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Tuberculosis as a zoonosis from a veterinary perspective

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Abstract

Tuberculosis is an important disease among many zoonoses, because both *Mycobacterium tuberculosis* and *Mycobacterium bovis*, which are the major causes of tuberculosis, are highly pathogenic, infect many animal species and thus are likely to be the source of infection in humans. In particular, monkeys are highly susceptible to these bacteria and are important spreaders. Recently, two outbreaks of *M. tuberculosis* occurred in four different kinds of monkeys and humans were also infected with the disease in Japan. In zoos, tuberculosis was reported not only in monkeys, but also in several different kinds of animals, including elephants. Pets such as dogs and cats are believed to be generally less susceptible to *M. tuberculosis*, but in this article we introduce a case of infection from man to dog by close contact. Japan is one of the few countries that have been able to control *M. bovis* infection. In other countries, however, cases of bovine tuberculosis and human *M. bovis* infection have been reported, and thus further attention is still required in the future.

Keywords: Zoonosis; *Mycobacterium tuberculosis*; *Mycobacterium bovis*; Monkey; Elephant; Dog

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Résumé

La tuberculose, parmi de nombreuses zoonoses, est une maladie importante, parce que ses deux causes principales, *Mycobacterium tuberculosis* et *Mycobacterium bovis*, sont toutes les deux très pathogéniques et infectent beaucoup d'espèces, ce qui les rend susceptibles d'infecter aussi les humains. Les singes, en particulier, sont facilement atteints par l'infection de ces bactéries, dont ils deviennent ainsi des propagateurs importants. Récemment, au Japon, il y a eu deux cas d'infection répandue de *M. tuberculosis*, qui se trouvait chez des singes de quatre espèces et aussi chez des humains. Dans les jardins zoologiques, l'infection a été rapportée non seulement chez les singes, mais aussi chez des animaux de plusieurs espèces, y compris les éléphants. On croyait que les chiens et les chats domestiques étaient moins susceptibles à l'infection *M. tuberculosis*, mais nous présentons ici le cas d'une infection transmise par un homme à un chien avec lequel il était en contact prochain. Le Japon est l'un des rare pays qui ont pu contrôler l'infection *M. bovis*. Dans la plupart des pays, des cas de tubercule bovine ont été rapportés de même que les cas d'infection *M. bovis* chex les humains, ce qui porte à croire que ce sujet mérite encore de l'attention future.

Mots clés: zoonose; *Mycobacterium tuberculosis*; *Mycobacterium bovis*; singe; elephant; chien

1. Introduction

Tuberculosis is a major emerging disease in humans and is now the leading cause of death in adults worldwide. According to WHO estimates, 2 billion people, about one-third of the world's population, are infected with tuberculosis. In 2003, about 8.8 million people were estimated to have developed tuberculosis (incidence rate 140 per 100,000 population), and 1.7 million people (mortality rate, 28 per 100,000 population) died of tuberculosis, with 99% of them being concentrated in developing countries, particularly Asia and Africa [1]. This situation is believed to be closely associated with the spread of HIV in developing countries, in addition to the poor sanitary and living conditions due to poverty and to delay in action against tuberculosis [1,2]. In contrast, the incidence rate of tuberculosis is low in developed western countries (7 per 100,000 population). In Japan, however, the tuberculosis incidence rate had steadily decreased until the 1970s, but the decrease slowed down and then in late 1990s showed a temporary upsurge, with the number of new tuberculous patients reaching 39,384 (incidence rate 31.0) in 2000. In 2005, with 28,319 patients (incidence rate, 22.2), Japan is still classified as a country of intermediate-level tuberculosis epidemic [3].

The pathogen that causes tuberculosis, which is a hazard to public health, is the (highly pathogenic) *Mycobacterium tuberculosis* complex (tubercle bacillus), which comprises *M. tuberculosis*, *Mycobacterium bovis*, *Mycobacterium africanum*, *Mycobacterium microti* and *Mycobacterium canetti* [4]. Of these five species, *M. tuberculosis* and *M. bovis* are most highly pathogenic. *M. tuberculosis* is prevalent all over the world and is the cause of almost all cases of mycobacteriosis in Japan.

