# Effectiveness of innovative interventions on curbing transmission of *Mycobacterium leprae*

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Colofon



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Effectiveness of innovative interventions on curbing transmission of *Mycobacterium leprae*

Doeltreffendheid van innovatieve interventies om de transmissie van *Mycobacterium leprae* tegen te gaan

Thesis

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# 1 General introduction

## 1. Leprosy disease

Leprosy, also known as Hansen's disease is an ancient, complex, and chronic malady. Since 1873 it is known to be caused by the bacillus *Mycobacterium leprae* [1] being the first human pathogen that was discovered. More recently, in 2008, *M. lepromatosis* has been also identified as a pathogen causing leprosy, [2] however its contribution to the burden of leprosy is still being studied. To date, major knowledge gaps on transmission, physiopathology, and reliable laboratory diagnosis remain and complicate leprosy control.

### 1.1 Natural history of leprosy

The most widely assumed mode of transmission of *M. leprae* is through the air. [3] Skin-to-skin transmission has been also postulated.[4, 5] For both routes, direct, frequent, and close contact favors transmission as demonstrated in one study that found that untreated multibacillary (MB) persons had Polymerase Chain Reaction (PCR) tests positive for *M. leprae* accounting for 80% and 60% in the skin and nasal samples compared to 17% and 4% of their household contacts respectively.[4] A few less frequent modes of transmission have been reported, i.e. tattooing,[6] transplacental, [7-9] percutaneous inoculation by arthropods [10], recently ticks have been identified in this latest pathway. [11] An infected human is the main source of transmission, nevertheless, *M. leprae* has been detected in soil, [12] armadillos, red squirrels, [13] chimpanzees, monkeys [10, 14], and recently rodents [15]. Infection with *M. lepromatosis* has also been identified in red squirrels. [13] Although zoonotic transmission from nine-banded armadillos has been documented, [16] the extent of the contribution of water, soil, parasites (amoeba), and other animals to zoonotic transmission is not fully understood.

Progress from infection to disease depends on host risk factors. Most humans (90-95%) clear the bacilli after exposure. In persons with relatively strong cellular immunity, the paucibacillary (PB) localized leprosy form may develop, in those with poor cellular immunity the multibacillary (MB) form may occur. The median incubation period is assumed to be approximately 3½ years for PB and 10 years for MB. [10, 17] However it could vary from less than one year [18, 19] up to thirty years. [20] Despite long incubation period children may constitute 20-30% of leprosy cases in endemic countries. [21] Gender predisposition varies according to age, in children ratio of male/female is 1/1 compared to 2-3/1 in adults. Among genetic host factors, Human Leukocyte Antigen – DR isotype (HLA-DR3) is associated with leprosy. [22] Also, among 21 monozygotic twins, there were 19(85%) both affected by leprosy, whereas among 12 dizygotic twins only two (17%) were both affected by leprosy. [23] Social determinants influence transmission. A lower prevalence of leprosy is correlated with good quality of living standards. Nowadays, leprosy is prevalent in unprivileged zones of the world mainly in the tropics. There, intestinal parasitosis is associated with three times more risk of having MB compared to PB. [24]

The probability of developing leprosy might also depend on the characteristics of the pathogen as observed in the prolonged survival of *M. Leprae* in amoebic cysts probably linked to its preserved infectivity and virulence. [25] Infectiousness is influenced by the optimal growth temperature of 30°C that correlates with a predilection for cooler parts of the body, i.e. upper respiratory tract and skin. [10] Around 50% of the *M. leprae* genome contains protein-encoding genes compared to 91% in *M. tuberculosis*, making it impossible to cultivate in vitro as slow multiplication (every 12-14 days) takes place inside of host's Schwann and macrophage cells. *M. Leprae*'s genome also explains the long incubation period, the chronic clinical course, and its reduced virulence.[26] MB patients are considered highly infectious, [10] but PB and sub-clinical infection might also contribute to transmission (Figure 1).

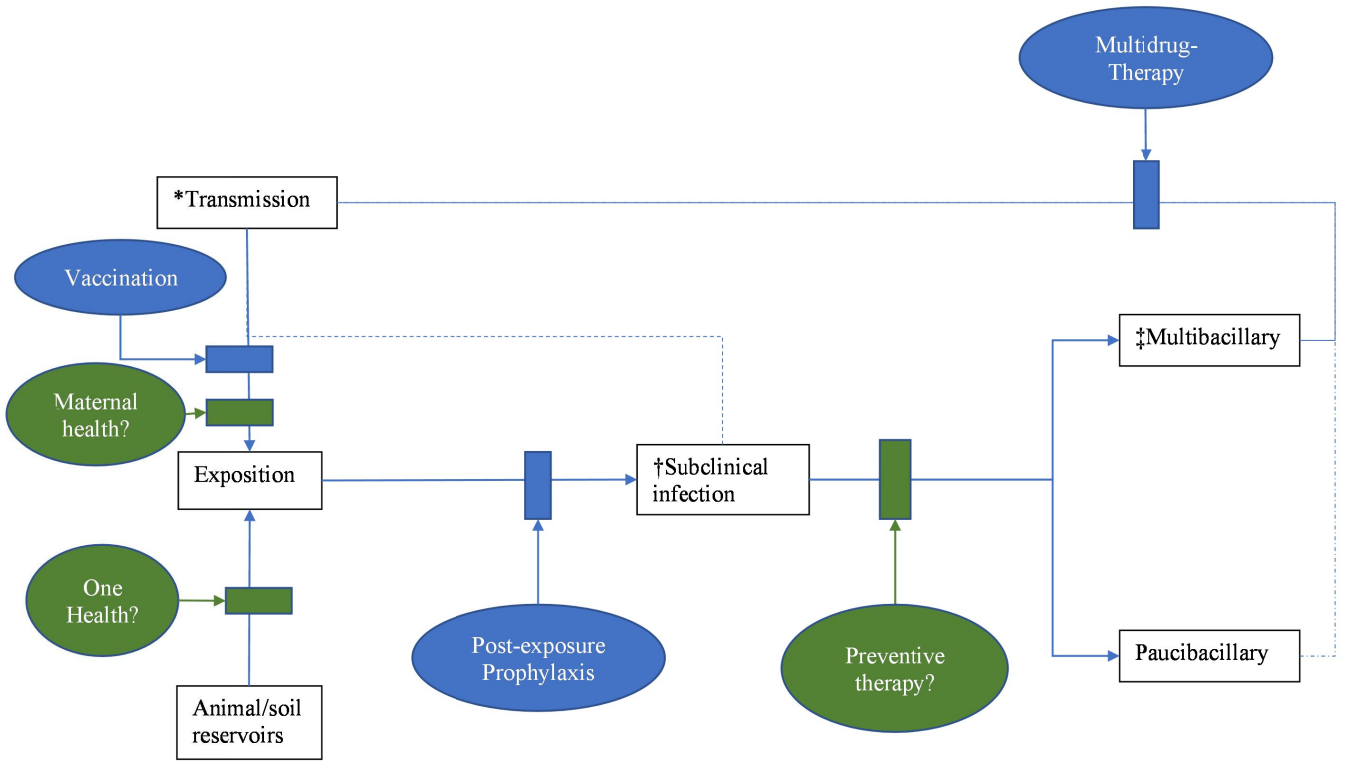


**Figure 1. Natural infection of leprosy and control strategies.** Source: based on Methods for Analysis of Health Problems (MAHP), Institute of Tropical Medicine.

*Air, skin-to-skin as main entry point. Tattooing, transplacental and arthropods are also plausible. †Disease progression depends on host risk factors (immunity, age, gender, genetics, close and direct contact, intestinal parasitosis, social determinants, etc.) and pathogen characteristics (virulence, infectiousness). ‡Considered highly infectious.

