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Transmission features of Mycobacterium leprae throughout the decline of leprosy incidence: A systematic review

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***Abstract*---**Background: Mycobacterium leprae causes leprosy, an infectious disease. As the incidence of the disease declines, the characteristics of new cases begin to diverge from those seen in highly endemic locations, offering potentially valuable insights into ongoing transmission sources. We wanted to see if undiagnosed and untreated new leprosy cases in the community drive transmission more than incompletely treated or relapsing cases. Principle findings/methodology: In January of 2020, a literature search of major electronic databases yielded 134 articles out of 4318 total entries found (PROSPERO ID: CRD42020178923). We presented quantitative data from leprosy case records, along with supporting evidence, to describe the drop in incidence in a variety of settings. The major measures used by countries that achieved a significant reduction in incidence included BCG vaccination, active case detection, adherence to combination therapy, and continuous surveillance after treatment. In a study of 3950 leprosy case data from 22 low-endemic nations, 48.3% were thought to be imported, beginning from transmission outside the country. With 122 cases of suspected relapse from earlier leprosy treatment, the majority of cases (64.4%) were multibacillary and frequently verified with skin biopsy. Conclusions/Significance: In recent decades, various successful leprosy control programmes have been launched, which have resulted in a significant decrease in incidence, in conjunction with

socioeconomic progress. The majority of the cases documented in these situations were multibacillary, and there were numerous cases of suspected recurrence. Despite these findings, there was little evidence that these instances resulted in an increase in new secondary cases, implying that they are not a major source of human-to-human transmission.

***Keywords*---**transmission, mycobacterium, leprae, leprosy, incidence.

Introduction

Leprosy is a contagious illness that continues to be endemic in many parts of the world, despite the fact that Brazil, India, and Indonesia account for over 80% of new cases worldwide [1]. Mycobacterium leprae and (less commonly) Mycobacterium lepromatosis produce a persistent infectious condition that affects infected people's skin and peripheral nerves [2, 3]. Delays in leprosy diagnosis and treatment can result in a variety of clinical symptoms, including irreversible deformity and disability, as well as stigma. Although there is evidence of an elevated risk of human-to-human transmission for those living in close proximity to untreated leprosy patients, most likely conveyed through infectious aerosols [4], the transmission mechanisms of M. leprae are not entirely understood. In addition, the nine-banded armadillo has been identified as a natural host and reservoir of M. leprae in the Americas, as well as a potential non-human transmission source.

Although the bacterium has recently been discovered in red squirrels in the British Isles, no human leprosy cases have been reported in their vicinity in the last century [5, 6]. In addition, wild chimps have lately been found to have leprosy, harbouring a type of M. leprae not found in humans [7]. The prevalence of diagnosed leprosy patients has decreased by 95% since the advent of multidrug therapy (MDT) in the 1980s. As a result of this drop, the World Health Organization (WHO) declared leprosy to be a public health hazard, with a prevalence of less than one leprosy patient per 10,000 people [8]. However, meeting this goal was mostly due to a reduction in treatment time after the implementation of MDT, as well as the cleaning of case registries, and did not coincide with a decrease in the number of new cases diagnosed. This emphasises the drawbacks of using prevalence as a leprosy epidemiological indicator [9]. In fact, following the year 2000, the number of new leprosy cases discovered worldwide began to decline.

The implementation of various control methods, such as national registries, contact tracing, BCG vaccination, and increased MDT coverage, has resulted in a significant decrease in leprosy prevalence in a number of nations. Age, sex, categorization, rate of leprosy in children, and impairment grade are all common factors that are reported in leprosy epidemiological patterns [10]. The profile of new cases has been demonstrated to shift towards older persons and an increased proportion of multibacillary (MB) cases as M. leprae transmission falls in a given population. This has been reported earlier in China, Norway, and Portugal [11–13]. Contacts of individuals with a high bacillary burden, such as

MB cases or PB cases with multiple lesions, have been shown to be at higher risk of contracting M. leprae infection in endemic areas [14–16].

We conducted a systematic literature review based on recommendations from The InternationalFederation of Anti-Leprosy Associations (ILEP) Technical Commission to determine whether M. leprae transmission is primarily driven by undiagnosed and untreated new leprosy cases in the community, or by incompletely treated or relapsing cases. This has been a topic of debate among leprosy researchers, and it has significant policy implications for leprosy control. Our work has three objectives: first, to assess case features as leprosy incidence declines; second, to identify possible remaining mechanisms of transmission of cases in low endemic areas; and third, to link these findings to the various leprosy control methods in place.

