

Armadillos and leprosy: from infection to biological model

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ABSTRACT

Mycobacterium leprae is the primary causative agent of Hansen's disease or leprosy. Besides human beings, natural infection has been described in animals such as mangabey monkeys and armadillos. Leprosy is considered a global health problem and its complete pathogenesis is still unknown. As *M. leprae* does not grow in artificial media, armadillos have become the primary experimental model for leprosy, mimicking human disease including involvement of the peripheral nervous system. Leprosy transmission occurs through continuous and close contact of susceptible people with untreated infected people. However, unknown leprosy contact has been reported in leprosy-affected people, and contact with armadillos is a risk factor for leprosy. In the USA, leprosy is considered a zoonosis and this classification has recently been accepted in Brazil. This review presents information regarding the role of wild armadillos as a source of *M. leprae* for human infections, as well as the pathogenesis of leprosy.

KEYWORDS: *Mycobacterium leprae*. *Dasypus novemcinctus*. *Euphractus sexcinctus*. Hansen's disease. Leprosy.

INTRODUCTION

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*¹ (Hansen's bacillus) and *Mycobacterium lepromatosis*². The most common causative agent is *M. leprae*, an obligate intracellular pathogen of high infectivity and low pathogenicity. Recent research has shown variation in the genetic diversity of isolates from different continents, ethnic groups and host species³. In addition, its clinical manifestation is broad, with widely divergent immunological characteristics⁴, hindering the diagnosis.

A susceptible individual, once infected, generally exhibits an incubation period of three to seven years until symptoms and physical signs of the disease are observed. Men are more affected than women, with signs in men usually starting in the second and third decade of life. Children may be affected mainly in areas where leprosy has high endemicity⁵. The disease mainly affects the skin and peripheral nerves, but the multibacillary form often affects the eyes, oro-nasal mucosa, testicles, bones and other tissues⁶.

The highest incidences are found in tropical and subtropical climates and, to date, it is a significant public health problem, especially in Asia, Africa and South America⁷. In 2017, 210,973 new cases of leprosy were reported by 147 countries or territories⁸.

Transmission of Hansen's disease generally occurs via droplets of secretions released from the oro-nasal cavity, through sneezing or coughing, from symptomatic

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or asymptomatic individuals with mycobacteria⁹. However, the exact mechanism of transmission of the disease in the population is still debated, especially regarding environmental sources of *M. leprae* and their role in human disease, as well as the classification of Hansen's disease as a zoonosis^{10,11}. Moreover, suspicions of the existence of infected animals such as armadillos and primates acting as environmental reservoirs and sources of *M. leprae* have increased¹². Issues related to individual immunological susceptibility in the pathogenesis of infections by *M. leprae* in humans and animals and the new causative agent identified the *M. lepromatosis*, still need to be clarified. The recently reported presence of *M. leprae* and *M. lepromatosis* in red squirrels (*Sciurus vulgaris*) in the British Islands does not appear to pose an increased risk to human health¹³. Difficulties inherent to the study of Hansen's disease include the shortage of bacillus for studies, the fact that the bacillus does not grow in artificial media and experimental animal models are rare⁴.

The objective of this manuscript is to review published studies on *M. leprae* research in wild armadillos combining results from different databases and summarizing current evidence on specific issues. We attempted to resolve conflicts between studies and to determine whether results could be summarized when individual studies were inconclusive or contradictory. We searched three electronic databases (PubMed, Scielo, and Web of Science) for observational and experimental studies published in indexed journals. Search terms included the keywords "armadillo", "*Mycobacterium leprae*", "Leprosy" and "Hansen disease". We included manuscripts written in English/Portuguese and

published between 1960 and 2018. This search strategy identified (after de-duplication) 58 articles describing leprosy in armadillos.

Armadillos as a model for Hansen's disease

To circumvent the problem that the bacillus *M. leprae* cannot be cultivated *in vitro*, Shepard in 1960¹⁴ established an animal model consisting of bacilli multiplication in the mouse pad. In 1971, Kirchheimer and Storrs¹⁵ achieved the spread of *M. leprae* in nine-banded armadillos (*Dasypus novemcinctus*) in captivity, and soon after in the seven-banded armadillo (*Dasypus hybridus*)¹⁶. Currently, *D. novemcinctus* is considered the most appropriate armadillo species for leprosy research^{4,17}.