## 1.2 Clinical manifestations of leprosy

The clinical manifestations of leprosy include slowly progressing skin and neurological signs that vary according to the immunological response, which can also trigger hypersensitivity reactions. If care provided for both leprosy clinical manifestations and reactions is late or inadequate, permanent deformity develops leading to stigma and discrimination. Diagnosis is based on three cardinal signs: skin lesions with loss of sensation, nerve affectation, and positive slit-skin smear (SSS). [27]
The spectrum of clinical presentation can be illustrated based on clinical signs, bacteriological load, and immune response. [28, 29]

| Ridley–Jopling | *WHO | †BI | Lepromine reaction | Skin Lesions | Nerve Involvement | Systemic Features |
|---|---|---|---|---|---|---|
| Indeterminate | PB | 0 | Weakley +ve or -ve | Single hypo-pigmented lesion <5cm. May become TT-like. | None clinically detectable. | Nil |
| Tuberculoid (TT) | PB | 0–1 | Strongly +ve | Few, mainly one macule or plaque & well-defined border & sensory loss. | May have one peripheral nerve enlarged or ‡PNF | Nil |
| Borderline tuberculoid (BT) | PB/MB | 0–2 | +ve | Several larger irregular plaques & partially raised edges. Satellite lesions at the borders. | Asymmetric multiple nerve involvement. | Nil |
| Borderline Borderline (BB) | MB | 2–3 | Weakley +ve or -ve | Many macular lesions & infiltrated lesions & less distinct borders. | Asymmetric multiple nerve involvement. | Nil |
| Borderline lepromatous (BL) | MB | 1–4 | -ve | Many small macular lesions and multiple nodules and papules | Extensive nerve enlarged. | Some of features listed below. |
| Lepromatous lepromatous (LL) | MB | 4–6 | -ve | Multiple skin nodules or papules symmetrically distributed, non-anaesthetic. Often thickened shiny ear lobes, loss of eyebrows, and diffuse skin thickening (leonine facies). | Widespread nerve enlargement. No glove and stocking anaesthesia until late. | Nasal stuffiness, epistaxis. Testicular atrophy. Ocular affection. Internal organs can be affected. |

†BI=Bacterial Index by slit-skin smear; *WHO=World Health Organization; +ve = positive; -ve = negative; ‡PNF= pure neural form.

**Table 1. Classification of clinical characteristics of leprosy according to WHO, bacillary load and immunity.**

## 1.3 Diagnosis of leprosy

Besides SSS or histopathological examination of biopsies associated with clinical signs, no other diagnostic tests are currently recommended by WHO. [27] Different types of tests have been studied because reliable tests for diagnosis could lead to better control of the transmission. Recently fluorescent *in situ* hybridization (FISH) microscopy has shown higher specificity compared to Ziehl-Neelsen staining. [30] Serological tests have been developed, one of those combining two protein antigens ML0405 and ML2331 diagnosed leprosy 6-8 months before clinical onset. [31, 32] The detection of antibodies to phenolic glycolipid-I (PGL-I) of *M. leprae* using a lateral flow test had a sensitivity of 97.4% for MB and 40% for PB, therefore could recommended for correct classification of leprosy and for screening contacts at risk of developing leprosy. [33] Polymerase Chain Reaction (PCR) tests have been developed and detect at least one-tenth of the *M. leprae* genome. [30] Real-time PCR was also documented effective for detecting pure neural forms of leprosy (PNF). [34]

## 1.4 Leprosy reactions

Leprosy clinical management is complicated by reactions provoking neuritis that can arise prior to diagnosis, during treatment, and even after release from treatment, causing disability if not properly managed. Leprosy reactions are caused by immune, molecular and biochemical mechanisms. Two main types are described: type 1 reactions (reversal) and type 2 reactions (*erythema nodosum leprosum*, ENL). Reversal reactions are present in around 22% of diagnosed patients, indicating upgrading cell-mediated immunity after a decline at the start of the disease and manifest as swelling, redness, heat, pain, and loss of function (neuritis). Treatment of reversal reactions is based on non-steroidal anti-inflammatory drugs (NSAIDs) if no neuritis is present, otherwise, steroids are recommended. ENL occurs in LL and BL patients with high bacillary load and can affect up to 50% of LL patients, it may be caused by underlying causes such as TB, sarcoidosis, and Chron's disease. Clinical presentation of ENL is recurrent and includes nodules, pain, fever, oedema, nerve tenderness, and iridocyclitis among others. ENL management depends on its severity and can include analgesic therapy for mild and thalidomide, clofazimine, or steroids for severe presentations. [35]

## 1.5 Treatment of leprosy

Multidrug therapy (MDT) is the standard treatment for leprosy. The duration and type of MDT depend on the WHO operational classification based on the bacterial burden and number of skin lesions with $\leq$ five lesions and negative SSS classified as PB and $\geq$ six skin lesions or positive SSS as MB. MDT for MB includes rifampicin, clofazimine, and dapsone and originally included the same drugs except clofazimine for PB. [36] Duration was shortened from two years to one year for MB. Currently, all three drugs are also recommended for PB, with the same six-month duration. Dosage for children depends on their weight. In case of rifampicin resistance, the recommended regimen includes two second-line drugs i.e. clarithromycin, minocycline, or a fluoroquinolone (ofloxacin, or levofloxacin, or moxifloxacin), plus clofazimine for six months, followed by 18 months of clofazimine and one of the second-line drugs. For rifampicin and fluoroquinolone resistance, clarithromycin, minocycline, and clofazimine for six months followed by clarithromycin or minocycline plus clofazimine for 18 months are recommended. [27]

## 2. Epidemiological burden of leprosy

### 2.1 Global overview

In 2020 the total number of new leprosy cases was 127,506, equivalent to a dramatic 37.1% reduction compared to 2019, in all probability because of reduced case finding and lack of accessibility of services due to the Covid-19 pandemic (Figure 2).

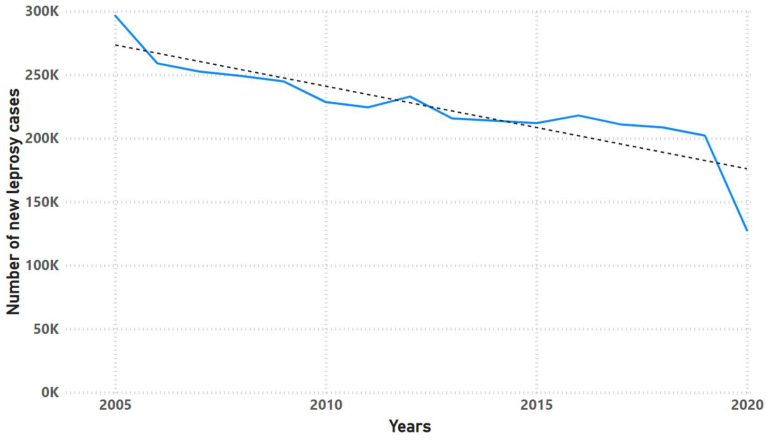


**Figure 2. Number of new leprosy cases notified worldwide, 2005-2020. Source: WHO.**

In the last decade, three countries (Brazil, India, and Indonesia) accounted for 80% of the annual global burden. In 2020, there were 127 countries reporting leprosy cases, and 12 reported more than 1,000 new cases of which seven were in Africa: Democratic Republic of Congo (DRC), Ethiopia, Mozambique, Madagascar, Somalia, Nigeria, and the United Republic of Tanzania (figure 3).

