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Current knowledge on *Mycobacterium leprae* transmission: a systematic literature review†

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Summary
Background: The transmission pathways of *Mycobacterium leprae* are not fully understood. Solid evidence exists for an increased risk for individuals living in close contact with leprosy patients, but the existence of zoonotic leprosy, environmental reservoirs and trauma-related transmission has also been established.
Purpose: To assess the current state of knowledge on *M. leprae* transmission, we conducted a systematic review of the peer-reviewed literature pertaining to this topic.
Method: Major electronic bibliographic databases were searched for relevant peer-reviewed articles published up to January 2014. No restrictions on study types, participants and location were applied, and all outcomes demonstrated to contribute to the transmission of *M. leprae* were considered. Included studies were grouped by mode of transmission, namely (i) human-to-human via aerosols or direct contact; (ii) direct inoculation (e.g. injury); and (iii) transmission to humans from environmental or zoonotic reservoirs, and by insects. The importance of the different transmission pathways and the strength of the evidence were assessed considering the number of publications describing similar findings, the consistency of the findings and the methodological quality of the studies.
Results: A total of 79 relevant articles were retained out of 3,805 hits resulting from the application of the search strategy. Solid evidence for transmission among contacts exists, and for zoonotic leprosy in the southern States of the USA. Based on the extant evidence, skin-to-skin contact, aerosols/droplets and shedding of bacteria into the environment and subsequent infection, e.g. through dust or small wounds, all remain possible options.
Conclusion: No study has unequivocally demonstrated the mechanisms by which *M. leprae* bacteria travel from one case of leprosy to another.

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Introduction

Leprosy (Hansen's disease) is caused by a chronic infection with *Mycobacterium leprae* of the skin, peripheral nerves and often the mucosa of the upper respiratory tract. If untreated, the infection can lead to damage of the skin, eyes and peripheral nerves.[1] Early diagnosis and completion of multi-drug therapy (MDT) are essential to preventing permanent disability. With the use of MDT and changes in disease recording, the worldwide prevalence of leprosy has fallen by 90% since the early 1990's. Globally, the number of leprosy cases is now below the elimination threshold of one case per 10,000 people as defined by the World Health Organization (WHO).[1] However, in several countries and sub-national regions, the number of leprosy cases remains above this threshold. Furthermore, despite near-universal use of MDT, the annual number of newly detected cases, including children, has remained fairly constant at around 200,000 – 300,000 cases in recent years.[2] These observations indicate that current control measures have not succeeded in halting the transmission of leprosy.[3,4]

Despite repeated attempts over the past decades to identify transmission patterns among affected communities, a full understanding of the transmission pathways of *M. leprae* has not been reached. Epidemiological studies have identified an increased risk for individuals living in close contact with leprosy patients. However, many new cases cannot identify an index case from whom they may have acquired the infection. Evidence for zoonotic leprosy in the USA and the discovery of *M. leprae* DNA in the environment are complicating the traditional paradigm that *M. leprae* is transmitted solely from human to human. To assess the current state of knowledge on *M. leprae* transmission, we conducted a systematic review of the peer-reviewed literature pertaining to this topic.

Methods

DATABASES, KEYWORDS AND SEARCH STRATEGY FOR STUDY IDENTIFICATION

The following electronic bibliographic databases were searched using the terms 'leprosy', 'Hansen's disease', '*Mycobacterium leprae*', 'transmission' and 'reservoir' in appropriate combinations: (i) PubMed: (Leprosy or Hansen's disease or *Mycobacterium leprae*) AND (transmission or reservoir); (ii) Virtual Health Library (VHL): (tw:(Leprosy OR Hansen's disease OR *Mycobacterium leprae*)) AND (tw:(transmission OR reservoir)); (iii) Web of Science: ((Leprosy or Hansen's disease or *Mycobacterium leprae*) AND (transmission or reservoir)); (iv) Science Direct: ((Leprosy OR Hansen's disease OR *Mycobacterium leprae*) AND (transmission OR reservoir)). The last search was stratified by content type groups to circumvent limits on the number of hits that can be downloaded from each search.

The search was last repeated on 23.01.2014 and no restrictions with regard to language and time of publication were applied.

CRITERIA FOR CONSIDERING STUDIES

The review focused on the transmission pathway of *M. leprae* to humans, including potential reservoirs (in animals or the environment), mechanisms for transmission (methods for propagation such as vectors, droplets and direct contact), and situational risk factors for infection (risk factors about which some level of control exists, e.g. housing conditions). Studies with 'transmission' or 'reservoir' (environmental or animal) mentioned in the title were initially considered. Further, original research articles were included if the title contained one of the following key concepts referring to *M. leprae* transmission that have been identified in a step-wise approach by screening and classifying the result of an initial search for ‘leprosy AND transmission’ in PubMed: (i) source and route of *M. leprae* infection; (ii) spatial and temporal epidemiology of *M. leprae* transmission; (iii) risk factors for *M. leprae* transmission.

The following topics were not included in the systematic review despite being related to *M. leprae* transmission: development of new methods (e.g. diagnostics), mathematical modeling, risk factors inherent to the host (e.g. host genetics), mere signs of exposure to *M. leprae* (e.g. sero-conversion), the experimental infection of laboratory animals, and speculations about transmission.

Only peer-reviewed publications were considered but no restrictions on study types, participants and location were applied. All outcomes demonstrated to contribute to the transmission of *M. leprae* were considered.

IDENTIFICATION OF POTENTIALLY RELEVANT STUDIES, FINAL SELECTION AND ANALYSIS

All references identified by applying the search strategy described above were downloaded and imported into a single EndNote X6 database, and duplicates were eliminated with the relevant automatic function. The titles of the articles in the resulting database were screened to identify additional duplicates, non-peer reviewed publications (e.g. letters), and articles pertaining to diseases other than leprosy.

Potentially relevant studies were then identified by screening the titles of the retained references, followed by the screening of abstracts for the presence of the term “transmission” or a synonymous expression (e.g. ‘route of infection’, ‘source of infection’) which were taken to indicate that the publication contained information that was relevant to this review. Both screenings were implemented by two reviewers, and the results compared. Discrepancies were resolved by jointly reviewing discordant results. Finally, the full texts of the provisionally included studies were scrutinised against the inclusion criteria to compile the final list of studies to be included in the review.

Using specifically designed forms, the following data were extracted from all included publications: (i) reference details (title, authors, journal, year of publication); (ii) study details (site, design, sample size); and (iii) main findings.

The retained publications were summarised in summary tables, grouping studies by the mode of transmission that was investigated: (i) human-to-human via aerosols or direct contact; (ii) direct inoculation (e.g. injury); (iii) transmission to humans from environmental or zoonotic reservoirs, and by insects.

The importance of the different transmission pathways and the strength of the evidence were assessed considering the number of publications describing similar findings, the consistency of the findings and the methodological quality of the studies. The latter was evaluated according to the following criteria: selection process of study participants to ensure representativeness of the study population, sample size calculation and adherence, participation, outcome assessment (diagnostic approach) and data analysis approach. When information in the publication was not sufficient, this was mentioned as such. No study was excluded based on the methodological quality.

No ethical approval was required as the review focused on published evidence. The selection of the papers was performed by the authors MWB and PS, without interference or involvement from the funding agency. The current manuscript was written jointly by all co-authors.

Results and Discussion

The implementation of the search strategy resulted in a total of 3,805 records (Figure 1) identified from PubMed ($n = 904$); VHL ($n = 515$); Web of Science ($n = 1{,}181$) and Science Direct ($n = 1{,}205$).

Automatic elimination of duplicates and manual identification of further duplicates, non-peer reviewed literature and publications not related to leprosy led to the elimination of 2,687 items. The screening of the remaining 1,118 titles resulted in the identification of 273

