From Michel Lechat's "Méandres" to recent advances in the fight against leprosy

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Foreword

This article is dedicated to Professor Michel Lechat (1927-2014), honorary member of the Royal Academy for Overseas Sciences (Belgium), who devoted a large part of his life to the fight against leprosy. In 1969, Lechat was recognized as a leprosy expert by the WHO and was President of the International Leprosy Association (ILA) for two terms (1978-1988). He has published over 300 scientific articles, including more than 200 on leprosy. His scientific work has covered all aspects of leprosy control, from basic research (Hanks, Chatterjee & Lechat, 1964; Blumberg, Melartin, Lechat & Guinto, 1967) to treatment and prevention (Lechat 1999a; 2001), with a particular focus on the epidemiological and public health aspects of the disease. He was the first to develop an epidemiometric model for leprosy, enabling the potential impact of different control strategies to be simulated and analyzed (Lechat, Misson, J. Y., Vellut, Misson, C. B. & Bouckaert, 1974).

In 2022, the memoirs of Professor Michel Lechat entitled "Méandres" were published by his wife, Edith Dasnoy. In his book, Lechat describes with lucidity his rich experience in the field of leprosy, and the obstacles to be overcome in controlling the disease (Lechat, 2022).

The field of leprosy control has come a long way since Lechat's time. We will discuss several aspects in this article.

Introduction

Leprosy is one of the skin-related neglected tropical diseases (skin NTDs). It is the second most frequent mycobacterial disease worldwide after tuberculosis (TB). The disease affects skin, nerves, eyes and the upper respiratory tract. According to the World Health Organization (WHO), in 2022, a prevalence of 165,459 cases and 174,087 new incident cases were reported worldwide (WHO, 2023a).

The disease is curable. Since 1982, the WHO recommends to use a multidrug therapy (MDT) consisting of a combination of three drugs: dapsone, rifampicin and clofazimine. The use of this polychemotherapy resulted in a dramatic reduction of the prevalence, counted as people on treatment, but not of the incidence, which has been stagnating for over 10 years at around 200,000 new cases a year, indicating that transmission is clearly continuing. This stagnating may be due to several factors, such as delayed diagnosis, loss of expertise and interest in leprosy, and transmission by asymptomatic patients or via animal reservoirs.

The aim of this article is to describe recent advances in the fight against leprosy, and the challenges to be met to reduce transmission and eliminate the disease.

Aetiologic agent

Leprosy is caused by *Mycobacterium leprae* and, to a lesser extent, by *M. lepromatosis*, a recently described species primarily found in patients with diffuse lepromatous leprosy (DLL), a severe form of leprosy. *M. lepromatosis* was first described in 2008, in two Mexican patients who died of DLL (Han *et al*., 2008). Although both species share a lot of features such as an unusual low G+C (Guanine-Cytosine) content (57.8%) compared to other mycobacterial species, and the inability to grow in vitro, comparative analysis of the genomic sequences of *M. leprae* and *M. lepromatosis* has justified the status of *M. lepromatosis* as a new species (Han *et al*., 2008). This new species status has been controversial because, from a clinical and treatment outcome point of view, there is no difference

between leprosy caused by either species. The histopathological features are also identical (Gillis, Scollard & Lockwood, 2011).

M. lepromatosis has been reported from patients from Brazil, Myanmar, and Philippines, three countries endemic for leprosy, and also from countries with a low prevalence of leprosy (Mexico and Malaysia). Co-infections with *M. leprae* are common but infections with *M. lepromatosis* alone have been reported mainly in Mexico. However, to date, the actual prevalence of leprosy attributed to *M. lepromatosis* remains unknown, as only a few articles have been published on patients infected by this new species (Collin *et al*., 2023).

The recent discovery of *M. lepromatosis* in red squirrels reinforces the epidemiological importance of the distinction between the two species in addition to the genetic differences between them (Scollard, 2016).

Diagnosis

Diagnosis of leprosy is primarily clinical (WHO, 2018). Classification of patients is based on the number of skin lesions i.e. one to five lesions for paucibacillary (PB) or more than five skin lesions for multibacillary (MB) patients, presence of nerve involvement and identification of bacilli on slit-skin smear (SSS). The use of laboratory tools remains limited.