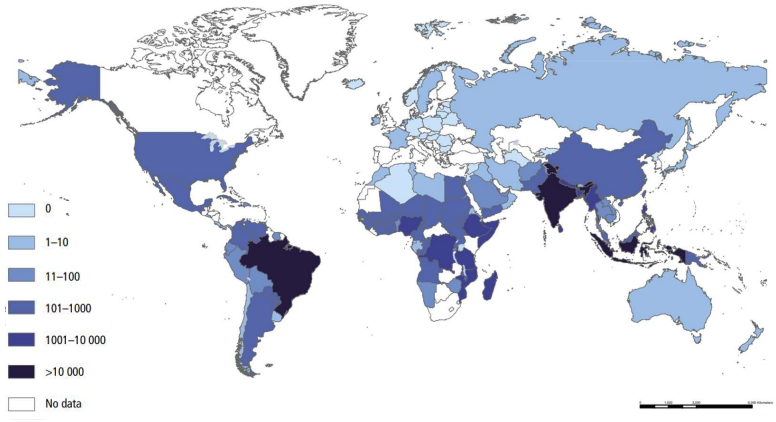


**Figure 3. Map with the distribution of new cases in 2020. Source WHO.**

The proportion of children below 15 years of age among new leprosy cases is a proxy indicator of transmission, it was 6.8% in 2020 compared to 9.2% in 2011 worldwide. During this period, while this proportion decreased in Asia, it increased in the African region.
The disability of patients is assessed according to the WHO grading: Grade 0 for no disability. Grade 1 includes anaesthesia but no visible deformity, and Grade 2 disability (G2D) includes visible deformity in hands and/or feet, and/or severe visual impairment, or iridocyclitis, or corneal opacities, or lagophthalmos in eyes. Monitoring G2D is imperative to assess proper and early access to care. In 2020, 7,198 G2D new cases were notified in 68 countries from which India and Brazil notified more than 1,000. There were 308 children with G2D, most from the African region. [37] It is estimated that there are 3-4 million people living with disabilities due to leprosy [38], however, the burden based on G2D could be largely underestimated. [39]

## 2.2 Leprosy in Comoros, India and Madagascar

This thesis includes studies conducted in Comoros, Madagascar, and India. All three countries are part of the 23 WHO priority countries for the control of leprosy. While Comoros is a small archipelagic country with less than one million population, it has the highest number of new cases per million inhabitants, 293 in 2020 versus 47 and 49 in India and Madagascar respectively. In both African countries, the leprosy control activities were only slightly affected by the Covid-19 pandemic, as opposed to India where they were seriously affected. The prevalence per million inhabitants shows the same trend as the case notification rates. When looking at the proportion of MB, Comoros which combines active case finding (ACF) with passive case detection activities has 44% compared to 58% and 89% in India and Madagascar respectively in 2020. Although both ACF and passive case detection are also in place in India and Madagascar, the distribution of leprosy is uneven and the variability is much higher compared to Comoros. An indicator of early care is the proportion of G2D, which in Comoros and India has been consistently lower, at 1% and 2% respectively compared to 21% in Madagascar in 2021. [40] In India, different tailored ACF strategies have been implemented resulting in decreasing G2D, 2% at present from 4% in 2013. [41] In Madagascar, the main factors associated with G2D are long delays due to limited access to care in rural areas, [42] [43] and low quality of care. [43, 44]
The proportion of children for the year 2020 is much higher in Comoros (33%) compared to India (3%) and Madagascar (7%). When looking at the number of children among new leprosy cases during 2013-2020, Comoros has notified more than 200 per million, with a peak of 808 per million in the year 2019. That year, the Post ExpOsure Prophylaxis for LEprosy (PEOPLE) study started in Comoros, and ACF in the selected 48 villages unveiled many hidden cases. In India, where leprosy care has been integrated into Primary Health Care combined with ACF, we observed a decreased number of children from 33 per million inhabitants in 2013 to 10 in 2020. In Madagascar there were 12 children per million inhabitants in 2013, the reduction is less important compared to India and Comoros. The high child proportion in Comoros clearly indicates ongoing transmission and the need to sustain/ innovate active case detection efforts. (Table 2 and figure 4)

| Year | 2013 | | | | | | | 2020 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Country | New cases | NC per million | *Preva-lence | (% children) | (% MB) | (% G2D) | (% women) | New cases | NC per million | *Preva-lence | (% children) | (% MB) | (% G2D) | (% women) |
| Comoros | 480 | 653 | 412 | (29) | (50) | (2) | (43) | 236 | 293 | 237 | (33) | (44) | (1) | (86) |
| India | 126,913 | 101 | 69 | (9) | (51) | (4) | (37) | 65,147 | 47 | 42 | (3) | (58) | (2) | (39) |
| Madagascar | 1,569 | 68 | 71 | (9) | (88) | (18) | (24) | 1,346 | 49 | 65 | (7) | (89) | (21) | (25) |

NC= New Cases. MB= Multibacillary. G2D= Grade 2 disability. *Prevalence per million.

Table 2. Key programmatic indicators comparing years 2013 to 2020, Comoros, India and Madagascar. Source WHO.

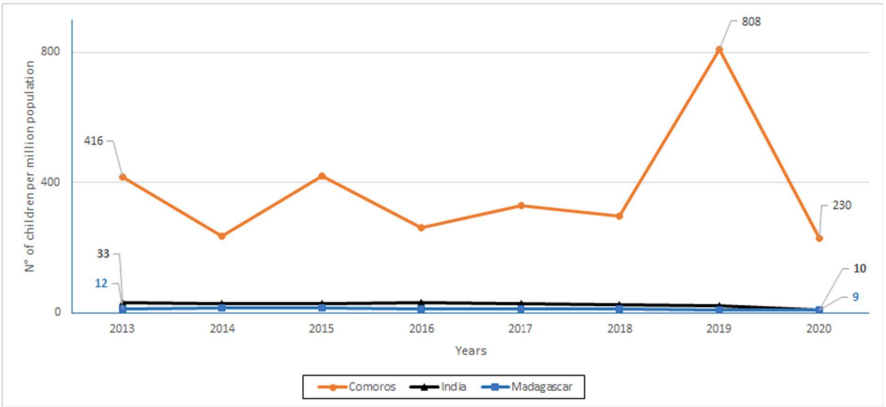


Figure 4. Number of children among new leprosy cases, 2013-2020, Comoros, India and Madagascar. Source WHO.

## 3. Control of leprosy

In 1991 WHO set the goal for elimination of leprosy as a public health problem by the year 2000, defined as a prevalence of less than one case per 10,000 inhabitants at the global level. [45] The Global Leprosy Strategy 2021-2030 aims for interruption of transmission targeting 120 countries reporting zero autochthonous cases, 70% reduction in annual number of new cases detected, 90% reduction in rate per million population of new cases with G2D, and 90% reduction in rate per million children of new child cases with leprosy in 2030. There are four strategic pillars:

1. Implement integrated zero leprosy roadmaps: which aim for national adaptation to the epidemiological situation incorporating political commitment, inclusion of stakeholders, capacity building, surveillance, and monitoring of antimicrobial resistance (AMR) and adverse drug reactions.
2. Extension of prevention with active case detection (ACD) including contact screening of all new cases, scaling up preventive chemotherapy, ACD in targeted populations, and vaccination with existing and potential new vaccines.
3. Manage leprosy, and leprosy complications and prevent new disabilities by the provision of early care, with comprehensive access including a referral system, care of reactions, neuritis, and disabilities, ensuring self-care, and providing care for mental well-being.
4. Combat stigma and ensure the respect of human rights by adopting the United Nations principles, inclusion of organizations of persons affected by leprosy, removal of discriminatory laws, reduction of stigma, and providing social support and rehabilitation. [40, 46]

The success of the control of leprosy is influenced by the different types of host exposition to the pathogen and by, variances in the host's susceptibility to progress to disease that ultimately influence the level of heterogeneity that is observed in the risk of developing leprosy among contacts. Leprosy is unevenly distributed over space, apart from differences in host susceptibility, this could be related to the distribution of contacts, social determinants (poverty), and relationships with specific geographical areas i.e. rivers, reservoir territories, etc. [47]