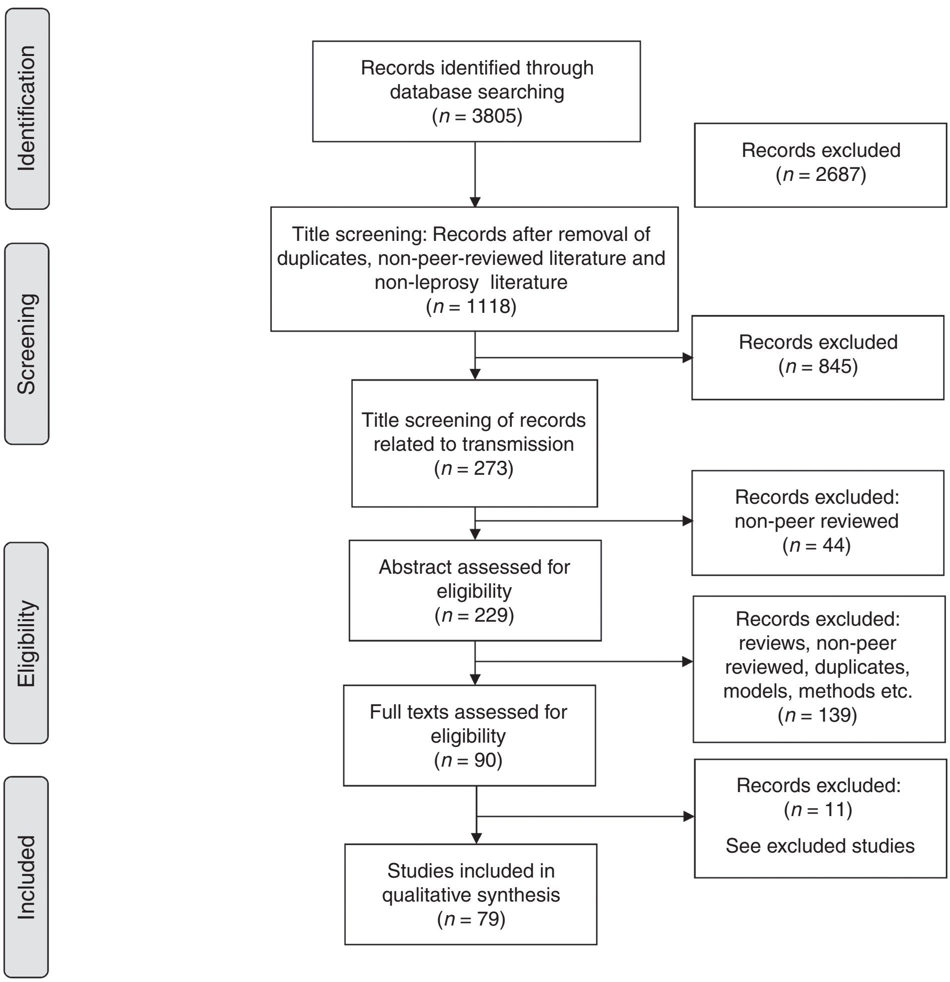

Figure 1. PRISMA Flow Diagram of systamtic literature review on on *Mycobacterium leprae* transmission.

that met the inclusion criteria. Among them, another 44 records were eliminated as non-peer reviewed, leaving 229 abstracts which were screened for inclusion. A total of 139 publications were removed at this step due to a variety of reasons, most notably for being reviews or non-peer reviewed publications - not identified as such in the title screening, or describing models and methods, or not identifying actual hypotheses for transmission. The full texts of three records could not be obtained. The full texts of the retained 90 articles were then scrutinised, resulting in the elimination of another 11 publications which did not contain relevant data.

HUMAN-TO-HUMAN TRANSMISSION

The 37 publications investigating human-to-human transmission of *M. leprae* reported findings from 36 studies (online Supplementary Table 1).[5–41]

With regard to design, most studies could be classified as cohort studies (14 prospective;[6,13,14,16,18,21–23,28,31,34,36,38,40] seven retrospective[9,10,12,20,24,33,39]). Eleven studies followed a cross-sectional design,[5,7,8,15,19,25–27,32,37,41] three were case-control studies[11,29,35] and two were case reports.[17,30] In terms of countries, the highest number of studies were conducted in India (13 studies reported in 14 publications[8,15–18,20–23,31,32,36,38,40]), followed by Brazil (five studies[5,9,26,34,35]), Bangladesh (four studies[11,14,28,33]), Indonesia (three studies[6,19,39]) and Thailand[33,37]). One study was conducted in each of the following countries: USA,[24] Cuba,[12] Colombia,[27] Venezuela,[10] Ghana,[29] Malawi,[13] Malaysia,[7] Bhutan[30] and China.[41] One study had been conducted in a laboratory.[25] The publication date ranged between 1956 and 2012, and 18 articles had been published in 2000 or later.

In addition to the risk of acquiring leprosy from other people through direct contact (e.g. skin-to-skin) or via aerosols, most studies investigated risk factors like household size, socio-economic status including education and sanitation, and the nutritional situation. Contact stratification by case type, nasal carrier status, closeness of contact, number of family members with leprosy and duration of contact was also common. The relative importance of contacts in high- and low-endemic areas has been assessed in one study.[33] The type of leprosy in secondary cases in relation to the primary case has also been investigated.[32] Most studies focused on household contacts but some studies also considered social contacts.[11,12,28,34,39] One study tracked the movement of leprosy bacteria through the skin to its surface[17] and one investigated the precise location of bacteria in the skin and its adnexa.[25] Another study focused on the release of bacteria from the nose.[30] Multiple studies investigated the specific site where bacteria were shed by cases, namely the skin as well as the nasal and oral mucosa.[5,19,23] The molecular identity of *M. leprae* strains in index cases and infected household contacts has been studied in two publications,[37,41] and the protective effect of the BCG vaccination in four.[8,9,29,36] Many large epidemiological studies made direct or indirect reference to the classical study of leprosy transmission conducted in the Philippines over several decades by Guinto and co-workers.[42]

Ample evidence exists for the clustering of leprosy cases. The relevant studies find an elevated risk of leprosy among contacts of index cases, both within the household and in social contacts. A clear stratification of the risk of disease emerged, with household contacts of lepromatous or multibacillary cases being at higher risk than household contacts of tuberculoid or paucibacillary cases, and individuals with more intensive social contact or living closer to leprosy cases being at higher risk than their peers without these characteristics. It was also found repeatedly that the risk of household members of contracting leprosy correlated with the number of leprosy cases in a household and the bacterial load of the index case. Of note, most secondary cases were of the paucibacillary/tuberculoid type. When interpreting this observation, the very long incubation period and the temporal limitations that most studies face as well as the ethical imperative to treat patients as soon as they have been detected, must be considered.

Presence of, and exposure to, *M. leprae* as determined by PCR or serology appeared to be dynamic over time, and links to clinical disease were suggestive of the possibility of transmission by subclinical cases. The notion of subclinical cases contributing to transmission is supported by the findings over recent years that treating index cases alone has been insufficient to halt transmission of leprosy on a global scale.[4] Molecular evidence showed that cases within households were often due to the same strain of *M. leprae* and that a variety of strains existed in the same area. However, a large proportion of the newly diagnosed cases could not be attributed to any known index case. The proportion of non-attributable cases was found to be higher in high-transmission areas compared to areas with a low number of incident cases, suggesting again that transmission might happen in the absence of overt disease, or that other contact patterns than long-term and close exposure to a source of infection were sufficient for transmission. An alternative explanation for these results is the presence of a large pool of undiagnosed cases that are sources of infection.

The quality of the identified studies varied considerably. Several large-scale prospective cohort studies, including entire communities, provided high-quality data (see for example[28,34]) while other designs or studies only focusing on household contacts, offered evidence of lower quality, due to issues with recall bias, unclear matching/absence of controls, neglect of the exposure history or small sample size. The studies establishing the skin as a source of bacteria shed into the environment were small[17,25] but studies focusing on the nose or buccal cavity as the location of entry and exit of *M. leprae* and asymptomatic nasal carriers offered high-quality evidence.[5,19,26,30,31,36] Of particular relevance were high-quality studies relying on molecular tools to identify *M. leprae* carriers and leprosy infections, and changes in their status.

DIRECT INOCULATION

Among the 11 publications focusing on the possible transmission of leprosy through direct inoculation into the skin[43–53] (online Supplementary Table 2), seven were case reports while another one summarised 31 cases arguably all linked to the same transmission source.[44]

A cross sectional study,[52] a retrospective cohort study[53] and a cross-sectional study of injuries in feral armadillos[47] were also identified. Six of the publications reported cases from India, two a case each from Ethiopia[43] and France;[48] the cohort study was conducted in Micronesia, the case control study was global in reach, and the study focusing on animals was conducted in Louisiana, USA. With the exception of the report from France published in 1934 and the case control study published in 1953, all publications dated from 1985 and later, including seven from the period 2002 to 2013.

The nature of the relevant injuries included tattooing (three studies, among them the case series involving 31 cases[44,50,51]), followed by falls (two studies[43,46]) and injuries involving objects (two studies[45,49]). Last, a case of inoculation in a medical setting through a contaminated needle was reported,[48] while the animal study implicated thorns pricking armadillos in the nose and ears.[47] The case-control study focused on the Buddhist practice of shaving the scalp of newborn infants and the cohort study on skin injuries sustained when sleeping on pandanus fibre mats.

Numerous further cases of inoculation of *M. leprae* are reported in the literature, mostly as case reports (often published as letters or other non-peer-reviewed formats). Of particular concern appear to be tattooing (mostly in India) but vaccination scars,[54,55] general injuries (major ones resulting from accidents (see for example[56]) as well as minor ones (e.g. in children[57]), and animal bites (see for example[58]) are also mentioned.

The identified studies point to the possibility of transmitting *M. leprae* through inoculation of *M. leprae* into wounds. This possibility has been recognised since at least the 1930s, and relevant observations have been made in different settings. The bacteria causing the infection in the injured individual appeared to be either environmental (e.g. in the case of skin abrasions and injuries contaminated with soil or dust) or mechanically transferred from infected people (e.g. with needles used in medical or aesthetic procedures). However, none of the studies succeeded in irrevocably proving the origin and means of transmission of arguably injury-related *M. leprae* infections and ruling out alternative transmission pathways. The case-control study that found much higher rates of alopecia leprotica in people affected by leprosy in Buddhist countries[52] and the study that implicated sleeping on pandanus mats,[53] point to small injuries as an important route of infection. Others have discussed whether traumata, especially in children, might play a more prominent role in *M. leprae* transmission than usually accepted.[57] Overall, the available evidence suggests that injuries as a mode of transmission are the exception rather than the norm. Epidemiologically, this transmission pathway thus appears to be insignificant but since high-quality studies systematically assessing the role of small injuries of children are lacking, a significant role of mechanical inoculation or wound contamination with *M. leprae* shed by infected individuals cannot be ruled out. From a hygiene and public health perspective, transmission by contaminated tattoo instruments appears to be a particular concern.