Humans are the only reservoir hosts for *M. tuberculosis*. The human-to-human infection cycle rotates; however, tubercle bacilli have a wide host range and *M. tuberculosis* has been detected in fish, reptiles, birds, and mammals including marine animals. Naturally, the first contamination of these animals with *M. tuberculosis* is caused by humans, and then infection occurs among animals, which become the source of infection in humans. Therefore, in this report, we describe tuberculosis, a zoonosis, particularly *M. tuberculosis* and *M. bovis* infections, from a veterinary perspective.

2. Tuberculosis in monkeys

Table 1 shows that different animal species have different degrees of susceptibility to tubercle bacilli and various frequency of open tuberculosis according to the animal species. From a public health print of view, the role of each animal differs according to its species. Animals belonging to the high-score group (Group 1), especially monkeys, are important sources of infection with tuberculosis in terms of susceptibility and transmission. Infection risks differ among different species of monkeys. Old-world monkeys are important from the viewpoint of public health, because they are by far the most susceptible to both *M. tuberculosis* and *M. bovis* and are likely to be unrestrained [5].

In Japan, tuberculosis in monkeys has been reported in zoos. Between 1960 and 1995, *M. tuberculosis* infection occurred in pig-tailed macaques, Taiwan macaques, orangutans, and chimpanzees [6,7, private communication]. In this report, we present the two outbreaks of *M. tuberculosis* infection that occurred recently. In an exhibition facility housing 17 Japanese macaques in the Kansai area, two monkeys that died in July and October 2004 were diagnosed with *M. tuberculosis* disease. The rest of the monkeys that were housed with these two monkeys were also found positive with tuberculosis skin test, and thus were euthanized [8].

The other outbreak involved three species of monkeys infected in succession (private communication) in the one facility. In this facility, two reptiles (a Malay gavial [*Tomistoma schlegelii*] and a spectacled caiman [*Caiman crocodilus*]) died in December 2000 and in February 2001 before the outbreak of tuberculosis in monkeys. Both these animals had disseminated lesions in the organs and numerous acid-fast bacteria in the lesions. In February 2001, a tuberculin-positive chimpanzee died. This animal had suppurative granulomatous inflammation with infiltration of multinucleated giant cells in the liver, and a small number of acid-fast bacteria in the lesions. In October 2003, an old Asian elephant died in the same facility. This animal had lung abscesses, and histopathological examination revealed acid-fast bacteria in the lesions. Although all these animals had acid-fast bacteria in common in their lesions, the bacterial species were not identified, because the bacteria were not cultured. PCR of paraffin sections of the lesions of the two different reptiles, however, revealed a band specific to *M. tuberculosis* complex when the IS1-2 (123 bp) primer was used, although no band was noted when the TB1-2 (320 bp) primer was used. In October 2003, when the Asian elephant died, the first of three prosimians

Table 1
Relative mycobacteria susceptibilities and spread

Group	Species 1	No. of bacilli in lesions[a]	Species 2	Susceptibility to infection with three types of tubercle bacilli[a]			Spread
				Bovine	Human	Avian	
1	Primitive humans #1	1		5	5	1	5
	Monkeys	2	Great apes	3	2	3	5
			Asian monkeys	5	5	2	
			African monkeys	4	4	2	
			South American monkeys	2	2	2	
	Guinea pigs	1		5	5	2	1
	Rabbits	2		1	5	4	1
	Mice	3		1	5	4	1
2	Modern humans #2	1		2	2	1	5
	Elephants	3		3	3	1	?
	Cattle	1		1	4	1	5
	Goats	1		1	4	2	1
	Pigs	1		2	4	2	1
3	Chickens	4		1	1	3	4
4	Horses, etc.	3		1	2	1	1
5A	Dogs	2		2	2	0	0
5B	Cats	3		1	4	2	1
	Ferrets	5		1	5	2	0
5C	Hamsters	4		5	5	1	0

The maximum value for each feature in this table is 5. The values for spread represent the degree of case with which tuberculosis spreads naturally between members of any one species. #1: aboriginal people, #2: contemporary human.