### 3.1 Case finding and case holding of leprosy

Intensified population-based case finding is no longer cost-effective because of decreasing number of new leprosy cases, lack of resources, and heterogeneity of risk factors among the general population. [47] As the probability of developing leprosy is complex and difficult to be predicted, and after observing that the provision of MDT is no longer reducing the burden of new cases, innovation of ACD strategies in high and low endemic countries is needed. Diagnosis of leprosy requires health staff expertise because it is mainly based on clinical examination. Active case-finding strategies should be accompanied by preventive activities to stop transmission. Current prevention of leprosy is based on early case finding and treatment, which can be combined with the provision of single-dose rifampicin as post-exposure chemoprophylaxis (SDR-PEP),[48] and BCG (Bacillus Calmette-Guérin) as immunoprophylaxis for newborns, targeting both leprosy and TB. Since the early '90s, Brazil a WHO high priority country for leprosy control includes the administration of additional

BCG vaccine doses besides the first dose provided to the newborns, as immunoprophylaxis for household contacts of leprosy patients. [49]

### 3.2 Leprosy vaccines

*M. leprae* antigens are shared with other atypical mycobacteria and *M.bovis,* which contributes to the protection induced by BCG vaccine. Protection of BCG varies from 20.4% [50] to 80%. [51] WHO recommends BCG at birth because apart from its protective effect against TB, it is also effective in reducing the leprosy burden in leprosy endemic countries.[52] There is low-quality evidence about the fact that BCG potentiates the protection of SDR-PEP and unclear effect of the additional doses of BCG for immunoprophylaxis, therefore WHO doesn't recommend those BCG vaccine indications. [27] A second vaccine *M. indicum pranii* (MIP) had a protective effect of 68% at three years of follow-up, 60% at six years, and 28% at nine years when administrated to leprosy contacts.[53] In patients, the MIP vaccine combined with MDT increased clinical recovery and smear negativity and reduced onset of reactions. [54]
Finally, there is a new vaccine named LepVax, developed by the Infectious Disease Research Institute (IDRI), showing good protection as pre and post-exposure immune-prophylaxis and reducing the frequency of disabilities.[55] Research on the latest two vaccines is ongoing.

### 3.3 Post-exposure prophylaxis

Based on findings from the pivotal study 'Contact Transmission and Chemoprophylaxis in Leprosy' (COLEP) conducted in Bangladesh, which documented a 57% reduction of leprosy incidence in contacts that received SDR-PEP over the first two years of follow-up, [56] WHO has since 2018 recommended provision of SDR-PEP to close contacts. [27, 48] Beyond the COLEP trial, the Leprosy Post-Exposure Prophylaxis (LPEP) study demonstrated the feasibility of SDR-PEP under programmatic conditions in seven leprosy endemic countries. [57] There is also evidence that SDR-PEP can be cost-effective. [58] A modelling study indicates that the implementation of SDR-PEP can contribute to the reduction of 90% of leprosy incidence in 22 years when contact tracing and screening coverage is 90%. [59] Despite this compelling evidence, the uptake of SDR-PEP is still low, and WHO integrated its scaling up in the new Global Leprosy Strategy 2021-2030. [38]
Other studies assessing the modality of provision and the type of contacts of SDR-PEP [60] [61] and reinforced chemoprophylaxis regimens are ongoing. [62]

### 3.4 Surveillance

To assess the achievement of the current vision of the Global Leprosy Strategy 2021-2030, there is a need for high-performing routine surveillance systems that include new cases of leprosy but also the prevalence of disabilities due to leprosy and that must be well integrated into the routine health information system. Another area for surveillance is anti-microbial resistance (AMR), as SDR-PEP implemented worldwide may increase the risk of inducing rifampicin resistance. Finally, a well-established surveillance system will allow proper follow-up of the post-elimination phase. [38]

## 4. Geographical information systems (GIS) for leprosy control

In the current phase of working towards interruption of transmission of *M.leprae,* we need a performant health information system that ideally includes: digital data collection systems, case-based data, including geolocation data that will allow sound evidence-based programme management. [38] As leprosy is known to be spread unevenly within districts, even within villages,[63] data even beyond the lowest administrative boundaries can be required for optimal targeting of interventions where high transmission is ongoing. [47, 64] The combination of person, time, and space can guide interventions. [65]

Although geographical information systems (GIS) have been recognized as extremely useful since John Snow used them for investigating the cholera outbreak in 1854,[66] GIS tools have so far been implemented only on an *ad-hoc* basis for outlining areas for targeted strategies. [67-69] However, GIS could be also used as a routine control tool for Neglected Tropical Diseases (NTDs) such as leprosy, schistosomiasis, post-kala-azar dermal leishmaniasis (PKDL), cutaneous leishmaniasis [63, 70-72]. With the advent of smartphones and applications for electronic data collection and georeferencing, mapping patients at household level is within reach of control programs. The Nikushth system being developed in India provides visualization of leprosy cases at Block level, equivalent to a district in most other countries. Names of diagnostic centers are also in the system but are yet to be georeferenced [73] Yet with the technologies currently available a much more granular level of mapping can be achieved. Whereas John Snow used such granular mapping to establish a causal relationship, in leprosy the primary aim would be identification of high transmission areas for targeted interventions. AI-enabled technologies could further be developed to allow for comprehensive, economical point-of-care services.[74] Thus, the inclusion of GIS can be of key importance for improved leprosy programme management, planning, and monitoring strategies and advocacy. [65]

### 4.1 Research priorities in GIS applied to programmatic conditions

The Global Partnership for Zero Leprosy (GPZL) workgroup on research priorities has identified two main areas for the integration of GIS within routine programmatic conditions with the ultimate aim of implementing tailored, actionable, and sustainable surveillance for leprosy care and prevention.
1) The identification of high local incidence/prevalence areas (clustering) using methods to stabilize rates in small areas where leprosy is rare and to detect spatial/spatiotemporal clusters or hot spots.
2) The development of focused and adaptive sampling methods for efficient detection of local hot spots. This requires efficient sampling of specific geographic areas for the identification of clusters (adaptive sampling) facilitating the implementation of surveillance in the areas identified with high rates including historical areas with high rates.

Both research areas can be implemented through operational research to strengthen health information systems, that later allow the implementation of GIS tools in programmatic conditions. [73] The Global Leprosy Strategy 2021-2030 has therefore incorporated geospatial distribution of leprosy and surveillance mapping as key research areas. [38]

## 4.2 Methods for detection of spatial clusters and level of clustering

The aim of spatial epidemiology is the description and understanding of spatial variations of disease risk. Typically four types of studies are used: disease mapping; geographical correlation; assessment of spatial risk to a point or line source; and cluster detection and disease clustering. Disease mapping describes the spatial and spatio-temporal variation in risk. Geographical correlation enquires about exposure to environmental factors (e.g. soil, water, or air) with health outcomes on a geographical (ecological) scale for etiological questions. Point or line source studies estimate the risk of exposure to a source point (i.e. chimney stack) or source line (i.e. road) or where the source is considered an environmental hazard. Finally, cluster detection within surveillance identifies the raised incidence of disease, and disease clustering identifies the tendency of disease to occur in a non-random spatial pattern relative to the pattern of non-cases. [75] Below we shortly describe spatial methods that were used for cluster detection and the level of clustering in the studies included in this thesis. Though many far more sophisticated methods have been described, our focus has been on methods that could be used in the routine of disease control programs, either at district level or above.