The microbiological confirmation may be done using several methods that are described elsewhere (Braet, Rosa, Spencer & Avanzi, 2023). The most widely used laboratory confirmation test for identifying leprosy bacilli in tissue involves microscopy on SSS, on biopsy of a skin lesion, and occasionally on a nerve biopsy. Ziehl-Neelsen staining is the conventional staining method for acid-fast bacilli (AFB) detected in smears, and Fite-Faraco staining, which is used for the detection of AFB in biopsies. Following staining, the rod-shaped bacilli typically appear uniformly pink (i.e. solid staining), and may be found individually or grouped in clusters known as globi, which are indicative of *M. leprae* infection. The bacteriological index is determined after staining using a semi-logarithmic scale ranging from 1+ to 6+. The morphological index reports the proportion of bacilli showing solid staining (viable bacilli), versus non-solid or beaded staining, indicative of non-viable bacilli (Rees, 1969). The repetitive element RLEP qPCR (quantitative polymerase chain reaction) is the most used molecular confirmation to detect *M. leprae* due to its high specificity and sensitivity, with the RLEP repetitive element occurring 37 times in the *M. leprae* genome (Braet *et al*., 2018). RLEP qPCR tends to be positive on biopsies from all microscopy positive MB patients, and around 65% of microscopy negative patients (whether clinically MB or PB) (Braet *et al*., 2021). For detecting *M. lepromatosis*, the repetitive element RLPM qPCR is commonly employed, also known for its high specificity for *M. lepromatosis* (Braet *et al*, 2023). Indeed, patients infected by *M. lepromatosis* are negative for RLEP qPCR.

Diagnosis of leprosy infection and disease

- **Detection of subclinical infection**

As Lechat has pointed out, greater attention should be paid to subclinical infections, as infected individuals could be a source of contamination and transmit the disease, and thus be partly responsible for the stagnation in incidence (Lechat, 2000). Moreover, patients with early, barely symptomatic multibacillary leprosy may have the highest number of viable bacilli in their nasal secretions, as was remarked half a century ago (Davey & Rees, 1974).

Subclinical infections are likely characterized by robust cell-mediated immunity that combats the disease, suggesting a need to focus on markers from the cell-mediated immune system for detection. In patients with PB leprosy (predominantly cell mediated immune response), ApoA1 has emerged as a significant biomarker. Additionally, levels of ApoA1 and S100A12 may differentiate between highly exposed contacts and endemic controls, potentially identifying *M. leprae*-infected individuals, although unable to distinguish between infection and disease (van Hooij *et al*., 2019). The aim is to

integrate humoral markers (αPGL-I IgM, IP-10, and CRP) and cell-mediated markers into a single minimally invasive test capable of detecting both PB and MB patients. All these markers can be detected in unstimulated blood serum/ fingerstick blood (van Hooij *et al*., 2021; Braet *et al.*, 2021).

- **Diagnosis of disease**

The need for improved microbiological confirmation of leprosy patients, spanning the entire spectrum of the disease, is crucial for effective disease control and management (Steinmann, Reed, Mirza, Hollingsworth & Richardus, 2017). Current diagnostic methods, such as SSS microscopy, often fail to detect PB patients, prompting the exploration of alternative techniques like Droplet Digital PCR, which is shown to be more sensitive than qPCR (Cheng *et al*., 2019). Additionally, the use of biomarkers (also for detection of subclinical infection) shows promise in identifying patients across disease stages (van Hooij *et al.*, 2021). Furthermore, advancements in portable DNA extraction and qPCR systems, like the one developed by Biomeme offer potential solutions for sensitive molecular confirmation in resource-limited settings (Frimpong *et al*., 2023). Future research should focus on developing better diagnostic tools, particularly suited for endemic regions, to enhance early detection, and thus control transmission effectively.