Search techniques

In January 2020, we did a systematic literature search of electronic databases, focusing on case studies, case series, and epidemiological records from countries where leprosy incidence has significantly decreased as a result of control measures. Below is a list of the databases and search phrases utilised (Table 1). We used the Preferred Reporting Questions for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for our search strategy, which are an evidence-based minimal set of items for systematic reviews and meta-analyses [17]. The PRISMA flowchart shows the search approach employed (Fig 1). Supplementary data includes the PRISMA checklist that goes with the PRISMA flow diagram: S1 PRISMA Checklist.

Table 1
Systematic review database and search strategy

Database	Search string
Embase	('leprosy'/exp OR 'Mycobacterium leprae'/de OR 'leprosy control'/de OR (lepros$^{\omega}$ OR Hansen OR lepra$^{\omega}$ OR leper$^{\omega}$):ab,ti,kw) AND ('case report'/de OR 'case study'/de OR 'case finding'/de OR (((case$^{\omega}$) NEXT/1 (report$^{\omega}$ OR stud$^{\omega}$ OR find$^{\omega}$ OR series)) OR ((review$^{\omega}$) NEAR/3 (literature$^{\omega}$))):ab, ti,kw) NOT ((animal/exp OR animal$^{\omega}$:de OR nonhuman/de) NOT ('human'/exp)) AND ([ENGLISH]/lim)
Medline	(exp "Leprosy"/ OR "Mycobacterium leprae"/ OR (lepros$^{\omega}$ OR Hansen OR lepra$^{\omega}$ OR leper$^{\omega}$).ab,ti, kf.) AND ("Case Reports"/ OR (((case$^{\omega}$) ADJ (report$^{\omega}$ OR stud$^{\omega}$ OR find$^{\omega}$ OR series)) OR ((review$^{\omega}$) ADJ3 (literature$^{\omega}$))).ab,ti,kf.) NOT (exp animals/ NOT humans/) AND (english).lg

Web-of-science	TS = (((lepros$^{\omega}$ OR Hansen OR lepra$^{\omega}$ OR leper$^{\omega}$)) AND ((((case$^{\omega}$) NEAR/1 (report$^{\omega}$ OR stud$^{\omega}$ OR find$^{\omega}$ OR series)) OR ((review$^{\omega}$) NEAR/2 (literature$^{\omega}$)))) NOT ((animal$^{\omega}$ OR rat OR rats OR mouse OR mice OR murine OR dog OR dogs OR canine OR cat OR cats OR feline OR rabbit OR cow OR cows OR bovine OR rodent$^{\omega}$ OR sheep OR ovine OR pig OR swine OR porcine OR veterinar$^{\omega}$ OR chick$^{\omega}$ OR zebrafish$^{\omega}$ OR baboon$^{\omega}$ OR nonhuman$^{\omega}$ OR primate$^{\omega}$ OR cattle$^{\omega}$ OR goose OR geese OR duck OR macaque$^{\omega}$ OR avian$^{\omega}$ OR bird$^{\omega}$ OR fish$^{\omega}$) NOT (human$^{\omega}$ OR patient$^{\omega}$ OR women OR woman OR men OR man))) AND LA = (English)
Cochrane	((lepros$^{\omega}$ OR Hansen OR lepra$^{\omega}$ OR leper$^{\omega}$):ab,ti,kw) AND ((((case$^{\omega}$) NEXT/1 (report$^{\omega}$ OR stud$^{\omega}$ OR find$^{\omega}$ OR series)) OR ((review$^{\omega}$) NEAR/3 (literature$^{\omega}$))):ab,ti,kw)
Google Scholar	Leprosy|leprae|lepra case|cases|review decline|declined|declining

Selection criteria for studies

When choosing documents from the literature search, the following criteria were used: Criteriafor inclusion:

- Individual-level data in case reports or case series
- Studies from countries or regions with less than one new leprosy case per 100,000 people • Epidemiological reports of aggregated data with full case details
- Descriptions of established control measures Criteria for exclusion:
- Studies with insufficient case details
- Studies from countries or regions where more than onenew leprosy case was discovered per 100,000 people
- Studies with data from before and after the decline

We used snowballing (scanning bibliographies for relevant publications) to uncover further studies and literature that had supporting data in addition to pulling data from peer-reviewed research articles found in our search.