The strength of the evidence from these studies was generally low. The prime argument for direct inoculation into the skin was the close spatial proximity of an injury and the localization of the clinical manifestation of leprosy. However, some cases were not diagnosed bacteriologically; none were confirmed with PCR, and for some cases, the locational congruence between the injury and the leprosy manifestation was not perfect. Also, studies generally did not comment on exposure to other possible sources of infection.

ZOONOTIC OR ENVIRONMENTAL RESERVOIRS, AND TRANSMISSION FROM INSECTS

A total of 14 studies focused on zoonotic reservoirs[59–72] while seven studies investigated environmental reservoirs[73–79] (online Supplementary Table 3). Transmission by insects was the topic of 4 studies[80–83] (Table 3).

All but one of the animal-related studies investigated the role of nine-banded armadillos (*Dasypus novemcinctus*) in the epidemiology of leprosy in the Americas. The remaining study focused on non-human primates in India.[67] The studies on *M. leprae* infections in armadillos were conducted in Brazil,[59] Colombia[62] and Mexico[70] while the nine studies focusing on the risk of armadillo contact for human *M. leprae* infection were conducted in the USA (five studies[61,63,66,68,69]), Brazil (three studies[64,65,71]) and across multiple countries (one study[72]). In terms of design, these studies included one cohort study,[61] five case-control studies,[63–66,71] two case reports[68,69] and one cross-sectional study.[72] All studies had been published after 1977 and nine were published in the year 2000 or later.

The identified studies focusing on the detection of zoonotic reservoirs attempted to establish the presence of *M. leprae* or acid-fast bacilli in cross-sectionally, but sometimes unsystematically, sampled animals by different means, including PCR. Studies endeavouring to identify a zoonotic origin of human leprosy infections considered contact patterns with armadillos and monkeys of varying degree (including injuries caused by armadillos) and eating armadillo meat. The possible role of injuries sustained while handling armadillos is highlighted repeatedly (see for example[61]).

The existence of a zoonotic *M. leprae* reservoir among the nine-banded armadillo is well established since the 1970s, at least for the southern States of the USA. Multiple studies have identified infected armadillos and have plausibly linked human cases to armadillo contact. The situation is less clear for other parts of the Americas where conflicting evidence exists: studies among armadillos generally failed to establish *M. leprae* infections but contact with armadillos has repeatedly been identified as a risk factor for *M. leprae* infection. Of particular interest is a high-quality study reporting the presence of a distinctive molecular pattern in *M. leprae* obtained from armadillos and leprosy cases residing in areas where infected armadillos live. That pattern was not observed in *M. leprae* isolated from humans in other parts of the Americas and in reference strains.[72] No good evidence exists for zoonotic reservoirs in other animals, and reported attempts to experimentally infect other animals, including primates, often failed.

Most studies pertaining to the risk of *M. leprae* transmission from a zoonotic reservoir were small in terms of sample size, samples were not always collected systematically or even randomly, and diagnostic methods were not always sufficiently sensitive or specific. Also, 'controls' of individuals with armadillo contact were often not matched with regard to key characteristics, contact to human leprosy cases was not systematically investigated, and evidence for leprosy among local armadillo populations was not always provided.

Numerous other publications focus on leprosy among armadillos, mostly in the southern States of the USA, but without direct reference to transmission of *M. leprae* to humans (see for example[84–87]). Another series of publications pertains to the experimental infection of a wide range of animals with leprosy, mostly primates and rodents but also frogs, fish and amoeba (see for example[88–99]). The few reports of naturally occurring *M. leprae* infections in primates relate to captive animals (see for example[100]).

Studies exploring the role of potential environmental reservoirs include experiments to demonstrate the viability of *M. leprae* outside the human body[73,74] and investigations focusing on bacteria in soil and water.[75–79] Additional studies were conducted in the laboratory.[73–75] In the other studies, soil and water samples collected in endemic areas in India[76,77,79] and Indonesia[78] were tested for the presence of *M. leprae*. The studies were published between 1977 and 2012.

Laboratory studies relied on the mouse footpad model to determine viability of *M. leprae* exposed to different conditions with regard to drying, humidity, temperature and sunlight exposure. All studies investigating the presence of *M. leprae* in soil and water samples used molecular techniques to detect bacterial DNA or RNA. In two studies, soil samples from patient areas were studied[77] or compared to samples from non-patient areas.[76] The opposite approach was pursued in another study that investigated the prevalence of leprosy among people using positive and negative water sources for bathing and washing.[78] Lastly, one study compared soil samples from washing and bathing areas with samples collected close to the houses of leprosy patients, and compared genetic characteristics of *M. leprae* from these sources with *M. leprae* obtained from local patients.[79]

The identified studies investigating a possible environmental reservoir of *M. leprae* showed that the bacteria can survive for several days in soil and water samples, and that they tolerated different climate conditions. However, the studies failed to establish the presence of a true environmental reservoir as long-term survival or replication of the bacteria could not be demonstrated. The viability of bacteria in field-collected samples remain unclear as do links between the human cases and evidence for *M. leprae* in the environment: none of the identified studies had convincingly linked a human case to exposure to such an environmental reservoir. Interestingly, one study found the same SNP-type of *M. leprae* in the soil as in patients living in the same area. With regard to environmental reservoirs, multiple studies only focused on the detection of *M. leprae* in vegetation, soil and water samples (see for example[101–103]). Of note, in several studies 'acid fast bacilli' were detected while *M. leprae* identification remained elusive.

The insect-related publications reported data from studies involving flies, mosquitoes and bedbugs, and focused on the question whether *M. leprae* could be taken up by insects and remain viable long enough to be transferred to humans.[80–83] All publications reported experimental studies conducted in the laboratory; one also included a small cross-sectional study.[81] The publications dated from 1914 to 1985.

Different insects appear to be potential carriers of *M. leprae* but no evidence for the actual transmission of *M. leprae* via insects to humans and subsequent development of leprosy has been published. Scientific interest in the role that insects potentially play in the epidemiology of leprosy appears to have waned as the last relevant study dates to 1985. The studies generally relied on microscopic identification of acid fast bacilli and thus neither established the precise nature of the observed bacteria nor their viability.

Several publications reviewed the extant evidence (see for example[104]) or dealt with the mechanical limits of *M. leprae* transmission by different groups of insects, mostly in terms of their ability to penetrate the intact skin (see for example[105]) or the likelihood that they bite or sting humans (see for example[106]).

ECOLOGICAL STUDIES, SOCIOECONOMIC SITUATION AND NO HYPOTHESIS

Six studies focusing on socio-economic and ecological risk factors[107–111] or failing to identify a source or means of transmission[112] (online Supplementary Table 4), had been conducted in Brazil, Bangladesh[108] and Malawi.[110]

Studies found that a low socio-economic status was a risk factor for leprosy. The socio-economic status was assessed in these studies by a variety of indicators including housing, water supply, educational status and food shortage. Besides their significance for signaling crowded conditions and difficult access to health care (both resulting in a higher chance to be in contact with untreated leprosy cases), these conditions might be a proxy for a weakened immune status and exposure to environmental transmission sources.

Conclusions

This review of the peer-reviewed literature on the transmission of *M. leprae* identified studies documenting the transmission of *M. leprae* over different pathways (e.g. direct contact, inoculation) and from various sources (e.g. man-to-man, armadillo-to-man). The identified evidence is of varying quality, and many studies have serious methodological shortcomings that undermine our confidence in the value of their findings. This is particularly noteworthy if we consider how fundamental the question is for the control of leprosy. This shortage in high-quality evidence probably is not least attributable to the challenges involved in the study of the epidemiology of leprosy, including: (i) difficulties in detecting *M. leprae* infections before the occurrence of clinical signs; (ii) the best animal model, armadillo, is not widely available nor easily studied for elements of human disease; (iii) the inability to culture *M. leprae in vitro*; (iv) the lack of a simple technique to determine the viability of *M. leprae* and (v) the presence of environmental *Mycobacteria* in many potential transmission sources and reservoirs.

In sharp contrast to the ample documentation of *M. leprae* transmission among contacts of leprosy cases is the dearth of information on the actual mode of transmission. No study has unequivocally demonstrated the mechanisms by which bacteria travel from one case to another. Based on the extant evidence, skin-to-skin contact, aerosols/droplets and shedding of bacteria into the environment and subsequent infection, e.g. through dust or small wounds, all remain possible options. The nose, the oral cavity and the skin have been tentatively identified as entry and exit points of *M. leprae*. The role of the nose in *M. leprae* transmission has found particular attention and the topical treatment of nasal carriers with the explicit aim of reducing leprosy transmission has been attempted.[113] The evidence for an increased risk of leprosy among close contacts provides the basis for post-exposure chemo- and immune-prophylaxis, the former of which has shown repeatedly to provide a degree of protection for limited periods.[114,115]

The results of this review combined with the conclusions reached at an International Symposium (see companion publication: Developing Strategies to Block the Transmission of Leprosy, Mensah-Awere, Bratschi, Steinmann, Fairley and Gillis. Leprosy Review (2015) **86**, 156–164) revealed the extent of the gap that exists in the knowledge we have about the transmission of *M. leprae*. It also demonstrated the potential over-reliance on a limited number of studies that undergird many of the accepted paradigms about the transmission of *M. leprae* and that inform and shape the global response to leprosy. Without significant investment and commitment to address these crucial gaps, evidence-based control program implementation and targeted interventions will be limited to a strategy that is reactive to infection rather than preventative in nature. Accordingly, current approaches will not be sufficient to change the dynamic of continued transmission within populations around the globe.