There is currently growing interest in the use of teledermatology and artificial intelligence (AI) for the diagnosis of skin NTDs. There are several reasons for this, including difficulty of accessing healthcare in remote or unstable areas, waning leprosy expertise of health care workers, shortage of dermatologists in some low-income countries, and the possibility of obtaining a more accurate clinical diagnosis. In October 2023, WHO launched new version of the WHO Skin NTDs mobile application “to furnish healthcare professionals with practical information for a particular disease, encompassing its clinical characteristics, treatment protocols, and geographic prevalence”. Commercially developed products such as the “BellePro™ app” also offer a probability of different skin conditions which can alert healthcare workers to the possibility of leprosy.

AI techniques have been used for the diagnosis of leprosy (Barbieri *et al*., 2022). A recent systematic review of the literature on AI as diagnostic aid, selected 29 studies, some being published in proceedings of conferences. They concern different skin diseases, including leprosy. According to the authors, the quality of most articles is low in terms of transparency, data sharing, and responsibility. They conclude that research in this field is still in its infancy and therefore not “mature enough to be transformed into clinical practice" (Fernandes *et al*., 2024). Apart from certain disciplines such as radiology or oncology, the use of AI in other fields requires additional studies to overcome its limitations, as Unger (2023) recently pointed out, and before we can reimagine the elimination of leprosy with the help of AI (Barbieri *et al*., 2022).

Treatment

WHO recommends MDT with dapsone, rifampicin and clofazimine during six months for PB patients and twelve months for MB patients (WHO, 2018). However, the risk of severe side effects (e.g. dapsone hypersensitivity) and the emergence of drug resistance underscore the need for alternative treatment strategies.

New drugs and regimens

Recent research has explored the potential of newer antimycobacterial drugs to enhance both therapeutic and prophylactic approaches to leprosy. Bedaquiline, originally developed for *M. tuberculosis*, has demonstrated efficacy in treating MB leprosy (Barreto *et al.*, 2024) and has also been incorporated into a PEP regimen (de Jong *et al.*, 2024). Another promising candidate, telacebec, has shown activity against *M. leprae* in mice, and could further be evaluated in human clinical trials to determine its potential role in leprosy treatment (Lahiri *et al*., 2022).

Drug resistance

Globally, dapsone resistance is found in 6.8% of relapsed leprosy patients and in 4% of new cases, while rifampicin resistance is present in 5.1% of relapse cases and 2.0% of new cases (Cambau *et al.,* 2018). Resistance in countries like Brazil is notably high, potentially by patients selectively discontinuing treatment due to skin discoloration caused by clofazimine, which intensifies stigma surrounding the disease (Nogueira *et al*., 2024). Ofloxacin resistance is comparable to rifampicin and dapsone resistance, occurring in 1.3% of cases, mainly in Benin, India, and Brazil (Cambau *et al.,* 2018; Andrade *et al.,* 2022). Clofazimine resistance is rare, and *M. leprae* lacks the MmpL5-MmpS5 efflux pump through which clofazimine resistance is mediated in *M. tuberculosis* (Hartkoorn, Uplekar & Cole, 2014), hence no molecular target for clofazimine resistance is known in *M. leprae* and such resistance can only be determined through mouse footpad inoculation based drug susceptibility testing (DST). The incidence of rifampicin resistance was highest in the Western Pacific (pooled incidence, 21% [95% CI, 13% to 29%]) and lowest in the Americas (pooled incidence, 4% [95% CI, 1% to 7%]) (Wang *et al.,* 2022). Systematic monitoring of drug susceptibility may be useful since signs of treatment inefficiency may not manifest until after 12 months of standard MDT. DST is now recommended by WHO in at least 10% of the multibacillary patients at treatment initiation, and in all patients when treatment failure is suspected, particularly in regions with reported drug resistance and available testing facilities (WHO, 2017).

Active case detection and contact screening

A number of studies have been published on active case detection. A recent study reviewed the methods used in areas of high and low leprosy endemicity (Brown, Fastenau, Penna, Saunderson & Klabbers, 2024).