Natural infection of *M. leprae* occurring in wild armadillos

Some primate species (*Pan troglodytes*, *Cercocebus atys* and *Macaca fascicularis*)¹⁸ and armadillos¹⁹ are susceptible to *M. leprae* infection and are naturally infected. In North America, where armadillos are considered a reservoir of Hansen's bacillus²⁰, strains of *M. leprae* from armadillos have been found in almost two-thirds of the autochthonous human leprosy cases in Southern USA²¹.

Table 1 shows published studies on the natural infection of *M. leprae* in wild armadillos. These studies strengthen the hypothesis of armadillos as a zoonotic source of *M. leprae*, and demonstrate that armadillos and humans develop a

Table 1 - Studies on *M. leprae* infection naturally occurring in wild armadillos

| Authors | Year | Location | Armadillo species |
|-----------------------|--------------------|--|---|
| Walsh et al. | 1975 ²³ | Louisiana/ USA | <i>Dasypus novemcinctus</i> |
| Stallknecht et al. | 1987 ⁵⁷ | Louisiana/ USA | <i>Dasypus novemcinctus</i> |
| Truman et al. | 1990 ⁵⁸ | Texas and Louisiana/ USA | <i>Dasypus novemcinctus</i> |
| Zumarraga et al. | 2001 ³³ | Corrientes/ Argentina | <i>Dasypus novemcinctus</i> |
| Deps et al. | 2002 ²⁹ | Espirito Santo/ Brazil | <i>Dasypus novemcinctus</i> |
| Deps et al. | 2007 ³⁰ | Espirito Santo/ Brazil | <i>Dasypus novemcinctus</i> |
| Deps et al. | 2008 ¹⁰ | Espirito Santo/ Brazil | <i>Dasypus novemcinctus</i> |
| Cardona-Castro et al. | 2009 ²⁶ | Barbosa/ Colombia | <i>Dasypus novemcinctus</i> |
| Antunes et al. | 2009 ³¹ | Espirito Santo / Brazil | <i>Dasypus novemcinctus</i> |
| Truman et al. | 2011 ²⁰ | Arkansas, Alabama, Louisiana, Mississippi, and Texas / USA | <i>Dasypus novemcinctus</i> |
| Frota et al. | 2012 ³² | Ceara / Brazil | <i>Euphractus sexcinctus</i> and <i>D. novemcinctus</i> |
| Sharma et al. | 2015 ⁴¹ | Mississippi, Alabama, Georgia, and Florida / USA | <i>Dasypus novemcinctus</i> |
| da Silva et al. | 2018 ⁴³ | Para / Brazil | <i>Dasypus novemcinctus</i> |

similar clinical picture (skin ulcers¹⁷ and infection of the peripheral nerves²²) of Hansen's disease⁶.

In 1975, Walsh *et al.*²³ reported that free-living armadillos from Louisiana harbored natural *M. leprae* infection and further investigations have shown the spread of the bacterium in Southern US armadillo population^{23,24}, Mexico²⁵, Colombia^{26,27}, Brazil^{10,28-32} and Argentina³³.

In 2002, Dets *et al.*²⁹ reported *M. leprae* infection in wild armadillos in Brazil using the Polymerase Chain Reaction (PCR), and afterwards by the lateral flow serological technique (ML Flow test³⁰). These studies established that, in Southeast Brazil, armadillos can be considered a natural reservoir of *M. leprae*. An epidemiological approach in the same area revealed that direct exposure through hunting or consumption of armadillo meat was associated with two-fold higher chance of leprosy in humans^{34,35}. These epidemiological studies in the USA and Brazil were supported by reports showing *M. leprae* infection occurring naturally in wild armadillos^{20,29,30,32}. In addition, a standard single genotype (SNP type) for the strain of *M. leprae* in armadillos and patients from the USA was reported²⁰.