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Competing interest statement

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Supplementary Table 1. Peer-reviewed studies focusing on human-to-human transmission of *M. leprae*; listed by study design and year of publication with more rigorous designs and more recent studies listed first.

Author; Year	Title	Study Site	Study Design	Sample Size	Main Findings	Quality Assessment
Sales *et al.*; 2011[34]	Leprosy among patient contacts: a multilevel study of risk factors	Rio de Janeiro State, Brazil	Prospective cohort	6158 leprosy contacts	Co-prevalent and incident cases were more likely in household contacts compared to non-household contacts. Bacterial index of more than 3 was significantly associated with co-prevalent cases. Bacterial index greater than 1 was significantly associated with higher incident leprosy cases compared to contacts of patients with a negative bacteria index.	No critical issues.
Fischer *et al.*; 2008[14]	The spatial distribution of leprosy in four villages in Bangladesh: an observational study	Rangpur Division, Bangladesh	Prospective cohort	4'123 villagers	19 new leprosy patients were identified but no spatial clustering at the spatial micro-level of 0·32–1·82 km^2 was observed.	Only considered geographic distance. Included rural as well as urban regions with differences in housing types and possibly different social network patterns. Low number of cases possibly not allowing for the detection of clusters.
Job *et al.*; 2008[23]	Transmission of leprosy: a study of skin and nasal secretions of household contacts of leprosy patients using PCR	Chettupattu, India	Prospective cohort	10 untreated MB patients; 10 treated MB patients; 101 contacts of MB patients	60% of untreated MB patients were found to have acid fast bacilli in the keratin layer of their skin. 80% of them had *M. leprae* DNA in skin washings and 60% had *M. leprae* DNA on swabs obtained from nasal mucosa. 17% and 4% of contacts of untreated MB cases showed signs of skin and nasal colonization. After 2 months	Controls and patients not matched. Patients for whom 1- and 2-year follow ups are reported are not the same as the untreated patients. Viability of bacilli not assessed.

Supplementary Table 1. *continued*

Author; Year	Title	Study Site	Study Design	Sample Size	Main Findings	Quality Assessment
					of treatment of the index cases, all contacts tested negative for *M. leprae* DNA. Follow up of MB patients treated for 1 year with MDT indicated that the majority of patients tested negative for *M. leprae* both in skin washings and nasal secretions (tested positive up to 3 months of treatment).	
Bakker *et al.*; 2006[6]	Risk factors for developing leprosy - a population-based cohort study in Indonesia	Indonesia	Prospective cohort	4903 HH contacts and 94 index cases	From the cohort, 44 persons developed leprosy within 4 years. Living in a household with more than 7 members entailed a 3·1 times higher risk for leprosy compared to households of 1–4 members. Contacts of MB cases had increased risk (adjusted hazard ratio 4·6) and contact of patients with PCR positive nasal swabs had even higher risk (adjusted hazard ratio 9·6). Contacts of more than one patient also had an increased risk, but lower than if nasal secretions of the index case were PCR positive. Multivariate analysis identified sex, household size, serological status at baseline and contact status as statistically significant. Household contacts of patients who did not carry	Only household contacts considered.

Supplementary Table 1. *continued*

Author; Year	Title	Study Site	Study Design	Sample Size	Main Findings	Quality Assessment
					M. leprae in their nose did not have an increased risk. The study found that seropositivity may be a marker for transmitters.	
Moet *et al.*; 2006[28]	Physical distance, genetic relationship, age, and leprosy classification are independent risk factors for leprosy in contacts of patients with leprosy	Bangladesh	Prospective cohort	1037 cases; 21870 contacts	155 cases were discovered. Contacts of PB patients with 2–5 lesions and those of MB patients had a higher risk of developing leprosy than did contacts of patients with single-lesion PB leprosy. The core household group has a higher risk than other contacts living under the same roof and next door neighbors had a higher risk than neighbors of neighbors. Disease classification of the index patient and physical and genetic distance were independently associated with the risk of a contact acquiring leprosy. Contacts living under the same roof but using a different kitchen as well as those using the same kitchen but living under a different roof did not show a statistically significant difference in risk compared to social contacts.	No critical issues.
Smith *et al.*; 2004[36]	An approach to understanding the transmission of *Mycobacterium leprae* using molecular and immunological	Maharastra, India	Prospective cohort	2552 villagers	1·6% of 2552 nasal swabs were positive for *M. leprae* DNA and DNA positivity did not persist over time.	Repeated sampling (also of the initially positive individuals) not always

Supplementary Table 1. *continued*

Author; Year	Title	Study Site	Study Design	Sample Size	Main Findings	Quality Assessment
	methods: Results from the MILEP2 study				Positivity was highest in the wet season. 68% of saliva samples were positive for ML-IgABCG and household contact status was associated with the mucosal immune response.	including the same individuals.
Halder *et al.*; 2001[18]	Role of paucibacillary leprosy in the transmission of disease	West Bengal, India	Prospective cohort	944 contacts of index PB cases; 760 non-case contacts	56 (including 4 MB) cases occurred among the contacts of PB cases and 2 cases occurred among the non-contacts (difference statistically significant). Contacts of index cases were at higher risk of having leprosy. Among the case contacts, risk of contracting leprosy was highest among those sharing the same bed as the index case.	Control households ill defined (suspected leprosy cases which never developed disease) and no matching of control households.
Vijayakumaran *et al.*; 1998[40]	Does MDT arrest transmission of leprosy to household contacts?	Karigiri, India	Prospective cohort	1094 and 567 HH contacts of 337 MB patients	65 new cases were detected among the contacts. The incidence was higher in children (5·1%) compared to adults (2·9%). If the bacterial index of the primary case was more then 2, the risk was increased by 3.01 times. The risk was also increased if disease duration of the index case was more than one year. The presence of co-prevalent case almost doubled the risk in household contacts. People joining a household after the primary case in that household was started on	Alternative sources of infection not investigated (e.g. community or social contacts).

Supplementary Table 1. *continued*

Author; Year	Title	Study Site	Study Design	Sample Size	Main Findings	Quality Assessment
					MDT, were over 4 times more likely to contract leprosy compared to the general population.	
Fine *et al.*; 1997[13]	Household and dwelling contact as risk factors for leprosy in northern Malawi	Northern Region, Malawi	Prospective cohort	1'887 cases, 80'451 at-risk individuals	331 new leprosy cases were diagnosed. Living in a household with a MB case increased the risk 5–8 times whereas living with a PB case increased the risk approximately 2 times. Speculate that PB cases may not be source of infection but indication that the household has come in contact with some outside source of infection. Only 15% of this study of the cases occurred among recognized household contacts.	Dynamic household structures may lead to an underestimate of the proportion of new cases among household contacts. Issues with the classification of contacts which could have led to misclassification of the contact status.
Ramaprasad *et al.*; 1997[31]	Transmission and protection in leprosy: indications of the role of mucosal immunity	Miraj, India	Prospective cohort	204 (133 re-tested)	sMLIgA positivity: 66% of treated patients, 76% of leprosy workers, 72% healthy contacts, 33 negative controls. PCR positivity: 2% of household contacts, 5% negative controls. Subclinical *M. leprae* transmission with transient nose infection: 3 PCR positive individuals were negative after 1 year but 2 out of 94 negatives became positive. 22 changed from sMLIgA positive to negative and 12 from negative to positive.	Small sample size. Contact status of negative controls prone to mis-reporting. No proof of actual transmission by nasal carriers.

Supplementary Table 1. *continued*

Author; Year	Title	Study Site	Study Design	Sample Size	Main Findings	Quality Assessment
George *et al.*; 1993[16]	Intrafamilial transmission of leprosy in Vellore Town, India	Tamil Nadu State, India	Prospective cohort	410 HH contacts; 210 index cases; 14 co-prevalent cases	In the course of the study 14 cases developed leprosy. Found no significant difference in the incidence rate between contacts of MB and PB patients (trend to higher incidence among contacts of MB cases). No added risk for contacts living in multi-case families. Speculate that risk of infection is mainly from within the family rather than from outside.	Only considered household contacts.
Sundar Rao *et al.*; 1989[38]	Impact of MDT on incidence rates of leprosy among household contacts. Part 1. Baseline data	Tamil Nadu State, India	Prospective cohort	8642 cases; 40625 controls	There were 1225 co-prevalent cases and 715 incident cases with an incidence rate of 4.06 per 1000 person years at risk among household contacts (6·40 in contacts of MB patients and 3.48 in contacts of PB patients). Child contacts had a statistically significantly higher incidence rate then adult contacts.	Only considered household contacts.
Jesudasan *et al.*; 1984[21]	Time trends in the analysis of incidence rate of leprosy among household contacts	Tamil Nadu State, India	Prospective cohort	9598 HH contacts of 1614 primary cases	228 incident cases were detected during the follow-up period. Incidence rate during the 1st year of follow-up was 3·8 per 1000 person-years of risk and after 10 years or more, it became 3 per 1000 person-years of risk. No significant fall in the incidence rate with time	Same data as next publication.[22]