[a]The rating scale is as follows: 1, not likely; 2, rare, 3, occasional; 4, common; 5, classic [5,16].

(red ruffed lemurs [*Varecia variegata rubra*]) died of tuberculosis. The remaining two developed the disease in succession by May 2004, as a result of which one died and the other one was euthanized. In addition, four out of nine old-world monkeys (Abyssinian colobus monkeys [*Colobus guereza*]) and eight new-world monkeys (tufted capuchin monkeys [*Cebus apella*]), both of which shared part of the animal facility with the red ruffed lemurs, developed tuberculosis from January 2004 and died or had a positive tuberculosis skin test and thus were euthanized. The acid-fast bacilli isolated from each monkey were identified as *M. tuberculosis*, and were found to be of the same strain belonging to the Beijing family, which is prevalent in the Far East. Subsequently, four out of ten workers, including two veterinarians who performed necropsy on the monkeys, were found to be infected with tuberculosis

(QuantiFERON-TB® Gold positive), and one of the veterinarians developed the disease. The *M. tuberculosis* isolated from this patient was identical to the bacterium isolated from the monkeys.

The type of lesion and amount of bacteria in the lesion varied depending on the species of monkey. The prosimians, in particular, presented suppurative changes, including suppurative pneumonia, lung abscesses, cervical lymph node abscesses, and pyonephritis, with acid-fast bacteria forming a large mass in the lesion. The exudate from the lymph node abscesses on the body surface which self-destructed contained large amounts of bacteria, detected positive on smear.

To detect tuberculosis in live monkeys, a tuberculin skin test, culture for acid-fast bacteria using gastric lavage fluid and/or feces, and chest radiography examination are carried out.

Tuberculosis in monkeys probably arises from the following two situations. One is the case where imported monkeys that were already infected with tuberculosis develop the disease after being imported. In Japan, this case is represented by an orangutan imported from Indonesia [private communication] which had been taking care by Indonesian staff with tuberculosis. However, of the 10,462 laboratory monkeys from 10 consignments imported between 2000 and 2004, none were reported to be positive for tuberculin skin test [7]. In Japan, the import of pet monkeys was completely banned in June 2004, and for exhibition monkeys, tuberculosis testing is obligatory, and thus it is unlikely that imported animals will be the source of infection.

The other situation is where infection occurs within the confines of the country. In this case, animals are generally infected from a human spreader of tubercle bacilli. This manner of transmission seems to be more likely in Japan, a country of intermediate-level tuberculosis epidemic. The original source of infection could not be identified in either of the two institutions referred to, because there was no introduction of an animal that could be the source of infection, nor were there any tuberculous patients among the zoo staff.

3. Tuberculosis in elephants and other exhibition animals

In Japan, infection with *M. tuberculosis* was reported in Asian elephants and polar bears as early as 1962 [6,7] and in Malayan tapirs (*Tapirus indicus*) in 1991 [7] and 2004 (private communication).

We describe here tuberculosis in elephants, which very common, and a problem not only in the country of origin, but also in Europe and America [9–15]. Susceptibility to *M. tuberculosis* depends on the species of elephant. Asian elephants are more susceptible to *M. tuberculosis* (susceptibility score, 4) than African elephants (susceptibility score, 1) and their level of risk to humans is 4 [5,16]. In Sweden there was an outbreak of tuberculosis in Asian elephants, which became the source of infection in giraffes [10]. In the US, eight out of 379 elephants in one report died of tuberculosis [9]. There have also been cases in which handlers were infected with tuberculosis from Asian elephants [9,11]. Therefore, in the US, the culture and

