol
752 (Wullenweber, 1995). Polymyxin B disrupts the structure of the membrane phospholipids and
753 the other antibiotics are involved in inhibition of DNA synthesis. The 13 isolates were
754 intermediate resistant against ciprofloxacin, another antibiotic that inhibits DNA synthesis.
755 Resistance against cephalosporins and aminoglycosides has also been reported (Cunningham
756 et al., 1998; Freunek et al., 1997).

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

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

767 **EPIDEMIOLOGY**

768 By one dimensional SDS-PAGE analysis of 22 different strains of *S. moniliformis*
769 from mouse, rat, the spinifex hopping mouse, turkey and humans 40-50 proteins ranging from
770 18-100 kDa were observed. Four major protein bands in the region 60-67 kDa accounting for
771 20-30% of the total protein were present in all strains (Costas and Owen, 1987). No clear
772 differences were found among the strains that could be related to geographical origin or host
773 species. The only exception was the unique position of the strain from the Australian spinifex
774 hopping mouse. It can not be decided whether this is a reflection of the geography or the host
775 species. Geographically related differences have been observed among rodent pathogenic
776 *Corynebacterium kutscheri* strains (Boot et al., 1995) and other rodent pathogens such as
777 *Pasteurella pneumotropica* show host species related differences in bacterial properties (Boot
778 et al., 1993a).

779 *S. moniliformis* isolates from guinea pigs are said to differ from those isolated from
780 rats (Smith 1941; Aldred and Young, 1974). This is difficult to verify since isolates from
781 guinea pigs have not been saved. Guinea pig *Streptobacillus* strains were reported to grow
782 only under strict anaerobic conditions unlike isolates from rats and mice (Smith, 1941;
783 Aldred et al., 1974) and special growth conditions for isolates from guinea pigs were
784 confirmed by Fleming (1976) who recommended the addition of neutralised liver digest to

785 the growth medium. Differences in the properties of rat and guinea pig *S. moniliformis* strains
786 are paralleled by differences in the *Pasteurellaceae* species obtained from naturally infected
787 conventional animals: whereas rat *Pasteurellaceae* belong to the so called Rodent cluster of
788 the bacterial family, guinea pig *Pasteurellaceae* belong to other phylogenetic clusters (Olsen
789 2005). In conventional animals the bacterial flora will have evolved with the host and
790 taxonomic studies indicated that guinea pigs do not belong to the Rodentia lineage (Adkins et
791 al., 2001). Guinea pigs were not easily orally and nasally infected with a rat strain of *S.*
792 *moniliformis* (Boot et al. 2007).

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

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

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

818 **TRANSMISSION**

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

822 **Bites or scratches**

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

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

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

838 **Ingestion**

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

848 **Unknown**

849 Several cases of human RBF without a history of bite or scratch incidents have been
850 reported (Rumley et al., 1987; Holroyd et al., 1988, Fordham et al., 1992, Rygg and Bruun,
851 1992; Pins et al., 1996). In some cases contact with rats or other rodents could be excluded
852 completely (Clausen, 1987; Pins et al., 1996; Torres et al., 2003; Kondruweit et al., 2007).

853 **PREVENTION**

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

859 Children handling pet rats may be a special risk group. In a series of RBF cases
860 children were exposed to a rat at school in 14% of the cases and the relative prevalence
861 among children seems to be much higher than among adults (Roughgarden, 1965; Hirschhorn
862 and Hodge, 1999; Graves and Janda, 2001). *S. moniliformis* infection has been suggested to
863 be a pediatric problem (Raffin and Freemark, 1979). More than half of the reported cases of
864 rat bite fever occurred in children (Freels and Elliott, 2004). Children presumably tend to
865 have closer contact with pet rats than adults but they may also be more susceptible to clinical
866 infection. Infection may also be contracted via small wounds when rat cages are cleaned.

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

872 Contact with rats is inherent to and hence unavoidable in some occupations such as
873 sewage workers, laboratory technicians and veterinarians working with laboratory animals.
874 Probably the first report of a laboratory worker suffering from RBF was by Levaditi et al.
875 (1925). The reported incidence of *S. moniliformis* RBF in laboratory personnel is low.
876 Thirteen cases have been documented between 1958 and 1983 (Anderson et al., 1983).
877 References to various other cases can be found (Wullenweber, 1995).