Supplementary Table 1. *continued*

Author; Year	Title	Study Site	Study Design	Sample Size	Main Findings	Quality Assessment
					among contacts of non lepromatous and lepromatous cases was observed even after treatment of the primary cases. 10 years after treatment initiation among primary cases, the incidence rate of household contacts was twice that of the general population.	
Jesudasan *et al.*; 1984[22]	Incidence rates of leprosy among household contacts of "primary cases"	Tamil Nadu State, India	Prospective cohort	1564 cases; 9162 HH contacts	228 incident cases. Incidence rate among household contacts of lepromatous primary cases was 5 per 1000 person-years of risk and 3.2 per 1000 person-years of risk for tuberculoid patient contacts. Compared to individuals not exposed to leprosy, household contacts of non-lepromatous patients had a 2 fold increased relative risk. The incidence rate was higher among household contacts of bacteriologically positive (significantly higher for primary cases with a bacterial index of 2 plus compared to primary cases with a negative bacterial index) patients, among closely related contacts and in households with multiple cases.	No information about past leprosy cases in the household of primary cases. Same data as previous publication.[21]

Supplementary Table 1. *continued*

Author; Year	Title	Study Site	Study Design	Sample Size	Main Findings	Quality Assessment
Richardus *et al.*; 2005[33]	Close contacts with leprosy in newly diagnosed leprosy patients in a high and low endemic area: comparison between Bangladesh and Thailand	Bangladesh and Thailand	Retrospective cohort	Bangladesh: 1333 cases; Thailand: 129 cases	Average new case detection rate over 10 years: 50 per 100,000 general population per year in Bangladesh, and 1·5 per 100,000 in Thailand. In the high endemic area 25% of newly detected cases were known to belong to one of 3 contact groups and in low endemic area 62% of newly detected cases belonged to a contact group. Just over half of the nearest index cases were found within the immediate family unit (‘kitchen’ in Bangladesh; ‘house’ in Thailand).	No critical issues.
Jain *et al.*; 2002[20]	Childhood leprosy in an urban clinic, Hyderabad, India: clinical presentation and the role of household contacts	Hyderabad, India	Retrospective cohort	306 cases	Contact history in 38.8% of patients (95% of them are family contacts). 38% of index cases were PB and the rest MB.	No controls included. Hospital-based study with possible selection bias.
de Matos *et al.*; 1999[9]	Leprosy epidemiology in a cohort of household contacts in Rio de Janeiro (1987–1991)	Rio de Janeiro State, Brazil	Retrospective cohort	88 PB cases; 670 contacts without symptoms	MB index case and immune status of the contact were found to be significant indicators for developing leprosy in household contacts. Not being vaccinated with BCG increased the risk of leprosy among household contacts.	Possible selection bias: access to the facility that manages the cohort is limited. No information about drop outs from the cohort.
van Beers, Hatta, Klatser; 1999[39]	Patient contact is the major determinant in incident leprosy: implications for future control	North Sulawesi, Indonesia	Retrospective cohort	101 cases	Cases were clustered in households. 79% of the cases could be classified as having had leprosy contact in the past (28% had household	No critical issues.

Supplementary Table 1. *continued*

Author; Year	Title	Study Site	Study Design	Sample Size	Main Findings	Quality Assessment
					contact; 24% had contact with a directly adjacent neighbor). Risk of leprosy was highest for household members of MB cases (13·7 times basic risk), followed by the risk of neighbors of MB households and household contact of PB patients. More MB than PB patients could be identified as the index case for more than one patient.	
Ferra Torres, Carrazana Hernandez; 1997[12]	Means of detection and source of infection of the incidences of leprosy	Camagüey, Cuba	Retrospective cohort	81 cases	Source of infection: neighbors (19.8%), family (14·8%). Spouses were no source of infections.	Source of a large fraction of the infections undetermined.
Escuder Navarro; 1961[10]	Considerations on the contagion of leprosy in convivial and non-convivial groups	Bolivar State, Venezuela	Retrospective cohort	332 leprosy cases (271 primary and 66 secondary); 1408 close contacts	47.3 leprosy cases per 1000 in close contacts versus 2·6 per 1000 in the general population.	Contacts not clearly defined.
Kluth; 1956[24]	Leprosy in Texas; risk of contracting the disease in the household	Texas, USA	Retrospective cohort	1522 contacts of lepromatous cases; 495 contacts of non-lepromatous cases	40 cases (2·6%) were found among contacts of lepromatous cases. 1 case (0·2%) among contacts of non-lepromatous cases.	Not all contacts were followed-up and it is probable that not all cases among the not followed-up contacts were diagnosed and reported.
Hatta *et al.*; 1995[19]	Distribution and persistence of *Mycobacterium leprae* nasal carriage among a population in which leprosy is endemic in Indonesia	South Sulawesi, Indonesia	Repeated cross sectional	418 local inhabitants	Presence *of M. leprae* DNA in 2·9% of surveyed population. PCR positivity was not persistent over 2 years (all the PCR positive persons in the first survey were negative in the second one). Widespread nasal carriage in the general population but nasal	No causality between nasal colonization and transmission. No proof of viability of colonizing bacteria and that they are of the same genotype as disease causing ones.

Supplementary Table 1. *continued*

Author; Year	Title	Study Site	Study Design	Sample Size	Main Findings	Quality Assessment
					colonization was inconsistent in place and time. No difference in PCR positivity was detected in patients plus their neighboring households and other individuals living in more distant households. Patients diagnosed with leprosy at the 2-year follow-up were all initially negative in terms of nasal colonisation.	
Rao *et al.*; 1975[32]	Transmission of leprosy within households	Gudiyatham Taluk, Tamil Nadu, India	Repeated cross-sectional	5088 families with 22652 contacts	Secondary attack rate: 6·8 per 1000 person-years (63.8% tuberculoid, 9·5% lepromatous, 9·7% borderline, 16·8% indeterminate). Population incidence: 0·8 per 1000 person-years. Males at higher risk than females, highest attack rates in 5–9 year olds. Risk doubles if there are 2 or more patients in the household. Relatively more lepromatous cases in adults, more tuberculoid cases in children. Higher risk if index case is lepromatous than if it is tuberculoid	Non-household contacts not considered.
Araujo *et al.*; 2012[5]	Unveiling healthy carriers and subclinical infections among household contacts of leprosy patients who play potential roles in the disease chain of transmission	Minas Gerais State, Brazil	Cross sectional	444 cases and 1352 contacts	By PCR, 34·2% of the patients and 4.7% of the contacts tested positive for *M. leprae* DNA in nasal swabs. No statistically significant correlation between the detection of	No proof of transmission from patients to contacts, e.g. by typing carriage and disease strains.

Supplementary Table 1. *continued*

Author; Year	Title	Study Site	Study Design	Sample Size	Main Findings	Quality Assessment
					M. leprae and the clinical form of the index case. Significant association between nasal swab PCR and anti-PGL-1 serology (63·3% of the patients and 13·3% of the controls were seropositive).	
Feenstra *et al.*; 2012[11]	Social contact patterns and leprosy disease: a case-control study in Bangladesh	Rangpur Division, Bangladesh	Cross sectional (case control)	90 cases; 199 controls	Leprosy was associated with a more intense contact pattern in the home (OR 1·09) and in the nearby neighborhood (OR 1·07). The mean social contact score (inside the home and within the neighborhood) of patients was higher than that of controls. Social contact patterns varied by gender. Conclude that social contacts outside of the household are important for the transmission of *M. leprae*.	Controls are not matched. Self-reporting of social contact with potential issues of recall bias.
Martinez *et al.*; 2011[26]	Oral mucosa as a source of *Mycobacterium leprae* infection and transmission, and implications of bacterial DNA detection and the immunelogical status	Ubrlandia, Brazil	Cross sectional	334 cases; 1228 HH contacts	18.3% of patients and 6.8% of contacts had *M. leprae* DNA positive buccal swabs. Positivity of buccal swabs increased towards the MB form of leprosy reaching 42·7% in lepromatous cases. *M. leprae* DNA was also detected in the oral cavity of tuberculoid patients, indicating that the mouth might function as point of entry of the infection (particularly in PB patients).	No information on the viability of the discharged bacteria.

Supplementary Table 1. *continued*

Author; Year	Title	Study Site	Study Design	Sample Size	Main Findings	Quality Assessment
Ofosu, Bonsu; 2010[29]	Case control study to determine the factors associated with leprosy in the Sene district, Brong Ahafo region of Ghana	Sene District, Brong Ahafo Region, Ghana	Cross sectional (case control)	24 cases; 48 controls	Contact with someone with leprosy in the same house and not having BCG vaccination was found to be associated with having leprosy. Close contact facilitates transmission. Duration of contact is not significantly associated with leprosy.	Small sample size.
Santos, Castro, Falqueto; 2008[35]	Risk factors for leprosy transmission	Jaguaré, Espírito Santo, Brazil	Cross sectional (case control)	90 cases, 270 controls	Risk of leprosy: odds ratio of 2·9 if current case of leprosy among relatives exists and odds ratio of 5·0 if old case of leprosy among relatives.	Non-household contacts not considered.
Srisungngam *et al.*; 2007[37]	Typing of Thai clinical isolates of *Mycobacterium leprae* and analysis of leprosy transmission by polymorphism of tandem repeats	Thailand	Cross sectional	100 cases	Patients in multi-case families were infected with a single strain of *M. leprae* in each family but strains differed between families (based on TTC repeats typing). In strains from patients in single case families differences in the copy number of the TTC repeats were observed.	No information on route of infection.
Weng *et al.*; 2007[41]	Identification and distribution of *Mycobacterium leprae* genotypes in a region of high leprosy prevalence in China: a 3-year molecular epidemiological study	Qiubei county, Yunnan province, P.R. China	Cross-sectional	68 cases	Multiple-locus variable-number tandem-repeat analysis (MLVA) was used to track leprosy transmission. Multiple clusters were found in China, and multi-case families were common: 23 of the 68 patients were from 11 families. Intra-familial	Small sample size. No discrimination between transmission intra-household and between social contacts.