Armadillos as a source of *M. leprae* for humans

The possibility of an active participation of armadillos in the transmission of human leprosy is reinforced in areas with infected armadillos, where people affected by leprosy report no previous contact with infected individuals³⁶⁻³⁸. An association between leprosy and contact with armadillos has been reported mainly in people who handled or ate armadillos^{34-36,38-40}. A case report from the USA describes a patient without travel history to endemic countries or contact with people infected with *M. leprae*, but who reported contact with armadillos³⁸.

The interaction between armadillos and *M. leprae* will lead to the development of a range of natural resistance among animals in the same locality, which will be strongly influenced by individual and genetic factors. Susceptible armadillo species from South America, such as *D. hybridus* and *E. sexcinctus*, do not exist in North America^{32,41}. Regarding the origin of leprosy in Brazil and the Americas, the dominant Single Nucleotide Polymorphism (SNP) types found in Brazil are SNP type 3, the same subtype found in Europe that was transported to the New World by European explorers, and SNP type 4 from West Africa, that was transported during the slave trade⁴². This supports the belief that animal infections in the Americas originated from humans who migrated from the places of origin of *M. leprae* (Europe and West Africa)⁴², as confirmed by Frota *et al.*³² who found the SNP type 3 in armadillos from Northeast Brazil, the

same genotype found in naturally infected armadillos in Louisiana, USA²⁰.

M. leprae infection occurring in wild armadillos is an emerging infection in Southern USA. In most of the infected animals, the agent is a single predominant *M. leprae* strain type, associated with the probable zoonotic transmission of leprosy²⁰. *M. leprae* genotypes 3I-2-v1 and 3I-2-v15 were detected in armadillos, and 42.3% (22/52) of people affected by leprosy were infected with one of these two strains⁴¹.

da Silva *et al.*⁴³ identified a significant relationship between armadillo meat consumption and transmission of *M. leprae*, probably indicating transmission through capture and maintenance of armadillos in captivity before consumption¹¹. On the other hand, Schmitt *et al.*⁴⁴ found no association between consumption of armadillo meat and the disease.

In Brazil, two species of armadillos, *E. sexcinctus* and *D. novemcinctus*, have been identified as natural carriers of *M. leprae*^{10,29,30,32,39}. Subsequently, Frota *et al.*³² sequenced the genotype of *M. leprae* from armadillos in Northeastern Brazil, finding the SNP type 3, the same identified in armadillos from Louisiana²⁰ and in people affected by leprosy in Brazil⁴⁵. Besides Brazil and the USA, direct contact with armadillos in Mexico and Colombia has been implicated in the zoonotic transmission of Hansen's disease^{25,26}. It is therefore highlighted that the most significant exposure to environmental *M. leprae* is through direct contact with armadillos, with potential zoonotic cases being of public health concern^{20,43}.

Descriptions of infection patterns in wild armadillos remain scarce, and transmission mechanisms are unknown⁴⁶. *M. leprae* infection in armadillos seems to spread naturally, probably increasing the likelihood of human infection^{25,40}. The transmission of *M. leprae* to humans presupposes contact between infected armadillos and susceptible individuals. There is an association between contact with *D. novemcinctus* and the development of leprosy in people living near the armadillo's natural habitat^{35,36,47}, suggesting the potential for these species to spread *M. leprae*¹⁸ into the environment.

Armadillos as animal models for the study of leprosy

Microbiological studies using the etiological agents are essential to understand any infectious disease. Because *M. leprae* and *M. lepromatosis* do not grow in artificial media, studies on leprosy are limited to sampling infected human tissues⁴⁸. However, researchers have to deal with ethical limitations, difficulties in accessing infected tissue, and samples that are not suitable for molecular analysis⁴⁹. The other option is to use animals as a source of *M. leprae*⁵⁰.

An ideal animal model should become infected

without immunosuppression and develop the disease like humans, with similar bacteriological and histopathological features⁵¹. Monkeys, chimpanzees, pigs, dogs and bats have unsuccessfully been explored as animal models for leprosy¹⁵. Animals with body temperatures below 37 °C seem to be more prone to *M. leprae* infection so that susceptible animal hosts are limited⁵⁰.