Clustering is defined as the differences between the pattern of the location of disease cases, compared to the pattern of the non-cases. These differences may occur because cases are more 'clumped' than non-cases. Clustering is explained because of an infectious agent or genetic susceptibility, and/or other measured and unmeasured risk factors. There may also be unmeasured risk factors that are the cause of residual (spatial) clustering. Diseases exhibit residual spatial clustering as it is usually impossible to measure all relevant risk factors. But even if we do not know the reasons behind clustering, the fact that cases are clustered can still be of major importance when targeting interventions. We, therefore, need to assess if clustering is present, whether it is epidemiologically significant and if the data available allow its detection. Cluster detection implies the detection of areas of high risk by statistical techniques expressed in terms of an excess of cases. [76]

The spatial scan statistics developed by Kulldorff superimpose circular or ellipsoid areas on the study area and determine whether the proportion of cases among the population within each circle/ellipsoid is different from that among the population outside the circle/ellipsoid for the identification of high or low incidence clusters. The associated SaTScan software package is a free software that allows to:

- Perform geographical surveillance of disease, to detect spatial or space-time disease clusters, and to see if they are statistically significant.
- Test whether a disease is randomly distributed over space, over time or over space and time.
- Evaluate the statistical significance of disease clusters.
- Perform repeated time-periodic disease surveillance for early detection of disease outbreaks. [77] [78]

To apply spatial scan statistics requires georeferenced data on cases but also disaggregated population data as denominator. We therefore outlined hamlets based on available population data in the form of georeferenced rasters (e.g. WorldPop Data and LandScan) making use of Kernel density estimation (KDE). KDE is a smoothing technique that allows visualizing the shape of data as a continuous replacement of a discrete histogram. [76] [79, 80] This was done in QGIS, which just like SaTScan is a free software. [26]

We used the distance matrix module in QGIS to calculate at individual level the distance to the nearest other person affected by leprosy. Thus we were able to fit a Poisson regression model with the distance to leprosy index case as explanatory variable and leprosy as outcome variable. To account for the fact that there may have been contextual risk factors not included in our analyses or not even measured, we used random effects models whenever appropriate.[81, 82]

## 5. Aim and research questions

The main aim of this PhD project is to develop and assess the effectiveness of innovative GIS-based strategies for curbing transmission of *M. leprae* in different leprosy endemic settings. We explored the use of GIS-based technologies for the analysis of clustering in Comoros and Madagascar. These studies were nested in a larger ongoing trial on post exposure prophylaxis (PEP) for leprosy (the PEOPLE trial), which required detailed mapping of entire village populations, including leprosy patients. In India, we assessed clustering of leprosy and mobility of leprosy patients, to identify hamlets (known as Tola) to be targeted by active case detection strategies coupled with prevention activities.

Our specific research questions are:

1) What are the patterns of clustering of leprosy in Comoros and Madagascar?
2) What is the pattern of clustering and mobility of leprosy patients in Bihar, India?
3) How to build an approach for exploring clustering at the lower administrative levels in Bihar, India?

## 6. Outline of the present thesis

In **Chapter 2,** we analysed door-to-door screening for leprosy in four endemic villages of Comoros that received SDR-PEP two years ago and we calculated the spatial risk of contracting leprosy for contacts and the protective effect of SDR-PEP that received it.

**Chapter 3**, is the protocol of Post ExpOsure Prophylaxis for Leprosy in the Comoros and Madagascar (PEOPLE), a cluster-randomized trial to assess the effectiveness of three modalities of implementing PEP.

**Chapter 4,** details the findings of the baseline survey of the first year of the PEOPLE trial in Comoros and Madagascar. We assessed clustering at the village level fitting a purely spatial Poisson model by Kulldorff's spatial statistic and assessed the distance risk of contact to the nearest leprosy patient.

**Chapter 5**, illustrates a different approach to retrospective active case finding. We screened for leprosy contacts of new leprosy cases in 32 villages not included in the PEOPLE trial in Comoros, disclosing clustering and hidden leprosy cases including children.

**Chapter 6,** documents the mobility of new leprosy cases in two endemic blocks of the State of Bihar, India. We also screened household contacts for leprosy. Finally, we developed a system to outline the lowest administrative level (hamlets known as Tola) for assessing clustering.

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# 2 Clustering of leprosy beyond the household level in a highly endemic setting on the Comoros, an observational study

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## Abstract

### Background

The island of Anjouan (Comoros) is highly endemic for leprosy with an annual incidence of 5–10/10,000. In May/June, 2015 single-dose Rifampicin post-exposure prophylaxis (SDR-PEP) was administered to 269 close contacts of 70 leprosy-patients in four villages as a pilot programmatic intervention. Two years later we revisited the villages for follow-up investigations. The main aim of our study was to quantify spatial associations between reported leprosy cases before and after PEP implementation. A secondary aim was to assess the effect of this single round of SDR-PEP at the individual level.

### Methods

We conducted door-to-door leprosy screening in all four villages in August/September, 2017. We screened all consenting individuals for leprosy and recorded geographic coordinates of their household. We also recorded whether they had received SDR-PEP and whether they had been diagnosed with leprosy, before or after the 2015 intervention. We fitted a Poisson model with leprosy as outcome and distance to the nearest pre- intervention case and SDR-PEP as predictors.

### Results

During the survey we found 114 new cases among 5760 contacts screened (2.0% prevalence), in addition to the 39 cases detected in the two preceding years. We found statistically significant associations of incident leprosy with physical distance to index cases ranging from 2.4 (95% confidence interval (95% CI) 1.5–3.6) for household contacts to 1.8 (95% CI 1.3–2.5) for those living at 1–25 m, compared to individuals living at ≥75 m.
The effect of SDR-PEP appeared protective but did not reach statistical significance due to the low numbers, with an incidence rate ratio (IRR) of 0.6 (95% CI 0.3–1.2) overall, and 0.5 (95% CI 0.2–1.3) when considering only household contacts.

### Conclusions

This pilot demonstrated an increased risk of leprosy in contacts beyond the household, therefore a wider circle should be considered for chemoprophylaxis. Baseline surveys and extended contact definitions are essential for improving SDR-PEP effectiveness.

## Background

Leprosy is an infectious disease caused by Mycobacterium leprae [1]. M. leprae is transmitted through the air [2] and after an incubation period of several months to 20 years, provokes skin lesions and nerve damage. Prolonged delay in diagnosis and treatment may cause permanent disability [3], which often leads to social stigma [4].
In 1991, the 44th World Health Assembly (WHA) set the year 2000 as a target to eliminate leprosy as public health problem, defined as a global prevalence of less than one leprosy case per 10,000 population [5]. Early diagnosis and multidrug therapy (MDT) contributed to attaining this goal, together with changes in case definition, achieving a prevalence reduction from more than five million cases in the 1980s to less than 600,000 by the year 2000 [6]. Nevertheless, the number of new leprosy cases reported annually has remained above 210, 000 since 2013 [7]. Combined with the persistence of leprosy in children, this implies that there is no decline of the transmission of M. leprae, a key step needed to achieve leprosy elimination.
The Global Leprosy Strategy 2016–2020 encourages implementation research on prevention of leprosy, including chemoprophylaxis [8, 9]. Single dose Rifampicin Post- Exposure Prophylaxis (SDR-PEP) given to the contacts of newly diagnosed leprosy cases has been documented as an effective strategy, reducing leprosy incidence at village/ neighbourhood level by approximately 50–60% [10, 11]. The success of implementing SDR-PEP under programmatic conditions relies on the integration of passive detection, active case finding and a strong monitoring and evaluation system [12]. Learning from the experience with SDR-PEP implementation of leprosy control programs is key to help identify its optimal implementation modalities. The Comoros is an archipelago in the northern Mozambique Channel in the Indian Ocean. The closest neighbours are Tanzania (Northwest), Mozambique (West), Madagascar (South) and Seychelles (Northeast). Figure 1 shows an overview map of the Comoros. The country has approximately 810,000 inhabitants [13], distributed over three islands with distinct geological features. Of the total population, 51% live on the main island Grand Comore, 42% on Anjouan, where mountains limit the inhabitable land, and 7% on Mohéli. Leprosy has all but disappeared from Grand Comore since 1980, but persists on the two other islands [14].
Despite its modest population size, the Comoros is considered one of the 22 high leprosy burden countries [9]. In 2016, the national detection rate was 3.8/10,000 inhabitants. Out of 310 new leprosy cases detected, 83 (27%) were children (below 15 years of age) [7].
On the island of Anjouan, leprosy has been highly endemic for decades, with a reported incidence above 7/10,000 inhabitants, with more than 30% of new