Supplementary Table 1. *continued*

Author; Year	Title	Study Site	Study Design	Sample Size	Main Findings	Quality Assessment
					VNTR profiles closely matched within six families, but were different between families. VNTR patterns related to those found in some multi-case families were also detected in patients in the same or adjacent townships, suggesting social contacts on village markets as transmission sites.	
Melendez, Fuentes, Rodriguez; 2006[27]	Conjugal leprosy	Atlántico Department, Colombia	Cross sectional	963 leprosy cases	Conjugal leprosy is not frequent and requires several years to develop in the second person. Lepromatous leprosy in index cases increased the risk of leprosy in the couple. No MB leprosy occurred in the secondary cases.	No controls. Selection bias (facility based) and information bias (records-based study).
George *et al.*; 1990[15]	The role of intrahousehold contact in the transmission of leprosy	Tamil Nadu State, India	Cross sectional	72 cases; 216 contacts	Persons with intra-household leprosy contact had a significantly higher risk of acquiring leprosy compared with those who did not (risk ratio 2·51).	Only included household contacts with a case at the time of the study, i.e. history of contact not considered.
Chen; 1988[7]	Longhouse dwelling, social contact and the prevalence of leprosy and tuberculosis among native tribes of Sarawak	Sarawak State, Malaysia	Cross sectional	467 residents in single dwellings; 315 in longhouses	Prevalence of leprosy was significantly higher among longhouse dwellers (106·4 per 100'000) compared with single house dwellers (47·9 per 100'000). It was also found that longhouse dweller social groups tend to be larger (higher proportion of groups exceeding 8 persons)	Matching not possible, i.e. differences in housing are associated with ethnic group and other differences.

Supplementary Table 1. *continued*

Author; Year	Title	Study Site	Study Design	Sample Size	Main Findings	Quality Assessment
					and persist for much longer compared to single house dwellers.	
Dave, Agrawal; 1984[8]	Prevalence of leprosy in children of leprosy parents	Chhattisgarh State, India	Cross sectional	212 children of leprosy cases; 240 children from non-leprous families	In the leprous families 25 cases were identified compared to 2 cases in the control group (prevalence 14·2 times higher). In leprous families, the prevalence was 3 times higher in families where there was more than one leprosy patient compared to single patient families (statistically significant) and 1·5 times higher if lepromatous leprosy cases as opposed to non-lepromatous cases were present. None of the identified children with leprosy had lepromatous disease. BCG vaccination provides 50% protection among child contacts.	No critical issues.
Kotteeswaran, Chacko, Job; 1980[25]	Skin adnexa in leprosy and their role in the dissemination of *M. leprae*	Laboratory	Cross sectional	20 cases	*M. leprae* are found in large numbers in sweat glands, sweat ducts, sebaceous glands, hair follicles and arrector pili muscles. Study showed that *M. leprae* are discharged and disseminated from unbroken skin. Only few bacilli were observed in the skin of tuberculoid patients.	No information on the viability of the discharge bacteria

Supplementary Table 1. *continued*

Author; Year	Title	Study Site	Study Design	Sample Size	Main Findings	Quality Assessment
Ghorpade; 2011[17]	Transepidermal elimination of *Mycobacterium leprae* in histoid leprosy: a case report suggesting possible participation of skin in leprosy transmission	Chhattisgarh State, India	Case report	1 case	Acid fast bacilli found in the dermis and epidermis. Suggest movement of bacteria with ultimate elimination from the stratum corneum into the environment. Speculate that skin is the portal of both entry and exit of the bacilli.	Viability of bacteria not assessed.
Pedley, Geater; 1976[30]	Does droplet infection play a role in the transmission of leprosy?	Bhutan	Case reports	2 cases	Patients with untreated or relapsing lepromatous leprosy release large numbers of *M. leprae* up to a distance of 30 cm upon sneezing, and smaller numbers up to 50 cm. Talking, snoring and panting did not result in measureable release of *M. leprae*.	Viability of released bacteria not assessed. No comparable experiments with patients with heavy infection involving the oral cavity.

HH: household

Supplementary Table 2. Peer-reviewed studies focussing on *M. leprae* transmission through direct inoculation; listed by study design and year of publication with more rigorous designs and more recent studies listed first.

Author; Year	Title	Study Site	Study Design	Sample Size	Main Findings	Quality Assessment
Lieber, Lieber; 1987[53]	Social and demographic aspects of a leprosy epidemic on a Polynesian atoll: implications of pattern	Kapingama-rangi Atoll, Micronesia	Retrospective cohort	136 cases	Transmission might be through floor and sleeping mats, the surface fibre of which can puncture the skin. Further found that *M. leprae* transmission appears to depend on patterns of personal mobility (varied by gender and age) and demography.	No controls, study is observational and speculative.
Job, Harris, Allen, Hastings; 1986[47]	Thorns in armadillo ears and noses and their role in the transmission of leprosy	Louisiana, USA	Cross sectional	Ears from 494 wild armadillos and noses of 224 armadillos	10/494 animals had lepromatous granuloma. 23% and 37% had thorns in the ears and nose, respectively. In one animal, there was evidence to suggest that *M. leprae* entered the tissue through thorn pricks, i.e. had only acid-fast bacteria in the nose at the site of the thorn and none in the ears.	Mycobacteria identified microscopically, could be *M. leprae* or other mycobacteria (authors state that using their staining for acid-fast bacteria they can differentiate between *M. leprae* and other mycobacteria). Not a true cross-sectional study but chance selection (road-kill).
Cleve, Pruitt; 1953[52]	Alopecia leprotica - its relationship to transmission of leprosy	Japan, Korea, Formosa (Taiwan), Non-Buddhist countries	Cross sectional (case control)	Buddhist: 1358 Controls: 12585	The prevalence of alopecia leprotica was 35·3% in Buddhist countries and 0.3% in the control cohort from non-Buddhist countries (Mexico, Venezuela, Philippines, Sumatra, Egypt, Palestine, Norway, South Africa, Argentina, USA). Since Buddhists shave the scalp of newborns, a link with this practice is postulated.	Cases and controls were selected based on the country of origin. No evidence that the cases had undergone scalp shaving is available, and no data on scalp shaving in controls is available.

Supplementary Table 2. *continued*

Author; Year	Title	Study Site	Study Design	Sample Size	Main Findings	Quality Assessment
Ghorpade; 2002[44]	Inoculation (tattoo) leprosy: a report of 31 cases	Chhattisgarh, India	Case series	31 cases	Description of 31 patients who developed leprosy 10–20 years after getting a tattoo from a roadside tattoo artist. 25 of the patients had lesions only at the site of the tattoo and 29 patients developed PB leprosy.	Patients are from a leprosy endemic area, but the fact that the diseases started at the site of the tattoo is a strong indication that the tattooing was instrumental in transmission.
Ghorpade; 2013[46]	Post traumatic borderline tuberculoid leprosy over knee in an Indian male	India	Case report	1 case	Leprosy lesion developed at a site with a history of traumatic injury (fell while playing football) after 2 years. Loss of sensation and histological findings suggestive of leprosy with no other symptoms or acid fast bacilli being reported.	No information on contact history with leprosy cases. Clinical presentation not very clear with diagnosis based on histology.
Ghorpade; 2009[45]	Post-traumatic inoculation tuberculoid leprosy after injury with a glass bangle	India	Case report	1 case	Indian woman who developed leprosy after about 2 years at the site of an injury obtained from her glass bangle.	Diagnosis by clinical evaluation, histopathology and based on the treatment response.
Sharma, Bhardwaj, Kar; 2009[49]	Inoculation leprosy and HIV co-infection: a rare case with nerve involvement preceding development of skin patch and type 1 reaction as immune reconstitution syndrome following antiretroviral therapy.	India	Case report	1 case	Leprosy developed close to site of local trauma (sharp wooden object) in HIV positive patient after an incubation period of 13–14 years.	Leprosy lesion not exactly at site of trauma but at site connected with a thickened cutaneous nerve.
Singh; 2009[51]	Tattoos and paucibacillary leprosy	Jharkhand, India	Case report	1 case	Patient developed leprosy at site of tattoo and other locations (first lesion at site of tattoo) after an incubation period of approximately 40 years	Diagnosis on clinical grounds. Very long incubation period (recall bias).

Supplementary Table 2. *continued*

Author; Year	Title	Study Site	Study Design	Sample Size	Main Findings	Quality Assessment
Brandsma *et al.*; 2005[43]	Leprosy acquired by inoculation from a knee injury.	Ethiopia	Case report	1 case	Dutch girl living in Ethiopia developed leprosy at the site of a skin injury she obtained while playing at school. Wound was originally dressed at a leprosy hospital. Incubation period was 4 years and infection appeared to be localized to the site of the scar. Infection was confirmed clinically and by laboratory examination.	Single case with good evidence that *M. leprae* was localized to the site of skin injury. However, the girl had multiple exposures to leprosy: father previously diagnosed with subclinical leprosy with enlarged nerves and she lived at the All Africa Leprosy, Tuberculosis and Rehabilitation Training (ALERT) Centre in Ethiopia.
Singh, Tutakne, Tiwari, Dutta; 1985[50]	Inoculation leprosy developing after tattooing - a case report	Maharashtra State, India	Case report	1 case	Patch with loss of sensation and histology suggestive of leprosy (no bacteria found) at site of tattoo after an incubation period of 2 years. Patient was also tattooed at a different location on his body at the same occasion with the same needle but leprosy did not develop at that site.	No bacteriological evidence. No information on contact to leprosy patients.
Marchoux; 1934[48]	Un cas d'inoculation accidentelle du bacille de Hansen en pays non lepreux	Paris, France	Case report	1 case	Accidental inoculation of *M. leprae* by medical professional using a needle. 10 year incubation period.	Good evidence that patient was infected by accidental needle prick as symptoms were focussed on site of prick.