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

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

886 In case animal bites and scratches occur, meticulous wound treatment is necessary
887 (Smith et al., 2000). After an animal bite or scratch the wound should be cleaned thoroughly
888 and tetanus prophylaxis might be advisable.

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

891 **FUTURE RESEARCH**

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

894 Efforts to culture *S. minus* do not seem very promising given all unsuccessful
895 attempts. In clinical disease suggestive of *S. minus* infection the detection of causative
896 bacteria might be attempted by culture free methods (Dong et al., 2008; Lynch et al., 2008).

897 Also for *S. moniliformis* each paragraph of this review shows a lack of basic information.

898 More insight into the **genetic properties** of the bacterium is basic to understanding most if
899 not all other aspects of the RBF and HF. Some issues that might be relevant here comprise

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

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

908 Whether **human infection** is genetically determined might be explored via identification
909 of susceptibility loci in rodents and their human orthologs by comparative genomic analysis.
910 The possible persistence of L-forms in the human body after antibiotic treatment and
911 relapsing fever after stopping treatment might be studied in experimental animal models and
912 in human patients. Real-time quantitative reverse transcription PCR can be used to detect
913 bacterial messenger RNA as a way to distinguish live and dead bacteria as an indicator of
914 active infection.

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

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

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

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

930

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939

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1363 **Legends to Figures.**

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1365 **Fig. 1. “Puffball” like growth of *S. moniliformis* strain CCUG 43797 in thioglycollate medium.**

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1367 **Fig. 2. Gram stain of *S. moniliformis* (strain CCUG 43797).grown in liquid culture.**

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1369 **Fig.3. Photograph of a painting by Johannes Arndt Jepsa, showing the rash on the body of a woman bitten**
1370 **by a squirrel. Reproduced from Schottmüller (1914) with permission from Thieme Verlag, Germany.**

1371

1372 **Fig. 4. Maculopapular rash on the hand of a patient with confirmed *S. moniliformis* rat bite fever.**
1373 **Courtesy of Dr. S.H.A. Peters (Flevostad Ziekenhuis, Lelystad, The Netherlands).**

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1375 **Fig.5. Photograph of *Spirillum minus* in the blood of an experimentally infected mouse. The preparation**
1376 **was fixed with methanol and stained with Giemsa stain. Reproduced from Adachi (1921) with permission**
1377 **from the Journal of Experimental Medicine.**

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Table 1. Comparison of rat bite fevers

Causal organism	<i>S. moniliformis</i>	<i>S. minus</i>
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 Onset (average)	Irregularly relapsing 2-3 days	Regularly relapsing 2-3 weeks
Arthritis	Common (49% of cases)	Rare
Rash – character % affected	Morbilliform to purpuric 75%	Macular, often confluent 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