leprosy cases being children [15]. The leprosy control program on the Comoros was launched in 1978 and has since benefitted from the support of two inter-national non-governmental organizations, Damien Foundation and AIFO (Associazione Italiana Amici di Raoul Follereau). Since 1986, tuberculosis (TB) and leprosy control have been integrated within the National Tuberculosis and Leprosy Programme (NTLP). On Anjouan 27 health facilities offer TB and leprosy care. The NTLP combines passive and active case finding to achieve early detection and cure. For active case finding, leprosy campaigns, where presumptive leprosy cases are examined in a designated location (also called ‘camp approach’), and contact tracing are in place [16]. These control strategies appear to have been effective in achieving early case detection, reflected in a proportion of new patients with visible disabilities of less than 2.5% [15]. The completion rate of leprosy treatment is also high; rates of above 85% for both multibacillary (MB) and paucibacillary (PB) leprosy have been reported for the period 2008

to 2014 [17]. Despite this apparently strong leprosy control program, the incidence of leprosy remains high.
In 2015, the NTLP decided to pilot implementation of SDR-PEP for household contacts in four highly endemic villages of Anjouan. One single round of SDR-PEP was provided to asymptomatic close contacts of recently diagnosed leprosy cases, with a focus on household contacts. The main objective of this intervention was to assess the feasibility of SDR-PEP under programmatic conditions and to document the lessons learnt before embarking on a larger prophylaxis strategy. The main aim of our study was to quantify spatial associations between reported leprosy cases before and after the 2015 intervention. The limited sample size precluded an accurate assessment of the effectiveness of SDR-PEP but we did take it into account as a potential confounder.

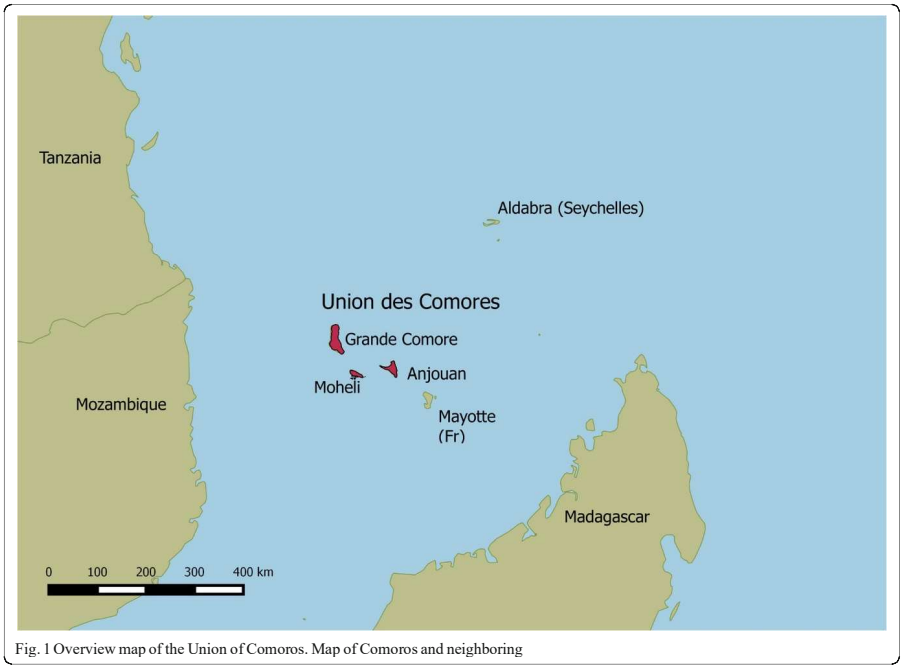

Fig. 1 Overview map of the Union of Comoros. Map of Comoros and neighboring

## Methods

### Setting

The study took place on Anjouan, the second largest island of the Comoros, with approximately 340,000 inhabitants. Anjouan has eight administrative districts, totalling 93 villages. Case finding for leprosy on Anjouan is based on a combination of active and passive approaches.
Four villages with an estimated population of 8400 had been selected for implementing SDR-PEP in May/ June, 2015. A total of 269 consenting close contacts from 70 households had received SDR-PEP, with rifampicin at routine dosing, around 10 mg/kg.
These persons were close contacts, mostly living in the same household as leprosy patients diagnosed over the preceding 3½-year period (since January 1st, 2012).

In this period altogether 176 patients had been diagnosed in the four villages.

**Study design**

The study was designed as a retrospective cohort study. During door-to-door surveys in August/September, 2017, all consenting individuals were examined clinically for leprosy. For each person examined we recorded whether or not the person had suffered from leprosy in the past, whether or not the person had received SDR- PEP in 2015, and whether or not the person was currently suffering from leprosy. For past leprosy patients we recorded the date of diagnosis. The diagnosis of leprosy was made on clinical criteria, following WHO guidelines [18], including examination for loss of sensation and nerve enlargement. In addition, skin biopsies were taken from newly diagnosed all patients identified during the survey. We also recorded geographic coordinates of all households visited.

**Data collection and mapping**

All data, including geographical coordinates of households visited, were recorded using a custom designed Android application in 'Open Data Kit' (ODK). Data were triangulated with the register of new leprosy patients and their records on contacts that had received SDR-PEP. Geographic coordinates of all households visited were plotted on a map using the Quantum Geographic Information System (QGIS) software package, with indication of whether or not there had been leprosy cases in the 3½-year period pre-intervention (index cases), or in the 2-year period after the intervention (incident cases).
We then created for all households screened a variable indicating the distance to the nearest index-case household ranging from 0 m (same household), to 1–25, 26– 50, 51–75, or more than 75 m. Thus, households were split into five categories of distance to an index-case.

**Statistical analyses**

We fitted a Poisson model with the count of leprosy cases detected since July 2015 as dependent variable, and the log of the population examined as offset. As independent variables we assessed the five categories of physical distance to the nearest index case and having been provided SDR-PEP. Those living at more than 75 m were used as reference category. Village of residence was included by default to control for potential confounding by contextual factors.
We calculated incidence rate ratios (IRR) and their 95% confidence intervals (95% CI). To assess a potential interaction between SDR-PEP and physical distance to an index case, we recoded the distance variable to a binary variable set to '1' for household contacts and '0' for all others. Bearing in mind that SDR-PEP was primarily provided to household contacts, we did a separate analysis restricted to household contacts only. A p-value
$< 0.05$ was considered statistically significant.

**Ethics**

This study is part of a larger study for which ethical approval was obtained from the institutional review board of the Institute of Tropical Medicine and the ethics committee of the Antwerp university hospital (both in Belgium), as well as from the ethics committee on Anjouan (Comoros). All subjects provided verbal consent for screening which was carried out by the national leprosy control program as part of their active case find- ing strategy. Leprosy patients identified were enrolled in the main study (reported separately) after providing

written informed consent. In case of illiterate individuals, a thumbprint and a signature of an independent witness were sought. For minors below the age of 18 years, a parent or guardian provided informed consent.