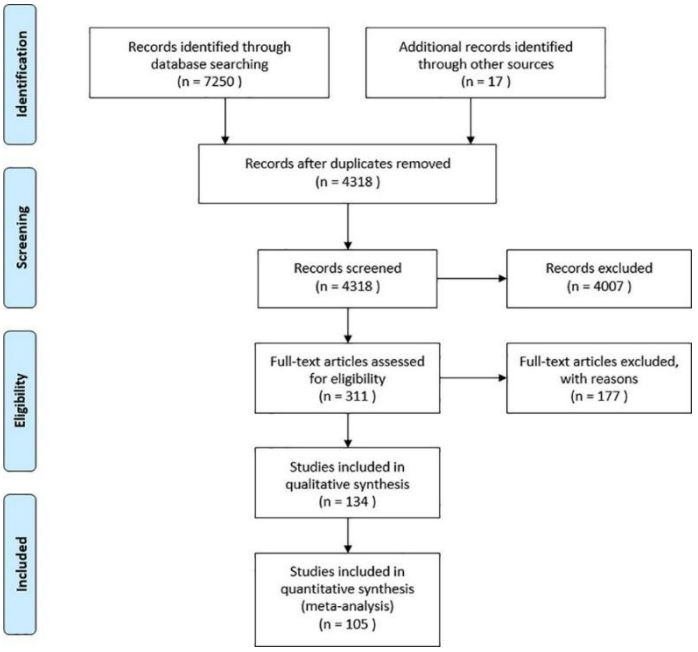

Fig 1. PRISMA flow diagram

Obtaining data

The database search was conducted by one of the authors . All records retrieved were subjectedto a review by two writers. After then, the lists were compared, and a decision was made as to which articles were eligible for full-text reading. The majority of the studies were case reports and series that were aggregated by nation, with epidemiological summaries added when adequate individual level data was available. The study authors, journal, or institutions were not hidden from the writers (supplementary data: S1 List of Peer-reviewed Studies with Case Data). Autochthonous cases were individuals suspected of contracting the disease within the country,and imported cases were those infected outside of the country in another leprosy endemic location. Additional clinical notes, such as details on previous exposure to a known leprosy patient or travel to a highly endemic region, were also collected. The WHO classification system, the Ridley Jopling classification system, or both were used to define leprosy subtypes(Table 2) [18].

Table 2
Diagnosis of leprosy under the WHO and Ridley Jopling classification systems

WHO Classification	Ridley Jopling Classification
Paucibacillary (PB) leprosy: 1 to 5 skin lesions, without demonstrated presence of bacilli in a slit skin smear	Tuberculoid leprosy (TT) Borderline tuberculoid (BT)

Multibacillary (MB) leprosy: Six or more skin lesions; or with nerve involvement (pure neuritis, or any number of skin lesions and neuritis); or with the demonstrated presence of bacilli in a slit skin smear, irrespective of the number of skin lesions	Mid-borderline (BB) Borderline lepromatous (BL) Lepromatous leprosy (LL)

Analysis and presentation of data

Because the relevant variables were gathered from a variety of research with varied data presentation methods, a descriptive analysis was used to summarise the findings acrossmultiple countries. For analysis, individual data were imported into Statistical Package for Social Sciences (SPSS) version 26. Total case count, proportions, and averages were the most used quantitative data display approaches. The study's goal was not to show a link between case factors and trends in case detection because of the data's heterogeneity in terms of geographical location and duration.

Results

Case-specific features

Table 3
Sources of individual leprosy case data from 22 low endemic countries

Country	Data sources	Total cases	Year of diagnosis (range)
Australia	8	11	1999–2017
Canada	3	186	1979–2017
China$^{\omega}$	3	785	1990–2017
Germany	6	8	1994–2016
Iran	2	207	1991–2009
Italy	10	27	1992–2017
Japan	9	20	1990–2017
Libya	1	54	1994–1998
Malta	1	136	1971–2000
Morocco	1	801	2000–2017
Netherlands	1	622	1970–1991
New Zealand	1	38	2004–2013
Oman	1	77	2000–2015
Portugal	1	15	1991–2011
Saudi Arabia	1	242	2003–2012
South Korea	1	24	2009–2013
Spain	7	97	1989–2018
Taiwan (Republic of China)	1	81	2002–2011
Thailand	1	108	1995–2015
United Kingdom	6	11	1977–2014
United States	39	304	1982–2018

Vietnam	1	96	2018
Total	105	3950	1970–2018

Summary. We retrieved data on 3950 leprosy cases from 22 low-endemic countries after conducting a literature search of major electronic sources (Table 3). Each country's year of diagnosis range was different, although they all fell during the time of diminishing leprosy incidence. Data was gathered on a variety of case features from the source papers (Table 4).