The Union of the Comoros is a high-burden country for leprosy. Its National Leprosy Programme has been organizing what are known as "mini campaigns" or "skin camps," utilizing the "camp approach," where the community is encouraged to present skin conditions at centralized screenings. However, subsequent door-to-door screenings, within the context of the PEOPLE study (Ortuno-Gutierrez *et al*., 2019), in villages previously covered by these mini campaigns, revealed a notable increase in newly identified leprosy cases, suggesting limited reach of mini campaigns alone. Additionally, on Anjouan, household contacts of diagnosed leprosy patients receive visits from nurses trained in leprosy at their homes or are invited to undergo leprosy screening at Primary Health Care facilities (Ortuno-Gutierrez *et al*., 2022).

Transmission

Transmission mechanisms remain poorly understood. At present, the main source of infection remains human-to-human transmission of *M. leprae* from nose and mouth during close and frequent contact with untreated patients. As Lechat has highlighted, the source of the infection remains, however, an unsolved question (Lechat, 2000). In addition to human-to-human transmission, other ways of transmission have been confirmed and nonhuman reservoirs have been discovered.

Nonhuman reservoirs

To date, three types of wild animals have been identified as reservoirs of leprosy bacilli: armadillos in the Americas, red squirrels from the British Isles and nonhuman primates from the Philippines and West Africa.

- **Armadillos**

The first case of "natural" leprosy in a wild nine banded armadillo (*Dasypus novemcinctus*) was described in the southern United States in 1975 (Walsh *et al*., 1975). Following this discovery, leprosy was investigated by various teams on thousands of wild armadillos. The origin of indigenous leprosy in

wild armadillos remains unclear. One possibility put forward is that *M. leprae* may have been transmitted via fomites (contaminated dressing or clothing) from multibacillary patients during the pre-sulfone era (Walsh, Meyers & Binford, 1986). Animals with leprosy have been described in the following states: Alabama, Arkansas, Georgia, Florida, Louisiana, Mississippi and Texas. Leprosy prevalence rates vary from 1 to more than 50%, depending on the study. The states most affected by "natural" leprosy are Louisiana and Texas, mainly in coastal regions and alluvial plains (Portaels & de Jong, 2014; Ploemacher, Faber, Menke, Rutten & Pieters, 2020).

The USA currently reports around 150 new cases of leprosy per year in humans, a third of them in so-called "native" patients, who have never travelled or resided in leprosy-endemic regions or been in contact with leprosy patients (Truman *et al*., 2011; National Hansen's Disease [Leprosy] Program, 2023). A case-control study showed an association between these cases and repeated contact with wild armadillos (Clark *et al*., 2008). A single genotype (31-2-v1) was found in both leprous armadillos and "native" human cases from the same regions (Truman *et al*., 2011). A second genotype (31-2-v15) has been described more recently in patients and armadillos from Florida (Sharma *et al*., 2015). *M. leprae* has also been found in 14,8% of armadillo tissues from museum collections. PCR-positive tissues came from animals from Texas, Paraguay and Bolivia. The entire genome of two strains was sequenced; the strains clustered with armadillos and human isolates from the United States (subtype 31-2) (Romero-Alvarez, Garzon-Chavez, Jackson, Avanzi & Peterson, 2023).

Recently, a growing number of patients in Florida have been diagnosed with autochthonous leprosy. Among the 159 cases reported in the US in 2020, 27 (17%) were from Florida (Mahase, 2023). Several patients deny having been exposed to armadillos. Some authors therefore suggest that international migration is responsible for the contamination (Rendini & Levis, 2017; Bhukhan, Dunn & Nathoo, 2023), while others point to indirect exposure to territories inhabited by armadillos, as the patients were gardeners or were mainly involved in landscaping (Greenwald & Domozych, 2017; Robbins, Luna-Wong, Adams & Ramos-Herberth, 2024). As autochthonous patients and armadillos share the same genotypes, it is very likely that leprosy is also an emerging zoonosis in Florida (Greenwald & Domozych, 2017).

If international immigration is responsible for the transmission of leprosy in non-endemic regions, one may wonder why such cases are not described in European countries where immigration from leprosy-endemic countries is high. The epidemiology of leprosy was analyzed in Spain over a 10-year period (2003-2013), during which immigration quintupled. Of the 168 leprosy cases recorded, 40 were Spanish-born patients and 128 were immigrants, most of whom came from Latin American countries where leprosy is still endemic. Although the risk of secondary transmission from foreign- to Spanish-born people is conceivable, the study could not confirm that Spanish cases were the result of transmission from immigrants. The authors conclude that the impact of secondary transmission, if it exists, is probably very limited (Ramos, Romero & Belichón, 2016).