Supplementary Table 3. Peer-reviewed studies focussing on *M. leprae* transmission from zoonotic or environmental reservoirs, and by insects; listed by study design and year of publication with more rigorous designs and more recent studies listed first.

Author; Year	Title	Study Site	Study Design	Sample Size	Main Findings	Quality Assessment
Zoonotic reservoir and transmission						
Clark *et al.*; 2008[63]	Case-control study of armadillo contact and Hansen's disease	Texas, USA	Retrospective case control	28 patients and 59 controls	Animal exposure (cleaning rabbits; eating armadillos) and having lived in Mexico were significantly ($p < 0{\cdot}05$) associated with leprosy. Having lived in Mexico was the most important risk factor (possible contact with uncharacterized, environmental reservoir).	Cleaning rabbits and living in Mexico may be confounders for unidentified environmental risk factors. Controls (suffering from TB infection) not matched.
Deps *et al.*; 2008[64]	Contact with armadillos increases the risk of leprosy in Brazil: A case control study	Southern Brazil	Retrospective case control	506 patients and 594 controls	Direct exposure to armadillos was found to be a risk factor (roughly doubling the risk; $p < 0{\cdot}001$) for leprosy.	Unmatched controls with other chronic diseases. No controlling for place of residence. Controls not asked about contact with leprosy cases.
Deps *et al.*; 2004[65]	Epidemiological features of the leprosy transmission in relation to armadillo exposure	Espírito Santo State, Brazil	Retrospective case control	136 patients and 173 controls	Armadillo meat consumption identified as possible source of *M. leprae* infection (90·4% of patients versus 15% of controls had eaten armadillo meat before the diagnosis). Armadillo contact might be particularly important for those who did not have contact to other leprosy patients (96·1% of them reported having eaten armadillo meat).	Controls are not matched. No statistical analysis, high chance of confounding.
Filice, Greenberg, Fraser; 1977[66]	Lack of observed association between armadillo contact and leprosy in humans	Louisiana, USA	Retrospective case control	19 patients and 19 controls	No difference in the nature and frequency of armadillo contact between patients and controls was found.	Age and gender matched controls. Excluded patients that had extended contact with other leprosy patients.

Supplementary Table 3. *continued*

Author; Year	Title	Study Site	Study Design	Sample Size	Main Findings	Quality Assessment
						All cases developed leprosy before 1975 and some as far back as 1941 (recall error).
Truman *et al.*; 2011[72]	Probable zoonotic leprosy in the southern United States	Southern USA	Cross sectional	*M. leprae* from 33 armadillos, 50 humans from Louisiana, 64 humans from Venezuela, and 4 reference strains	Identified a unique and highly distinctive SNP-VNTR pattern which is present in most armadillos (28 of 33) and most of the patients (25 of 39) who had a history of residence in areas where exposure to armadillo-borne *M. leprae* is possible. Lack of diversity of *M. leprae* in the armadillos suggests that interspecies transfer of *M. leprae* is uncommon and inefficient and happened recently.	Provide solid evidence that certain patients in the southern USA are infected with the same strain of *M. leprae* which also occurs in naturally infected wild armadillos in the same area. No causality for the link between human and armadillo cases.
Barboza Pedrini *et al.*; 2010[59]	Search for *Mycobacterium leprae* in wild mammals	São Paulo and Mato Grosso do Sul, Brazil	Cross sectional	54 animals	No naturally infected armadillos were found.	Sample size is small and sampling not random (road kill).
Schmitt *et al.*; 2010[71]	Armadillo meat intake was not associated with leprosy in a case control study, Curitiba (Brazil)	Paraná State of Brazil	Cross sectional (case control)	121 patients and 242 controls	The frequency of armadillo meat intake (used as a proxy for other forms of direct armadillo contact) did not vary between patients and age and gender-matched controls after adjusting for demographic and socioeconomic covariates. Also no association when analysing only the cases with no known contact to leprosy	High-quality case control study, but cases not matched for hometown and socioeconomic status. No evidence for infected armadillos in study area presented.

Supplementary Table 3. *continued*

Author; Year	Title	Study Site	Study Design	Sample Size	Main Findings	Quality Assessment
					patients. Differences observed between patients and controls included: hometown population size, family income, and contact with leprosy patients and access to treated water. Found that previous leprosy contact and socioeconomic indicators (poverty and possibly poor sanitation, nutrition and health care) were related to leprosy.	
Cardona-Castro *et al.*; 2009[62]	Detection of *Mycobacterium leprae* DNA in nine-banded armadillos (*Dasypus novemcinctus*) from the Andean region of Colombia	Colombia	Cross sectional	22 armadillos	41% of the armadillos were positive for *M. leprae* by PCR. *M. leprae* sequences were all identical.	No evidence that armadillos had clinical leprosy and that they carried viable bacteria.
Bruce *et al.*; 2000[61]	Armadillo exposure and Hansen's disease: An epidemiologic survey in southern Texas	Texas, USA	Cross sectional	101 patients	71% of non-Asian patients reported direct or indirect armadillo contact (none of the Asian patients reported such contact). Some non-Asian patients had very extensive contact with armadillos and some of them reported leprosy starting at site of injury sustained during direct exposure to armadillos. Conclude that direct transmission of *M. leprae* from armadillo is likely in non-Asians and that the Asian patients were infected in their respective countries of origin.	No controls included. 10 of the 69 non-Asian patients also had contact with other leprosy patients. Some Asian patients had been diagnosed already before coming to the USA and are therefore not really suitable as "controls".

Supplementary Table 3. *continued*

Author; Year	Title	Study Site	Study Design	Sample Size	Main Findings	Quality Assessment
Quesada-Pascual *et al.*; 1999[70]	Does leprosy in Mexico occur as a zoonosis between wild armadillos (*Dasypus novemcinctus*)?	Mexico	Cross sectional	134 armadillos	Acid fast bacilli were not detected in secretions or tissue imprints of any of the tested armadillos.	Method for the detection of *M. leprae* infection in the armadillos has quite a low sensitivity (and specific) and infections could have been missed.
Blake *et al.*; 1989[60]	Earthworms near leprosy patients' homes are negative for acid-fast bacilli by fite stain, providing no link between leprous armadillos (*Dasypus novemcinctus*) and human leprosy	Louisiana, USA	Cross sectional	38 worms	None of the tested earthworms were positive for acid fast bacilli.	Small sample size.
Hagstad; 1983[67]	Leprosy in sub-human primates: potential risk for transfer of *M. leprae* to humans	India	Cross sectional	26 owned monkeys	Despite a prevalence of 98·6/1000 among the humans in contact with the monkeys, none of the monkeys had any evidence for a current infection with *M. leprae* (6 ear lobe smears of monkeys with known contact with leprosy patients, 26 clinical examinations of moneys).	Limited number of monkeys examined; risk of missing subclinical infections and infections with negative skin smears.
Lumpkin, Cox, Wolf; 1983[69]	Leprosy in five armadillo handlers	Texas, USA	Case series	5 patients	Report of five patients with extensive and chronic armadillo contact and no other known risk factor (including no contact with leprosy patients). Four of the patients had positive acid fast bacilli stains and three of them developed lepromatous leprosy. Contact with armadillos was very close including getting cuts and being bitten. All patients had clinical lesions on the hands.	Case series with no controls.

Supplementary Table 3. *continued*

Author; Year	Title	Study Site	Study Design	Sample Size	Main Findings	Quality Assessment
Lane *et al.*; 2006[68]	Borderline tuberculoid leprosy in a woman from the state of Georgia with armadillo exposure	Georgia, USA	Case report	1 patient	Leprosy case with no known contact with other patients but who worked for many years in a garden where armadillos burrowed or were buried. Histological case confirmation with detection of acid fast bacilli. Authors speculate about inoculation from the soil into the skin through trauma or by inhalation.	Single case. Indirect evidence of zoonosis.
Environmental reservoir and transmission						
Turankar *et al.*; 2012[79]	Dynamics of *Mycobacterium leprae* transmission in environmental context: deciphering the role of environment as a potential reservoir	West Bengal, India	Cross sectional	207 soil samples	In 34% of soil samples DNA was detected and in 39% of them (14% of total) *M. leprae* 16S rRNA was also detected. In 18% of the samples collected near washing and bathing places RNA was detected and in 7% of samples collected near houses of leprosy patients RNA was found. SNP typing of selected soil samples showed that sequences were of the same genotype as the *M. leprae* isolated from the local patient.	Detected bacilli not tested for viability (e.g. by mouse footpad inoculation).
Lavania *et al.*; 2008[76]	Detection of viable *Mycobacterium leprae* in soil samples: insights into possible sources of transmission of leprosy	Uttar Pradesh, India	Cross sectional	40 soil samples each from patient and non-patient areas	In 55% of the soil samples collected in patient areas, 16S rRNA was detected versus in 15% from no-patient areas. Also the mean copy numbers of the *M. leprae* target	Limited number of samples. Detection of DNA and RNA is no absolute proof of viability.