## Results

During the surveys in 2017 we registered a population of 5908, out of which 5760, were screened for leprosy. Among those were 133 out of 176 former leprosy patients diagnosed in the 3½-year period before the intervention (January 2012 to May 2015) and 259 out of 269 close contacts who had been provided SDR-PEP in June, 2015. Out of those 259 close contacts, 240 (92.7%) were household contacts. At the time of the surveys we detected 114 new cases, equivalent to a prevalence rate of 198/10,000.
Thirty-nine more cases had been detected previously in the period since SDR-PEP was provided, resulting in a cumulative incidence of 153 new cases since June, 2015.
There were statistically significant associations with physical distance to the nearest index case, the IRR for household contacts being 2.4 times higher (95% CI 1.5– 3.6) than for those living at more than 75 m. For non-household contacts living within 25 m of an index case there was still a statistically significant increase in risk (IRR 1.8, 95% CI 1.3–2.5), beyond 25 m associations be- came statistically non-significant (see Table 1). The interaction term between household contact and SDR-PEP was statistically not significant (p = 0.23).

Out of the 259 close contacts screened in 2017 who had received SDR-PEP in 2015, seven (2.7%) had developed leprosy versus 146 out of 5501 (2.7%) among those who had not received PEP. Controlling for distance to the nearest index case and village of residence, the IRR for SDR-PEP was 0.6 (95% CI 0.3–1.2).
When looking at household contacts only, the effect of PEP was stronger but still not statistically significant. Among 240 current household contacts that had received PEP, six cases had occurred (2.5%) versus 21 among 432 (4.9%) that had not received PEP. Controlling for village of residence, the incidence rate ratio was 0.5 but similarly not statistically significant (95% CI 0.2–1.3).
Figure 2 shows the distribution of leprosy patients in one of the four villages. Despite a very high prevalence there was still apparent clustering, with incident cases clustered around index cases but also around other incident cases.

Table 1 Frequency and risk of being diagnosed with leprosy in relation to having received SDR-PEP and physical distance (in meters) to the nearest index case in four villages of Anjouan (Comoros)

| Factor | Population ($n$ = 5760) | (%) | No. of leprosy cases ($n$ = 153) | (%) | IRR | (95% CI) |
|---|---|---|---|---|---|---|
| SDR-PEP provided | | | | | | |
| - Yes | 259 | (4.5) | 7 | (2.7) | 0.6 | (0.3–1.2) |
| - No | 5501 | (95.5) | 146 | (2.7) | Ref. | |
| Distance to index case | | | | | | |
| - Same household | 672 | (11.7) | 27 | (4.0) | 2.4 | (1.5–3.6) |
| - 1-25 m | 1373 | (23.8) | 49 | (3.6) | 1.8 | (1.3–2.5) |
| - 26- 50 m | 1604 | (27.9) | 36 | (2.2) | 1.2 | (0.8–1.7) |
| - 51- 75 m | 654 | (11.3) | 16 | (2.4) | 1.3 | (0.8–2.1) |
| - > 75 m | 1457 | (25.3) | 25 | (1.7) | Ref. | |

*SDR-PEP* = Single Dose Rifampicin – Post Exposure Prophylaxis, *Ref.* = reference category

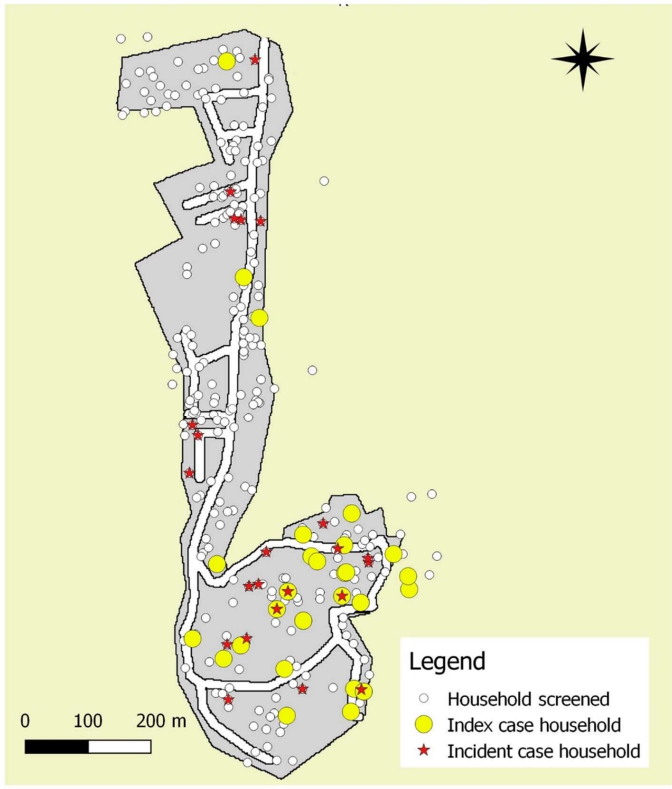


Fig. 2 Distribution of index cases (January 2012–June 2015) and incident cases (July 2015–October 2017) in a village on Anjouan (Comoros). Legend: the map plots the household screened, incident leprosy cases households and incident leprosy cases in a village of Anjouan

**Discussion**

Through door-to-door surveys in four villages on the island of Anjouan of the Comoros that had been targeted for many years with active case-finding activities using a camp approach (i.e. inviting people with skin conditions for free diagnostic screening in a central location in the villages), we found 114 new cases among 5760 contacts screened (2.0% prevalence). Thirty-nine more cases had been detected in the two preceding years. The chances of having leprosy were statistically significantly higher for those residing close to index cases (< 25 m). Two years earlier, in 2015, 269 close contacts from 70 households of leprosy patients in these villages had been provided with a single round of SDR-PEP.

We did assess the potential impact of the intervention and found that taking into account all contacts the overall effect of SDR-PEP appeared protective. But as we knew from the start, due to the low numbers (insufficient power) this effect was statistically not significant, with an incidence rate ratio (IRR) of 0.6 (representing a protective effect of 40%). When considering only household contacts the protective effect was somewhat stronger but still statistically not significant, with an incidence rate ratio of 0.5 (representing a protective effect of 50%). This is comparable with the results of the COLEP trial, which showed a 57%

reduction in leprosy incidence over a two-year period after SDR-PEP was provided to contacts, in comparison to placebo [11]. Furthermore, 240 out of 259 contacts provided with PEP included in our survey (93%) were household contacts and therefore mainly blood-related. A higher effectiveness of SDR-PEP can be expected among non-blood related close contacts [19].

The main focus of our study was to assess the risk of being diagnosed with leprosy as a function of physical distance to an index case. Here we found a statistically significant IRR of 2.4 for household contacts compared to those living at more than 75 m distance. This result is close to the IRR of 2.1 (CI95% 1.6–2.7) for household contacts compared to non-contacts found in Malawi by Fine et al. [20], but lower than the IRR of 9.4 for household contacts compared to their neighbours found in Indonesia by Van Beers et al. [21]. The different grading of IRR could be explained by the type of population and their leprosy endemicity, however the physical distance to an index case related to the closeness and intensity of the contact is clearly the most important risk factor in our population, as also described elsewhere [22]. We found statically significant clustering up to 25 m from any index case.

This is similar to findings from Brazil by Moura et al. who reported equally high yields of active case finding among household contacts as among neighbours of index cases [23]. In our population the mix of different approaches of case finding could have weakened the spatial associations between index cases and incident cases detected because an important number of existing cases must have been missed at baseline.

In a trial reported by Bakker et al. [24] on highly endemic islands in Indonesia two doses of Rifampicin PEP were given three months apart, after which a three- fold reduction in incidence of leprosy was observed on islands allocated to blanket treatment (i.e. treating the entire eligible population), whereas no effect was observed on islands where PEP was provided to household contacts and neighbours only. The islands in Indonesia had a high leprosy incidence (0.9% over three years in the non-intervention group), which is comparable to the incidence in our study villages on the Comoros (0.6% the last five years). With such high incidence levels, PEP given to close contacts alone may not have sufficient impact at the community level because there are many sources of transmission other than the reported cases. Such sources may include asymptomatically as well as symptomatically infected individuals [25, 26]. In such high prevalence situations, virtually all members of a community could be considered as a contact and the whole community would be eligible to a PEP intervention [27–29].