In Latin America, especially in Brazil, several studies have also highlighted the possible role of armadillos in the transmission of leprosy to humans (Deps, Antunes, Santos, & Collin, 2020; Deps, Antunes & Collin, 2021). Two armadillo species had leprosy: the nine banded armadillo (*D. novemcinctus*) and the six banded armadillo (*Euphractus sixcinctus*) (Deps *et al*., 2020). *M. leprae*-infected armadillos have also been detected in Argentina, Colombia and Mexico, with prevalence rates ranging from 2 to 50% (Ploemacher *et al*., 2020).

A case-control study in Brazil concluded that people directly exposed to armadillos were twice as likely to develop leprosy as those who reported no exposure (Deps *et al*., 2008). A recent study carried out in the Brazilian Amazon has highlighted the important role played by eating wild armadillos in the transmission of leprosy (da Silva *et al*., 2018).

- **Monkeys**

Monkeys kept in captivity

In Japan and the USA, cases of leprosy have been diagnosed in chimpanzees (*Pan troglodytes*) (Leininger, Donham & Rubino, 1978) and sooty mangabeys (*Cercocebus atys*) (Fukunishi *et al*., 1984; Meyers *et al*., 1985) imported from West Africa (Meyers, Gormus, Walsh, Baskin & Hubbart, 1991; Suzuki, Tanigawa, Kawashima, Miyamura & Ishii, 2011), and in one cynomolgus macaque (*Macaca fascicularis*) imported from the Philippines for medical research (Valverde, Canfield, Tarara, Esteves & Gormus, 1998). Complete genome sequencing of *M. leprae* from three of these imported nonhuman primates showed that *M. leprae* from African monkeys belong to a human lineage frequently found in West Africa while the cynomolgus macaque strain is closely related to a human strain from New Caledonia (Honap *et al*., 2018).

Wild monkeys

Leprosy cases have also been recently reported in two wild populations of chimpanzees from Africa (Côte d'Ivoire and Guinea-Bissau). In addition to numerous photos showing clinical signs of leprosy, stool and necropsy samples confirmed the presence of *M. leprae*. Complete genome sequencing confirmed that the chimpanzee strains belong to rare genotypes different from those of humans and other animals (armadillos and squirrels) (Hockings *et al*., 2021). Direct contact between humans and chimpanzees in these regions is uncommon and human-to-chimpanzee transmission is therefore unlikely. The origin of the *M. leprae* infection of wild chimpanzees remains unclear but the results of this study point to a nonhuman or environmental reservoir for *M. leprae*, and call for research into its distribution and prevalence in wildlife and the environment.

Unlike armadillos, no transmission of leprosy from wild monkeys to humans has been reported to date. However, genome sequencing of imported nonhuman primates suggests the possibility of *M. leprae* transmission between humans and nonhuman primates (Honap *et al*., 2018).

- **Squirrels**

Since 2014 leprosy has been reported in Eurasian red squirrels (*Sciurus vulgaris*) in the British Isles (Avanzi *et al*., 2016; Schilling *et al*., 2019a). *M. leprae* was found in red squirrels from Brownsea Island and *M. lepromatosis* in red squirrels from Ireland, Scotland, England and in the Isle of Wight. Animals with clinical signs of leprosy and seemingly healthy red squirrels were infected with *M. leprae* or *M. lepromatosis*. Genome sequencing of the *M. leprae* strains from red squirrels from Brownsea Island were closely related to human strains found in medieval England suggesting that *M. leprae* was probably introduced in red squirrels when leprosy was present in humans in this region (Avanzi *et al*., 2016). Interestingly, the *M leprae* strains from Brownsea Island were closely related to the strains found in wild armadillos (Truman *et al*., 2011). These findings are unexpected since autochthonous leprosy has currently disappeared in the UK and is only diagnosed in people who lived or spent some time in leprosy endemic countries (Lockwood *et al*., 2022). The *M. lepromatosis* strains isolated from red squirrels were slightly different from the *M. lepromatosis* strains from Mexican patients (Avanzi *et al*., 2016).