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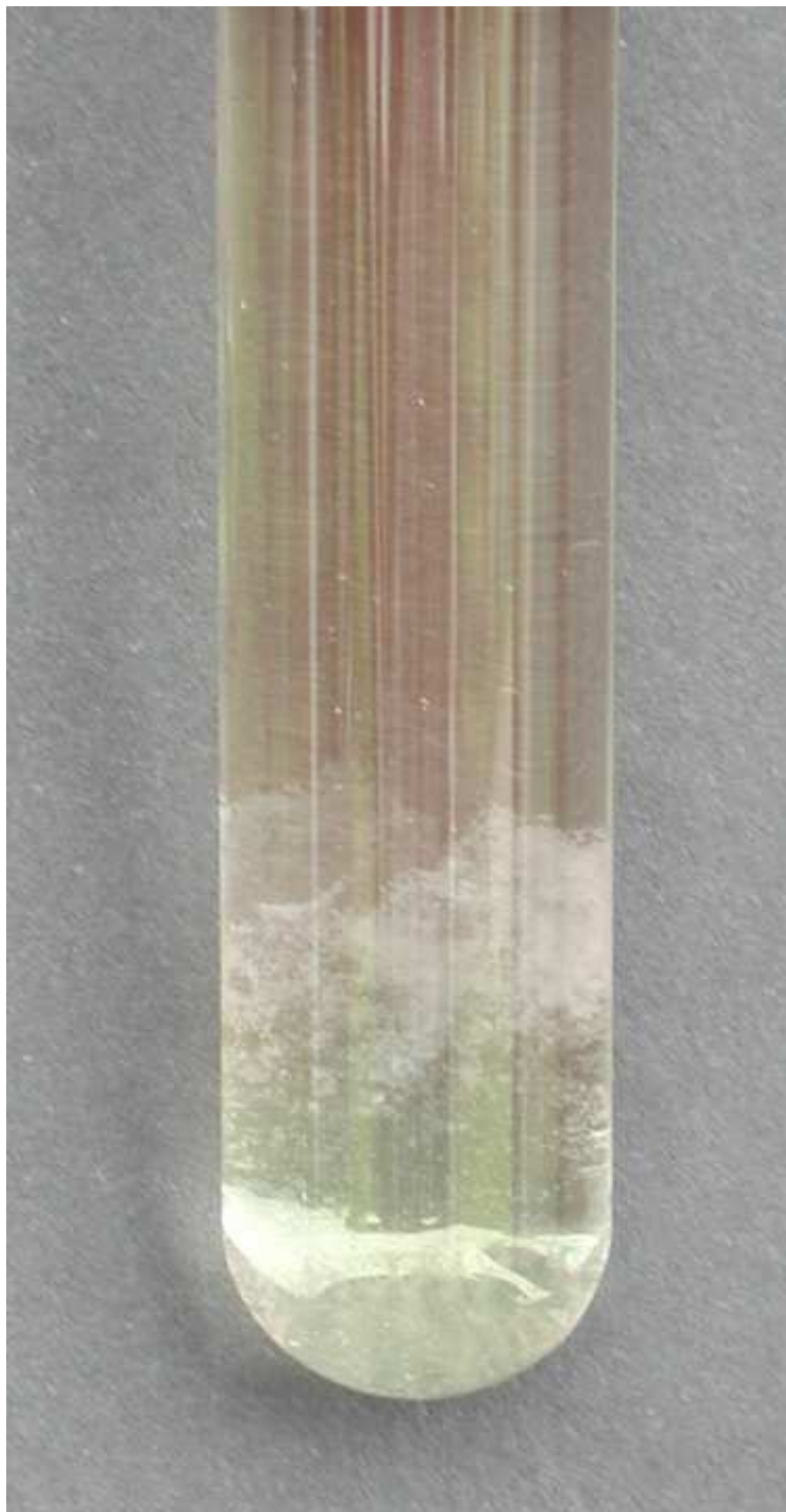