PCR of trunk wash is officially carried out regularly to detect tuberculosis in elephants in captivity [15,17]. In one report 12 of 118 elephants (10.1%) were found positive for tubercle bacilli by culture of trunk wash samples [12], while another report stated that 3.3% of the elephants in captivity in North America have active disease [5]. The fact that Asian elephants have a much higher carrier rate of *M. tuberculosis* and a much higher incidence rate of the disease than African elephants is attributed to both greater susceptibility and greater risk of exposure to *M. tuberculosis* in Asian than in African elephants [5]. Asian countries originally have a high level of tuberculosis prevalence in the human population [1] and elephants are raised in close contact with humans, who are reservoirs. These factors are considered to result in the high infection rates in the elephant population. Particularly in Thailand, the number of tuberculous patients is increasing with increased incidence of HIV [1]. Therefore, a further increase in the infection rate among animals and particularly elephants is feared [18].

In Thailand, periodic tuberculosis screenings are performed on elephants, but positive elephants unlikely to receive treatment partly because of high medical costs [18]. In Japan, where about 120 elephants are in captivity, tuberculosis tests are not performed.

Tapirs are less susceptible to *M. tuberculosis* complex than elephants but are slightly more susceptible to *M. bovis* than to *M. tuberculosis* [1]. In Japan, *M. tuberculosis* infection occurred in four Malayan tapirs (*T. indicus*) spanning three generations within one pedigree (private communication).

4. Tuberculosis in pets

Public health risks from dogs and cats are classified as group 5, as shown in Table 1, because these animals are less susceptible to *M. tuberculosis* and, moreover, are not likely to be spreaders. Even dogs, which are more susceptible than cats, have a low incidence of tuberculosis [19]. Most cases of canine tuberculosis are transmitted by human reservoirs; dog-to-dog transmission is very rare [20]. Therefore, the incidence of canine tuberculosis is closely related to the incidence of human tuberculosis. In one study, *M. tuberculosis* was isolated from 75% of dogs with tuberculosis, and 88% or more of these dogs were known to have contact with patients with active tuberculosis [20]. The incidence is also higher in urban areas, where human patients are concentrated, than in the suburbs [19,21]. In addition, from the 1930s to the 1950s, in Europe and America, the incidence of canine tuberculosis was between 0.1% and 4.6% among dogs necropsied [20,21], but now there are hardly any cases of canine tuberculosis with a decrease in the number of human tuberculous patients. In Japan, only four cases have been reported, in 1954 [22]. In 2004, however, canine tuberculosis was reported in US [23] and we have presented a case that occurred in Japan (private communication).

The affected dog was a 3-year-and-8-month-old miniature dachshund. In April 2003, one of the owner's family developed tuberculosis, was isolated in a hospital, and was discharged in July after receiving treatment. As the dog developed a

respiratory symptom (wet cough) in December, it was brought to a veterinary clinic. Since it did not respond to treatment and a family member had open tuberculosis, the dog's pharyngeal swab and bronchial lavage fluid were cultured, and *M. tuberculosis* was isolated. The dog was euthanized and necropsied in January the following year. The RFLP patterns of bacteria isolated from the owner (Fig. 1), those isolated from the dog before its death, and those isolated from its organs collected during necropsy were completely identical. Considering the time course, it was thus concluded that the disease was transmitted from human to dog.

This case shows that although dogs are only weakly susceptible to *M. tuberculosis*, they may be infected if they come in close contact with a source of infection (e.g. human). The dog did not have any findings suggesting immunosuppression.

On the other hand, dogs can very rarely be the source of infection in humans. In the present case there is a possibility that the dog might have been the source of infection, because *M. tuberculosis* was also isolated from the dog's pharyngeal swab. Afterwards, the health of veterinary staff involved in the treatment or necropsy of the dog was investigated. It was found that the person who necropsied the dog had a strongly positive tuberculin reaction and a positive QuantiFERON test. These findings suggested infection with tuberculosis during necropsy. Extreme care must be exercised in the necropsy of animals infected with tuberculosis, as in the aforementioned cases of tuberculosis in monkeys.