To date, leprosy bacilli have not been detected in other squirrels or other wild rodent species within or outside the UK. Therefore, only red squirrels of the British Isles are reservoirs of leprosy bacilli (Schilling *et al*., 2019b; Tió-Coma *et al*., 2020).

- **Reservoirs of leprosy bacilli and transmission routes of leprosy**

As pointed out by Lechat, leprosy elimination strategies have been based primarily on interrupting human-to-human contamination, "the two basic premises being that humans are the only reservoirs and that the leprosy patient with clinically detectable disease is the only potential source of infection"; these premises are questioned by Lechat (Lechat, 1999b; 2000). As mentioned above, transmission

from other sources could partly explain why the incidence of the disease has remained stable for several decades despite the use of effective MDT. The presence of an animal reservoir and zoonotic transmission are probably insignificant in countries with a high prevalence of leprosy, but can become important in areas where leprosy has been eliminated and where man is no longer the main source of contamination, as in the southern United States. Transmission routes from potential nonhuman reservoirs should not be underestimated and should be taken into account in studies aimed at interrupting transmission. Research into other reservoirs must be encouraged to better understand the mechanisms of leprosy transmission.

Zoonotic transmission may represent a difficult challenge which must be taken into account to achieve the complete elimination of leprosy (Scollard, 2016; da Silva *et al*., 2018). A transdisciplinary "One Health" approach - a concept that aims to optimize the health of humans, animals and ecosystems- will enhance our understanding of the different factors involved in the transmission of leprosy bacilli, towards a world free of leprosy (Ploemacher *et al*., 2020; Deps & Rosa, 2021).

Possible ways to interrupt transmission

In 1999, Lechat had already argued that the MDT-based strategy should not be the only means of solving the leprosy problem and that complementary strategies such as prevention should be explored to interrupt transmission (Lechat, 1999a).

To interrupt transmission and reduce the incidence of new leprosy cases, WHO recommends tracing contacts of leprosy patients (family, social and neighbourhood contacts) and administering a single dose of rifampin (SDR) as post-exposure prophylaxis (PEP). Apart from SDR, other strategies are presently investigated.

- **Post-Exposure (chemo)prophylaxis**

Several studies have investigated the impact of PEP on the incidence of leprosy. PEP with SDR is advocated to reduce leprosy transmission through reduction of incident leprosy. WHO recommends SDR based on studies, including one in Indonesia in 2000 (Bakker *et al*., 2005) and the COLEP trial in Bangladesh (2002-2007), showing a 57% reduction in leprosy incidence among close contacts (Moet, Pahan, Oskam & Richardus, 2008). The MALTALEP trial in Bangladesh (2012-2017) found a 42% reduction in leprosy incidence with SDR given after BCG vaccination (Richardus *et al*., 2019). The LPEP trial (2015-2019) showed SDR-PEP is generally well-accepted but did not specify to which type of contacts to offer PEP (Steinmann *et al*., 2018). Ongoing trials investigate optimal dosing, target populations, and strategies. The PEOPLE trial (2018-2022) compared different strategies of double-dose SDR (SDDR) offered to different types of contacts around leprosy patients (Ortuno-Gutierrez *et al*., 2019). SDDR provided individual protection similar to the level of protection shown in the COLEP trial. When given to contacts living up to 100 m from persons who experienced leprosy in the past 5 years, SDDR was also shown to reduce incident leprosy at the population level (Hasker *et al*., 2024). The PEP4LEP trial (2018-2023) compared skin camp vs. health center-based interventions (Schoenmakers *et al*., 2021). The PEP++ trial (2020-2024) tests three doses of rifampicin and clarithromycin given one month apart (Hinders *et al*., 2024), results of which are pending. The BE-PEOPLE trial (2022-2026) evaluates bedaquiline with rifampicin as PEP in the Union of the Comoros (Younoussa *et al*., 2023), after this combination was found to be safe. SDR-PEP is likely time-dependent and unable to provide lasting immunity (Richardus *et al.,* 2013).