Figure 2
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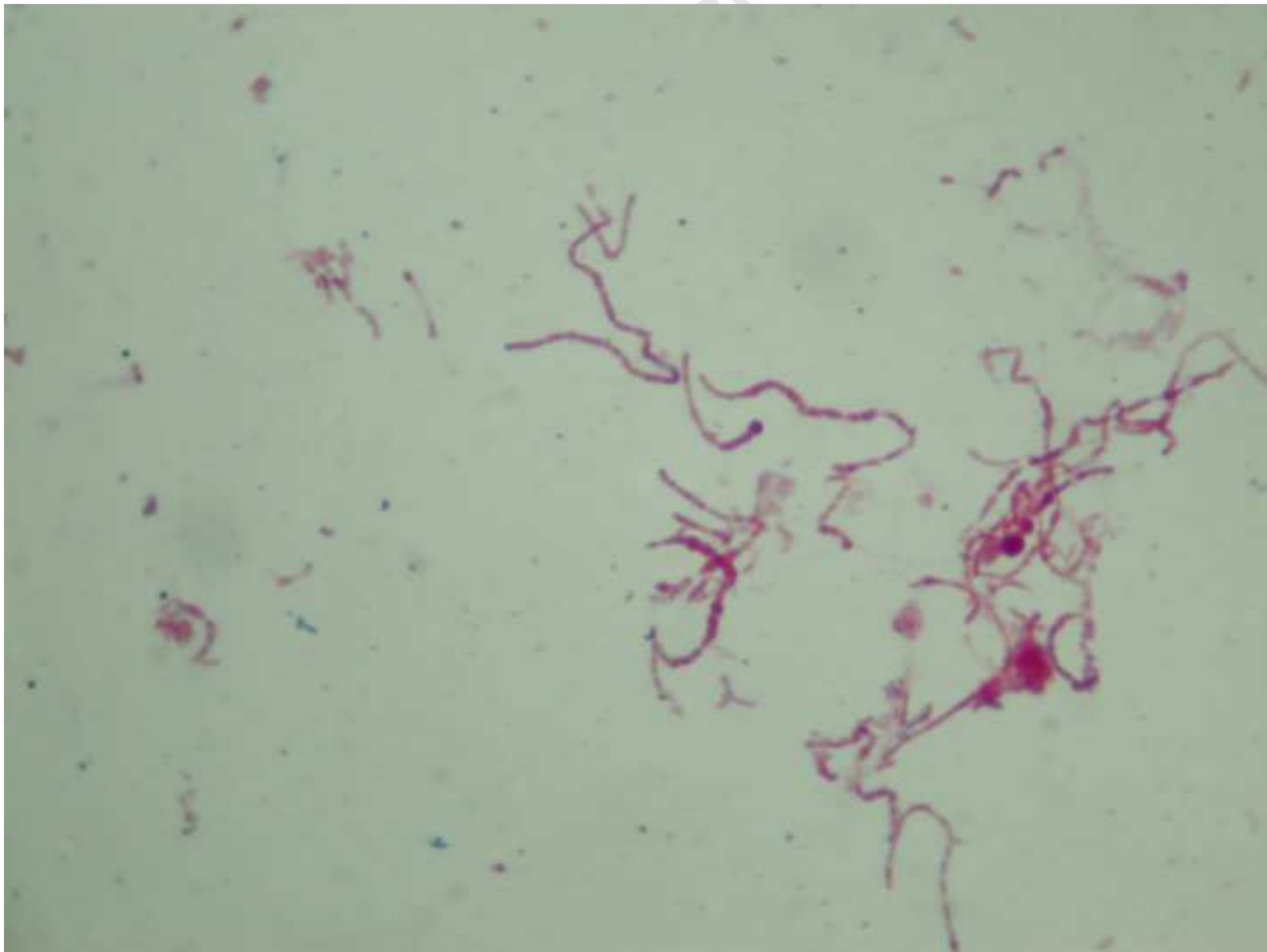
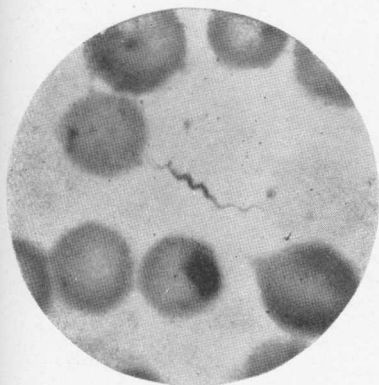


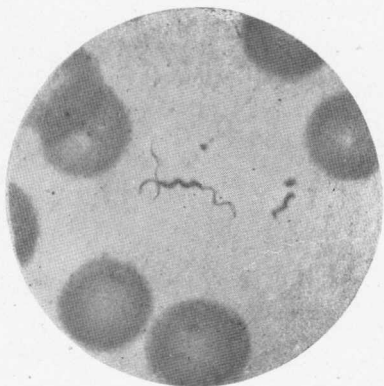


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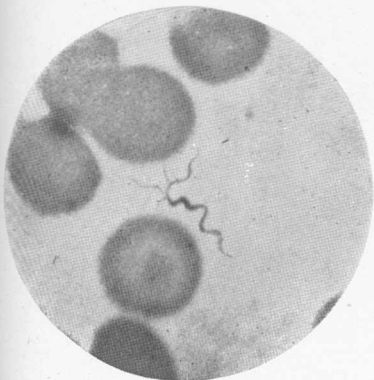




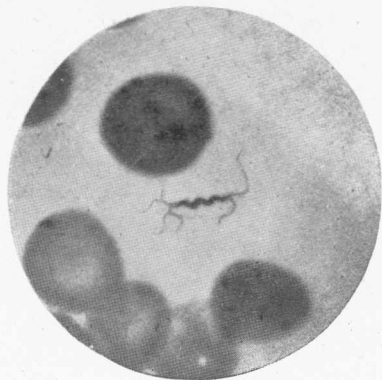
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