5. *M. bovis* infection

M. bovis is an important species from the viewpoint of public health for the following reasons: it is the second most pathogenic mycobacterium, following *M. tuberculosis*; it has a wider host range and thus infects more varied animal species, including ruminants, its original host, as shown in Table 1; many of the animals it affects, which can become sources of infection, are in the human living environment [5,24].

Human infection with *M. bovis* is mostly caused by the intake of contaminated milk or dairy products. Transmission by direct contact or droplet transmission is also possible among high-risk people, such as veterinarians and animal keepers, who are in frequent contact with animals. Unlike *M. tuberculosis*, however, it is considered that *M. bovis* does not transmit easily from human to human or by air [5], expect in the case of carriers with lung lesions [25]. Therefore, the public health risks of *M. bovis* should be reduced if it is controlled sufficiently in affected animals such as cattle.

In Japan, dairy cattle receive a tuberculin skin test under a bovine tuberculosis eradication project established in 1901 and the Animal Infectious Diseases Control Law enacted in 1951, and cattle found positive are culled. The number of cases has been reduced to 0–2 per year since 2000, although there were as many as 100 or more cases per year in the 1980s, a relatively large-scale outbreak also involving deer occurred between 1992 and 1993, and an outbreak among beef cattle in 1999 (Table 2). *M. bovis* as such, however, was not detected in any of the culled