Subsequent advancements in post-exposure prophylaxis may involve investigating alternative strategies beyond SDR (Scollard, 2023). For instance, exploring higher doses of rifampicin could be beneficial, as studies have indicated that its bactericidal activity is dose-dependent, without causing any increase in adverse reactions . Another potential avenue is rifapentine, a compound within the same class as rifampicin, which has demonstrated superior bactericidal efficacy and possesses an extended half-life (Wang et al 2023). Rifapentine 1200 mg daily for 4 months has shown to be safe for

TB (Dorman *et al*., 2021), which might justify using 1200 mg rifapentine as PEP for leprosy. Additionally, further testing of promising antimycobacterial drugs may allow to enhance or substitute the current single-dose rifampicin PEP, such as bedaquiline (BE-PEOPLE study) and telacebec to which *M. leprae* is very sensitive (Lahiri, Adams, Thomas & Pethe, 2022) . Implementation of such new strategies should always go hand in hand with careful surveillance for drug resistance in both leprosy and TB patients.

- **Drug resistance in PEP areas**

Although the COLEP study in Bangladesh produced encouraging results (Moet *et al.,*2008), the administration of PEP could nevertheless present certain risks, as recently highlighted (Lockwood *et al*., 2021). These risks include the possibility of selection of *M. leprae* rifampicin resistance. However, a recent study of drug resistance in the Union of the Comoros showed that, so far, PEP has not selected rifampicin-resistant strains (Braet *et al*., 2022).

Towards zero leprosy

In 2021, WHO has launched a new Global Leprosy Strategy 2021-2030, entitled "Towards Zero Leprosy". This strategy has three major goals: Zero transmission, zero disability, and zero stigma and discrimination (WHO, 2021).

- **Zero transmission**

Interrupting transmission is a priority for reducing the incidence of leprosy and eventually achieving the elimination of leprosy. MDT alone has not been able to interrupt transmission. Improved and shortened treatment regimens should be found to improve MDT. New molecular approaches are now available to better understand the transmission routes of leprosy bacilli (Braet, 2023). Prophylactic treatment of contacts is one possible way of interrupting transmission, but a good contact tracing program is a prerequisite which is not easy to implement. PEP using SDR is currently implemented in several countries but significant limitations have been identified. More effective schemes should be investigated and implemented (Scollard, 2019; Richardus, 2021; van Brakel, 2022). Implementing PEP involves contact tracing and active case identification, which are also important interventions in achieving the goal of "zero leprosy" (Richardus, 2021).

As van Brakel (2022) points out, two distinct concepts need to be considered when referring to the elimination of leprosy: "interruption of transmission, and elimination of leprosy" because of the long incubation time of leprosy (up to more than 20 years in some cases). A "Technical guidance on interruption of transmission and elimination of leprosy disease" has been prepared by WHO. The document "emphasizes that eliminating leprosy is an ongoing, long-term journey" (WHO, 2023b).

- **Zero disability**

Among bacterial pathogens, leprosy bacilli are the only ones to attack nerves. Nerve damage is responsible for deformities and disability. Earlier diagnosis and prompt treatment with MDT can help but are not enough to reduce the risk of developing nerve damage and prevent disabilities. The WHO has published a technical guidance to prevent disabilities (WHO, 2022b). Since the various mechanisms of nerve injury are poorly understood, research in this field should be encouraged to prevent or reduce disabilities in leprosy (Scollard, 2019; van Brakel, 2022).

- **Zero stigma and discrimination**

The fight against leprosy is far from over, despite the success of MDT in reducing the prevalence of the disease in the last century. One of the most difficult aspects to control is probably the fight against stigma and discrimination. Prejudice and discrimination against persons associated with leprosy still exist although the disease has been curable for decades (Santacroce, Del Prete, Charitos & Bottalico, 2021; Scollard, 2019).