Table 4
Overview of case characteristics using combined individual leprosy case data

Characteristic	N	%	Mean
Age (years)	1807	-	46.1
Case detection delay (months)			
China	778	-	31.7
Outside of China	96	-	28.8
Both	874	-	31.4
Sex			
Male	2529	65.2	-
Female	1351	34.8	-
Suspected autochthonous			
No	1329	48.3	-
Yes	1420	51.7	-
Family history			
No	942	81.3	-
Yes	216	18.7	-
Subtype (WHO)			
Paucibacillary (PB)	1379	35.6	-
Multibacillary (MB)	2497	64.4	-
Subtype (Ridley-Jopling)			
Tuberculoid (TT)	341	23.0	-
Borderline Tuberculoid (BT)	294	19.8	-
Mid-Borderline (BB)	114	7.7	-
Borderline Lepromatous (BL)	282	19.0	-
Lepromatous (LL)	433	29.2	-
Indeterminate (IL)	21	1.4	-
Suspected relapse			
No	496	80.3	-
Yes	122	19.7	-

Relapse and treatment

When treatment information was available, the majority of cases (82.2 percent) underwent MDT according to WHO treatment guidelines for PB and MB cases at the time. The remaining cases were treated with a variety of regimens, including DDS monotherapy or ofloxacin and/or minocycline-containing regimens. Alternative regimens were used to treat the cases mentioned in Japan and Malta. Articles from 12 nations described whether a case had undergone no previous leprosy treatment or if a suspected relapse had occurred after previous treatment, which was largely DDS monotherapy, with a total of 122 (19.7%) cases of suspected relapse.

Discussion

We wanted to examine case features during the falling stages of leprosy incidence, identify probable remaining sources of transmission in low endemic areas, and relate these findings to the various leprosy control efforts implemented in this comprehensive review. Along with socioeconomic progress, many of the countries that have seen significant reductions in incidence in recent decades have shared certain key strategies. These included BCG vaccination, active case discovery, MDT adherence, and post-treatment surveillance. Despite the prevalence of chronic cases of probable relapse and a high proportion of multibacillary forms of the disease, we observed that the number of new cases reported remained low. According to the facts, such cases do exist. With less than one new leprosy case discovered per 100,000 population, all nations included in the quantitative component of this study are now deemed low endemic. Many of the new instances that were recorded in these settings came from other parts of the world.

Canada, New Zealand, South Korea, the United States, and much of Europe were particularly affected. Non-autochthonous cases might be difficult to trace since information on previous diagnoses, treatments, and contact with probable transmission sources in their home country is typically lacking. Patients who report travelling or living abroad are classed as non-autochthonous, albeit it is impossible to know with confidence where they contracted their infection. Family history, past contact with a person known to have leprosy, and armadillo exposure in North America were the most commonly reported probable sources of transmission in these low endemic settings. There is evidence that an individual's vulnerability to infection has a hereditary component, most likely due to a failure to control the infection adequately through cell-mediated immunity after exposure [15, 18]. Despite the fact that the specific route of transmission of M. leprae is unknown, continuous contact with someone who has the disease, whether in the same household or in the community, has been shown to increase the risk of infection [10].

This was the first systematic review to look into the evidence and sources of ongoing M. leprae transmission utilising case data from a variety of low-endemic countries and compare them to past control methods. When the dataset was large enough, it allowed us to get insights at the country level while simultaneously presenting features from a range of global contexts. We were able to demonstrate many cases of proven sources of infection after completing a thorough evaluation

of case reports. We discovered challenges in discriminating between endemic and imported instances, as well as matching certain characteristics to one another, most notably between relapse cases and past treatment regimens, as we pulled data from a variety of sources with data presented in different ways.
nstrates the success of many leprosy prevention and control efforts, particularly during periods of socioeconomic progress. However, in order to establish policies in the WHO global priority countries and continue working toward zero leprosy, a deeper understanding of the ongoing sources of transmission is essential. During periods of declining incidence, the majority of cases were multibacillary, with numerous cases of suspected recurrence documented. Despite these findings, there was no evidence that the instances presented here resulted in an increase in new secondary cases, implying that they are not a significant ongoing source of human-to-human transmission.

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