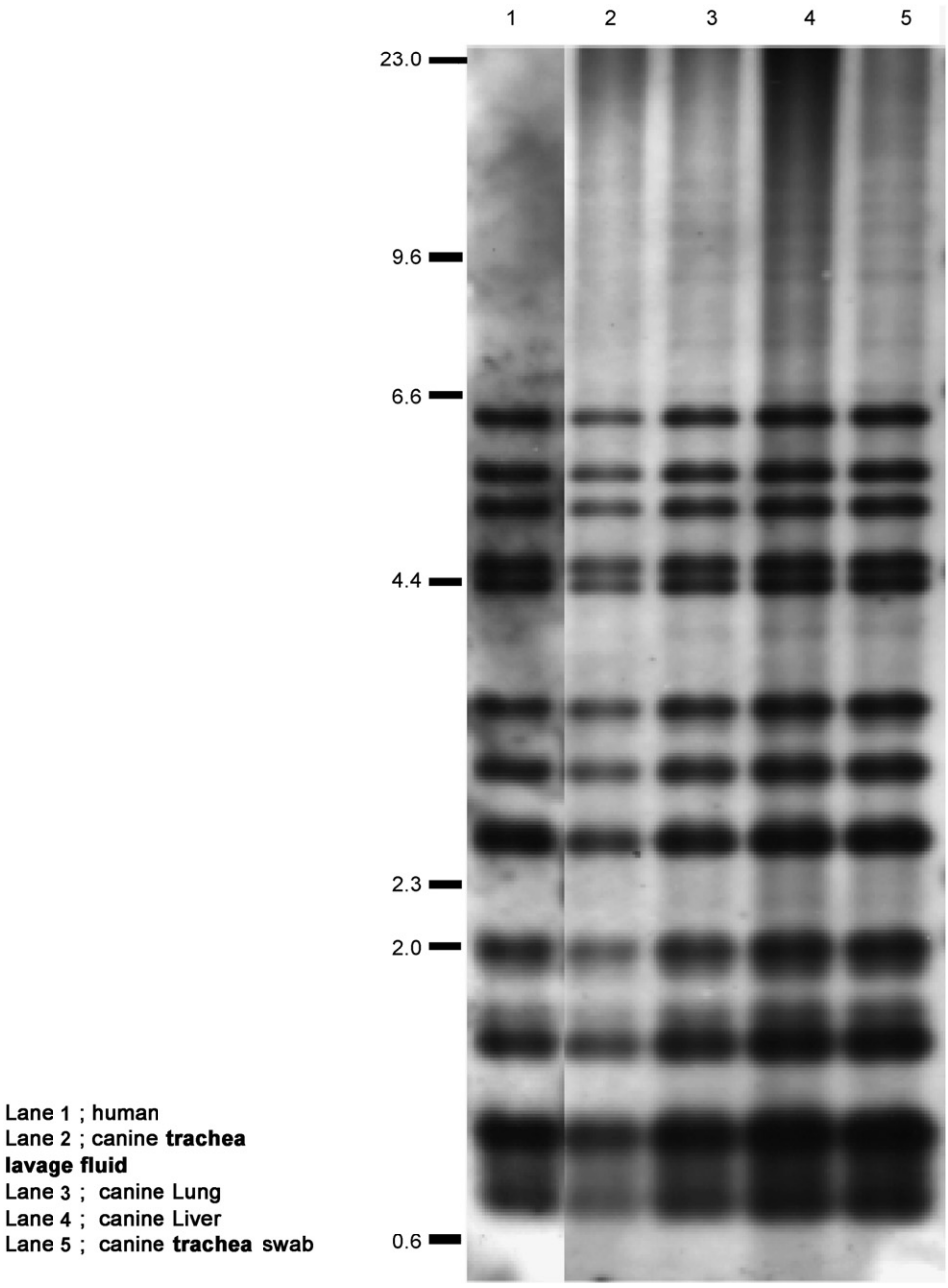

Fig. 1. *Mycobacterium tuberculosis* restriction fragment length polymorphism pattern using IS6110.

Table 2
Changes in population of cattle with positive TB skin test in Japan

Year	No.	Year	No.	Year	No.
1980	120	1989	35	1998	1
1981	121	1990	32	1999	37
1982	45	1991	33	2000	2
1983	35	1992	195	2001	0
1984	18	1993	203	2002	1
1985	32	1994	10	2003	1
1986	45	1995	9	2004	1
1987	89	1996	8	2005	1
1988	40	1997	2		

tuberculin-positive cattle, which are so-called reactors with no visible lesions, and thus they are very unlikely to transmit *M. bovis* to humans. There have been no reports of isolation of *M. bovis* from wild animals in Japan. Cases of *M. bovis* were reported between 1954 and 1976 in rhinoceroses, camels, giraffes, goats, and raccoon dogs in Japanese zoos [6,7], but there have been no such cases since then.

Japan, however, is one of the few countries that have been able to control *M. bovis*. Cases of human *M. bovis* infection are reported worldwide. In Asia, *M. bovis* infection has been occurring in Korea and Taiwan [1].

One of the reasons *M. bovis* is difficult to control in livestock even in developed countries is that wild animals are contaminated with this bacterial species. As described earlier, many animals are highly susceptible to *M. bovis* and thus are potential sources of infection. In fact, bovine *M. bovis* is transmitted from badgers in the UK, from wild pigs in Australia, and from opossums in New Zealand [24].

M. bovis is very well controlled in Japan. To maintain the high level of control of *M. bovis* in Japan the culling of tuberculin-positive cattle should be continued and the introduction of *M. bovis* infected animals from other countries which can contaminate wild animals with *M. bovis* should be prevented. In particular, in the case of imported animals, a certificate showing that the animal is free of *M. bovis* infection should be requested according to the Office International des Ēpizooties (OIE) guidelines.

6. Conclusions

Thus far, 700 or more different zoonoses have been identified. Among them, tuberculosis is especially important because of the large numbers of human patients and of animals susceptible to this disease. In Japan, tuberculosis in livestock is controlled by the Animal Infectious Diseases Control and has been virtually eradicated in dairy cattle. Therefore, there is a very low risk to humans. Human tuberculosis is controlled by the Tuberculosis Prevention Law, but Japan is still a

country of intermediate-level tuberculosis epidemic. Under the present circumstances, incidences of tuberculosis have occurred in pet animals and monkeys, causing a public health problem, yet neither of the relevant laws applies to these animal species. In Japan at present, revision of the Infectious Diseases Control Law is under discussion for more effective control of tuberculosis transmitted from animals.

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