Shepard¹⁴ introduced the mice plantar foot pad cushion model, but replication of the bacilli is much more emphatic in the footpad and there is no nerve involvement. Subsequently, naturally acquired and experimental *M. leprae* infection was described in chimpanzees (*Pan troglodytes*), mangabey monkeys (*Cercocebus atys*), cynomolgus monkeys (*Macaca fascicularis*)¹⁹ and armadillos (*D. novemcinctus*)²⁶. In 1971, the armadillo was established as the best experimental model of *M. leprae* infection due to its ability to mimic human disease and produce a good number of bacilli¹⁵.

Infection in these animals manifests systemically, especially in reticuloendothelial tissues⁵², with intermittent bacteremia in all organs; extremities of the body with lower temperatures are more affected⁵³. Experiments infecting lower body temperature (32-35 °C) nine-banded armadillos using various routes of infection (intravenous, intradermal, percutaneous, inhalation, intraperitoneal) established that this species and the intravenous route provide the most useful animal model¹⁷ in terms of a good number of mycobacteria in the first 18 months of infection^{6,54}. However, even following this infection protocol, 15-20% of animals do not develop the disease⁵⁰. In naturally infected animals, about 5% develop clinical features of leprosy¹⁰ and 90% of the animals that show signs of systemic dissemination die from leprosy⁵⁵. The most common clinical signs observed are typical plantar ulceration (Figure 1), and skin wear around the eyes, nose, feet, and parts of the body subject to friction (Figure 2). In the laboratory, foot ulcers increase as the infection progresses due to decreased extremity sensitivity¹⁷.



Figure 1 - Plantar injury in a naturally infected *E. sexcinctus* (Source: JMAP Antunes, Brazil).

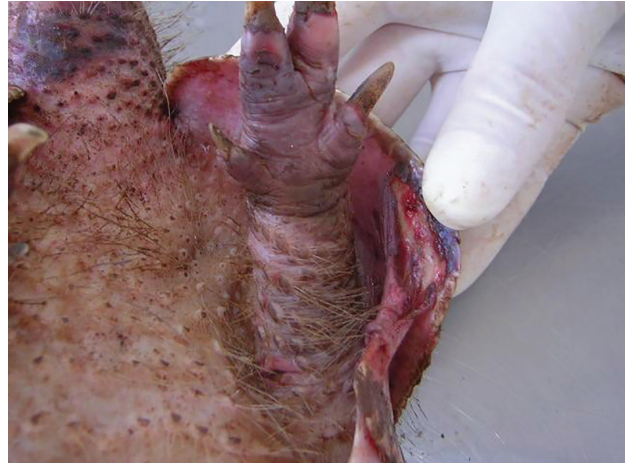


Figure 2 - Injury in a carcass of a naturally infected *D. novemcinctus* (Source: JMAP Antunes, Brazil).

The most important similarity between human and armadillo disease is nerve involvement^{50,56}. The unique attributes of the armadillo as an experimental model are the state of controlled and known infection, the duration of disease and the functional similarity with leprosy in humans. Armadillos can also be examined for rare neurological events occurring over time⁵⁰. Histopathological images of armadillo tissues reveal infiltration of macrophages infected with *M. leprae* in the liver, spleen and lymph nodes, and sometimes in lips, tongue, nose, nasal mucosa, skin, bone marrow, eyes, lungs and nerves⁶. Although the interval between infection and developing the disease in experimental infection in armadillos (4 to 24 months) is shorter than in human infection, there is an opportunity to evaluate pathogenesis in preclinical stages that have never been observed in humans⁵⁰.

Perhaps the most critical limitation of the use of armadillos in experiments is the difficulty of the animal reproduction in captivity. Pregnant armadillos, when captured from the wild, provide descendants that may be models for studying the role of host genetics and genomic factors in leprosy susceptibility⁴⁸.

CONCLUSION

Natural *M. leprae* infection was first observed in free-living armadillos of the *D. novemcinctus* species in the USA in 1975²³ and in Brazil in 2002²⁹. Interest in natural infection in armadillos has increased sharply over the last five years and, in Brazil, we still have much to learn about this disease. *E. sexcinctus* has become the target of research related to natural leprosy in armadillos, and studies on this zoonosis in Brazil should focus on this species.

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CONFLICT OF INTERESTS

The authors state no conflicts of interest.

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