Supplementary Table 3. *continued*

Author; Year	Title	Study Site	Study Design	Sample Size	Main Findings	Quality Assessment
					sequences in the samples from the patient area where significantly higher compared to the samples from non-patient areas. Conclude that *M. leprae* can be found in the soil which could be the source of continuous transmission.	
Lavania *et al.*; 2006[77]	Detection of *Mycobacterium leprae* DNA from soil samples by PCR targeting RLEP sequences	Uttar Pradesh, India	Cross sectional	18 soil samples	In 33·3% of soil samples collected from areas inhabited by leprosy cases, *M. leprae* DNA was detected by conventional PCR.	DNA detection: risk of cross-contamination with conventional PCR, unclear specificity of target sequence with respect to other environmental mycobacteria, no information about the viability of the detected mycobacteria. No samples from non-leprosy endemic areas.
Matsuoka *et al.*; 1999[78]	*Mycobacterium leprae* DNA in daily using water as a possible source of leprosy infection	North Maluku province, Indonesia	Cross sectional	44 water sources	In 48% (21/44) of the water sources tested, *M. leprae* DNA was detected by PCR. The prevalence of leprosy was higher among the people using the positive water sources for bathing and washing compared to those using the negative ones (12% versus 4%; p-value < 0.001). No such difference was detected when looking at the water source for drinking (water was reported to always be boiled to avoid gastrointestinal	No assessment of viability of the *M. leprae* bacilli which were detected by PCR. No causality can be established (not clear whether leprosy patients contaminated the water or became infected by using this water).

Supplementary Table 3. *continued*

Author; Year	Title	Study Site	Study Design	Sample Size	Main Findings	Quality Assessment
					infection). Conclude that water could be a reservoir and source of infection with *M. leprae*.	
Desikan, Sreevatsa; 1995[74]	Extended studies on the viability of *Mycobact-erium leprae* outside the human body	Laboratory	Laboratory	NA	After drying *M. leprae* was viable (as assessed by inoculation into mouse footpad) for up to 5 months; on wet soil for 46 days; in saline at room temperature for 60 days; with three hours of direct sun light every day for 7 days; at 4°C for 60 days; at −70°C for 28 days. Bacteria were rapidly killed if exposed to antiseptics. Humidity during drying appears to play a role: bacteria dried at 72-80% humidity survived for >=28 days whereas those dried at 44–28% humidity survived <=14 days.	Environmental conditions not controlled for.
Harris *et al.*; 1990[75]	Viability of *Mycobacterium leprae* in soil, water and degenerating armadillo tissue and its significance	Laboratory	Laboratory	NA	*M. leprae* can survive (as assessed by the mouse footpad model) exposure to soil and water for up to three days or up to 21 days in sterile tubes. Exposure to light resulted in a dramatic decrease in the viability of the bacilli.	No critical issues.

Supplementary Table 3. *continued*

Author; Year	Title	Study Site	Study Design	Sample Size	Main Findings	Quality Assessment
Desikan; 1977[73]	Viability of *Mycobacterium leprae* outside the human body	Laboratory	Laboratory	NA	*M. leprae* remained infectious (as assessed by inoculation into mouse footpad) for at least 9 days (as a dried suspension kept at 24–39°C).	Experiment only ran for 9 days.
Insects and transmission						
Honeij, Parker; 1914[81]	Leprosy: flies in relation to the transmission of the disease: (a preliminary note)	Unknown	Laboratory cross sectional	12 flies	Of the 12 flies captured in the rooms of leprosy patients only two showed acid fast bacilli in excreta. The excreta of six flies allowed to feed on lesions of patients were negative. Excreta of flies allowed to feed on pustules were found to be frequently positive for acid fast bacilli.	The number of samples collected from the proximity of patients was limited and acid fast bacilli were only identified by microscopy.
Saha *et al.*; 1985[83]	Viability of *Mycobacterium leprae* within the gut of *Aedes aegypti* after they feed on multibacillary lepromatous patients - a study by fluorescent and Electron microscopes	Laboratory	Laboratory	NA	Acid fast bacilli in the gut of mosquitoes allowed to feed on lepromatous patients became non-viable after 4 days of blood meals; some multiplication of viable bacilli was detected during the early days. Conclude that the possibility of *M. leprae* transmission by mosquito bites to humans seams remote because of the short viable time of the bacilli and the quick fragmentation and elimination of the ingested bacteria from the gut. Furthermore, the study	Viability was only assessed by microscopy and methods used did not clearly differentiate between viable bacteria and dead bacilli. Increase in bacteria numbers is slight and not very strong evidence for actual multiplication. Small numbers of mosquitos examined.

Supplementary Table 3. *continued*

Author; Year	Title	Study Site	Study Design	Sample Size	Main Findings	Quality Assessment
					concludes that replication in mosquitos is unlikely since replication time of *M. leprae* is long compared to the lifespan of the insects.	
Geater; 1975[80]	The fly as potential vector in the transmission of leprosy	Laboratory	Laboratory	NA	*Musca* (housefly), *Calliphora* (bluebottle) and *Stomoxys* (biting stable fly) were able to take up large numbers of acid fast bacilli from muscus and skin lesions of lepromatous patients (bacteria found in gut). *Musca* and *Calliphora* could deposit bacteria at a distant surface. *Stomoxys* mouthparts were contaminated (possibility for direct inoculation).	Bacilli just identified microscopically (controls were all acid fast bacilli free).
McFadzean, Macdonald; 1961[82]	An investigation of the possible role of mosquitoes and bed bugs in the transmission of leprosy	Laboratory	Laboratory	NA	Found no evidence that mosquitoes or bed bugs could take up *M. leprae* from lepromatous patients and introduce them into the skin of another individual.	Inoculation of *M. leprae* was evaluated by biopsies, which would likely not detect small numbers of introduced bacilli.

Supplementary Table 4. Peer-reviewed studies focusing on socio-economic risk factors for *M. leprae* transmission or no specific transmission hypothesis; listed by study design and year of publication with more rigorous designs and more recent studies listed first.

Author; Year	Title	Study Site	Study Design	Sample Size	Main Findings	Quality Assessment
Ponnighaus *et al.*; 1994[110]	Extended schooling and good housing conditions are associated with reduced risk of leprosy in rural Malawi	Karonga District, Malawi	Prospective cohort	71,499 individuals; 358 incident cases	Rate ratio decreased markedly with increasing duration of schooling. Leprosy incidence rate ratios increased as the standard of housing fell.	Self-reporting of schooling.
West *et al.*; 1988[112]	Leprosy in six isolated residents of northern Louisiana. Time-clustered cases in an essentially non-endemic area	Northern Louisiana, USA	Retrospective cohort	6 cases	No risk factors for infection could be identified. Considered were contact, travel, residence and exposure (e.g. to armadillos) risk factors.	Small sample size. No controls.
Feenstra *et al.*; 2011[108]	Recent food shortage is associated with leprosy disease in Bangladesh: a case-control study	Rangpur Division, Bangladesh	Cross sectional (case control)	90 patients; 199 controls	Recent period of food shortage (reduced number of meals or reduced intake of foods other than rice) and not poverty *per se* or food shortage at any time in life was identified as the only socioeconomic factor associated with the clinical manifestation of leprosy (OR 1.79). Found a non-significant trend of decreasing leprosy prevalence with increasing socio-economic status. Speculate that lack of nutrients leads to changes in immunity allowing *M. leprae* to cause clinical disease.	Multiple risks of bias: e.g. self-reported food shortage. Study excluded cases that reported changes in economic status or living conditions due to the disease.
Kerr-Pontes *et al.*; 2006[109]	Socioeconomic, environmental, and behavioural risk factors for leprosy in Northeast Brazil: results of a case-control study	Ceara State, Brazil	Cross sectional	226 cases; 857 controls	Leprosy significantly associated with low educational level, ever having experienced food shortage, bathing weekly in open waters 10 years previously and a low	Potential of recall bias as exposure to risk factors dated 10 years ago.

Supplementary Table 4. *continued*

Author; Year	Title	Study Site	Study Design	Sample Size	Main Findings	Quality Assessment
					frequency of changing bed linens. No environmental or demographic variables were associated with an increased risk of leprosy. Presence of a BCG vaccination scar was protective.	
de Andrade, Sabroza, de Araujo; 1994[107]	Factors associated with household and family in leprosy transmission in Rio de Janeiro, Brazil	Rio de Janeiro State, Brazil	Cross sectional	Cases: 20% of HH with a case; controls per case: 4 neighbor houses, 5 houses from a sector without any cases	The following household characteristics were associated with leprosy: less than 2 rooms, non-permanent building material, dirt floor, not having a water source inside the house. Low educational level also increased leprosy risk.	Unit of analysis: Household Unclear if controls are matched.
Xavier Silva *et al.*; 2010[111]	Hansen's disease, social conditions, and deforestation in the Brazilian Amazon	Brazilian Amazon	Ecological	All cases reported in 2006	The new case detection rate was positively correlated with the total deforested area and the percent of households with rudimentary septic tanks, and inversely with the human development index.	No actual reference to the source or route of transmission.

HH: household