From Michel Lechat's "Méandres" to recent advances in the fight against leprosy

In his memoirs written in the last years of his life, Lechat had already lucidly and realistically described some of the above-mentioned problems that needed to be addressed to reduce transmission and eliminate leprosy (Lechat, 2022). His scientific contribution has focused mainly on the epidemiological and public health aspects of the disease. Using the epidemiometric model developed in 1974 (Lechat *et al*., 1974) , he simulated the effect of factors such as earlier detection, patient isolation and MDT on leprosy incidence. Simulations showed that earlier detection and patient isolation did not significantly reduce long-term incidence (Lechat, 1992). MDT led to a sharp reduction in incidence, but relapse rates had a negligible impact on long-term incidence (Lechat, Misson, Vanderveken, Vellut & Declercq , 1987). The current global leprosy situation confirms Lechat's findings that early detection and treatment are not sufficient to stop transmission. Lechat stressed that preventive treatment should not be neglected as an adjunct to leprosy control, despite the success of MDT (Lechat, 1999a). He reminds us that the source of infection remains an unresolved question, and that the potential role of non-human reservoirs should not be overlooked (Lechat, 2000). These considerations demonstrate that Lechat was not only an excellent scientist, but also a visionary, in addition to his human qualities.

Conclusion

- It has now been confirmed that leprosy can be caused by two different species: *M. leprae* and *M. lepromatosis.* The distinction between the two species may be relevant to epidemiological studies.
- Teledermatology and AI are promising screening techniques in support of the clinical diagnosis of leprosy.
- Leprosy is not only acquired through human-to-human transmission. There are several nonhuman reservoirs of leprosy bacilli (armadillos, monkeys, squirrels). Leprosy has been recognized as a zoonosis in the United States where wild armadillos infected with *M. leprae* play a role in transmission to humans. Nonhuman primates and red squirrels are reservoirs for leprosy bacilli but to date, their roles in the zoonotic transmission of leprosy has not been established.
- Interrupting transmission is a priority for reducing the incidence of leprosy for which innovative approaches are key.
- Early case detection and treatment, and contact screening followed by post-exposure prophylaxis are promising tools for interrupting transmission. PEP studies gave some encouraging results but more effective PEP regimens are needed.
- To date, the implementation of SDR or SDDR did not lead to the emergence of drug resistance.
- On the road towards the "zero leprosy" objective, a multidisciplinary approach including a "One Health" approach may be helpful.

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Summary

Leprosy is a skin related neglected tropical disease caused by *Mycobacterium leprae* and *M. lepromatosis*. While its prevalence has declined considerably since the 1980s, thanks to multidrug therapy, its incidence has stagnated this century. Around 200,000 new cases are notified each year, reflecting ongoing transmission. This impaired control may be due to several factors, such as delayed diagnosis, loss of expertise and policy interest in leprosy, and transmission by asymptomatic patients or by animal reservoirs. In his memoirs "Méandres", Michel Lechat describes the obstacles to be overcome in controlling the disease. This article presents recent advances in the fight against leprosy and the challenges to be met for better disease control. Possible reservoirs and transmission routes are detailed, as are new ways of interrupting the transmission of leprosy bacilli. The WHO's "Towards Zero Leprosy" strategy is also discussed. Together these should herald improvements towards leprosy elimination.

Résumé

La lèpre est une maladie cutanée tropicale négligée causée par *Mycobacterium leprae* et *M. lepromatosis*. Si sa prévalence a considérablement diminué depuis les années 1980, grâce à la polychimiothérapie, son incidence a stagné au cours du siècle. Environ 200 000 nouveaux cas sont notifiés chaque année, ce qui témoigne d'une transmission continue. Ce manque de contrôle peut être dû à plusieurs facteurs, tels que le retard de diagnostic, la perte d'expertise et d'intérêt politique pour la lèpre, et la transmission par des patients asymptomatiques ou par des réservoirs animaux. Dans ses mémoires "Méandres", Michel Lechat décrit les obstacles à surmonter pour contrôler la maladie. Cet article présente les avancées récentes dans la lutte contre la lèpre et les défis à relever pour un meilleur contrôle de la maladie. Les réservoirs et les voies de transmission possibles sont détaillés, de même que les nouveaux moyens d'interrompre la transmission des bacilles de la lèpre. La stratégie de l'OMS "Vers zéro lèpre" est également abordée. L'ensemble de ces mesures devrait permettre de progresser vers l'élimination de la lèpre.