Whereas the Indonesian islands had only a few thousand inhabitants [24], Anjouan has more than 340,000. Subjecting them all to SDR-PEP seems not very feasible. If, on the other hand, it could be demonstrated that transmission clusters mostly within certain (parts of) high-endemic villages, targeting entire villages or parts of them would be feasible.

Two important lessons can be learned from this pilot study. Leprosy geographical clusters in space at the sub-village level, and targeting not only household members but also neighbours of index cases with active case finding and post-exposure prophylaxis seems indicated. Secondly, in an environment with (very) high leprosy incidence, active case finding needs to be intensified prior to providing SDR-PEP to ensure that there is no hidden leprosy prevalence, otherwise many contacts of leprosy patients will not receive SDR-PEP.

## Conclusion

This pilot study demonstrated an increased risk of leprosy in contacts beyond the household, therefore a wider circle should be considered for chemoprophylaxis. Baseline surveys and extended contact definitions are essential for improving SDR-PEP effectiveness.

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# 3 Protocol, rationale and design of PEOPLE (Post ExpOsure Prophylaxis for LEprosy in the Comoros and Madagascar): a cluster randomized trial on effectiveness of different modalities of implementation of post-exposure prophylaxis of leprosy contacts

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**Abstract**

**Background**

Leprosy is an ancient infectious disease with a global annual incidence that has plateaued above 200,000 new cases since over a decade. New strategies are required to overcome this stalemate. Post-exposure prophylaxis (PEP) with a single dose of Rifampicin (SDR) has conditionally been recommended by the World Health Organization (WHO), based on a randomized-controlled-trial in Bangladesh. More evidence is required. The Post ExpOsure Prophylaxis for Leprosy (PEOPLE) trial will assess effectiveness of different modalities of PEP on the Comoros and Madagascar.

**Methods**

PEOPLE is a cluster-randomized trial with villages selected on previous leprosy-incidence and randomly allocated to four arms. Four annual door-to-door surveys will be performed in all arms. All consenting permanent residents will be screened for leprosy. Leprosy patients will be treated according to international guidelines and eligible contacts will be provided with SDR-PEP.
Arm-1 is the comparator in which no PEP will be provided. In arms 2, 3 and 4, SDR-PEP will be provided at double the regular dose (20 mg/kg) to eligible contacts aged two years and above. In arm 2 all household-members of incident leprosy patients are eligible. In arm 3 not only household-members but also neighbourhood contacts living within 100-m of an incident case are eligible. In arm 4 such neighbourhood contacts are only eligible if they test positive to anti-PGL-I, a serological marker. Incidence rate ratios calculated between the comparator arm 1 and each of the intervention arms will constitute the primary outcome.

**Discussion**

Different trials on PEP have yielded varying results. The pivotal COLEP trial in Bangladesh showed a 57% reduction in incidence over a two-year period post-intervention without any rebound in the following years. A study in a high-incidence setting in Indonesia showed no effect of PEP provided to close contacts but a major effect of PEP provided as a blanket measure to an entire island population. High background incidence could be the reason of the lack of effect of PEP provided to individual contacts. The PEOPLE trial will assess effectiveness of PEP in a high incidence setting and will compare three different approaches, to identify who benefits most from PEP.

## Background

We describe the protocol of the PEOPLE study, a randomized controlled trial on post-exposure prophylaxis (PEP) for leprosy on the Comoros and Madagascar. Leprosy is an ancient infectious disease caused by *Mycobacterium leprae*. In humans, it is probably transmitted through the air provoking skin and nerve lesions after years without clinical manifestations. Delayed treatment leads to complications including permanent deformity, which in its turn leads to stigma.
Since 2000, leprosy has been declared eliminated as public health problem worldwide, on the basis of a prevalence rate of less than one per 10,000 population [1]. Leprosy incidence however has plateaued above 200, 000 cases annually illustrating uninterrupted transmission. The study countries, Comoros and Madagascar, both have high leprosy incidence and are included in the list of 23 priority countries for leprosy control drawn up by the World Health Organization (WHO) [2]. The islands of Anjouan and Mohéli on the Comoros have been reporting incidence rates close to 10 per 10,000 population for years. In some villages on Anjouan door-to-door screening in 2017 revealed prevalence rates of up to 2% [3]. Madagascar notified 1424 new leprosy cases in 2018 on a population of approximately 26 million, 9% were children. (2) However, the epidemiological burden varies between the districts, explained by different access related issues such as geographical, availability of qualified health staff, health-seeking awareness, etc. For this study, a hyperendemic district, Miandrivazo, has been selected.
Providing a single dose of Rifampicin (SDR) as PEP to contacts of leprosy patients has been conditionally endorsed by WHO as a strategy to overcome the current stalemate [4, 5]. This recommendation is mainly based on the 'contact transmission and chemoprophylaxis in leprosy' (COLEP) trial in Bangladesh that demonstrated a 57% reduction of leprosy incidence over a two-year period following provision of SDR to household and social contacts of leprosy patients [6]. However in high endemicity settings in Indonesia, two monthly doses of Rifampicin administered to household and social contacts of leprosy patients had no effect, in contrast with providing PEP to an entire island population that resulted in a threefold reduction of leprosy incidence [7].

## Methods/design

### Objectives and hypothesis

In this study we intend to compare effectiveness as well as cost-effectiveness of three different modalities of SDR-PEP to a comparator arm in which no PEP is provided.

### Study design

The study has been designed as a cluster randomized trial in which villages will be randomly allocated to four arms. All villages will be subject to four annual rounds of door-to-door screening. Leprosy patients identified will be treated in accordance with international guidelines, contacts will be provided PEP in accordance with the study arm. In arm 1, the comparator arm, no PEP will be provided. In arm 2 all asymptomatic household members will receive SDR-PEP. In arm 3 SDR-PEP will be provided to all leprosy asymptomatic household members plus neighbourhood contacts residing within a 100-m radius from an index case household. Finally, in arm 4 SDR-PEP will be provided to all household members and to those residing within 100-m of an index case and testing positive to anti-phenolic glycolipid-I (anti- PGL-I), a test for detection of IgM antibodies to *M. leprae*. If the village population in a

100-m radius around households of index cases comprises ≥50% in arm 3 or ≥ 75% in arm 4, the entire village will in principle be eligible for SDR-PEP.

**Setting**

The Union des Comores is an island nation in the Indian Ocean, north of Madagascar. On the main island, Grande Comore, leprosy has become a rare disease but the islands of Anjouan and Mohéli are still notifying around 400 new leprosy cases annually on an estimated population of 450,000.
The Comoros has for decades had a strong leprosy control program, achieving good coverage and fully in line with the strategies recommended by WHO. Even
though early case finding is achieved, with less than 3% of visible deformities in new leprosy patients, transmission has remained high. This is reflected in a 27% proportion of children under 15 years of age among new patients.
Madagascar has a population of 26 million and notifies around 1500 leprosy cases annually. However, leprosy control program coverage is patchy and case detection is often late, reflected in a proportion of new patients pre- senting with visible deformities close to 20%. The proportion of children among incident leprosy patients is lower than on the Comoros but remains significant at 9% [2]. The district of Miandrivazo selected for this study is located in the Menabe area on the central west of Madagascar. More specifically, the study takes place in the southern part of the district which is mainly rural and relatively sparsely populated with numerous small and remote villages. Coverage of leprosy control services in that area has been limited and reliable incidence data have not yet been available for recent years. The first round of screening in Madagascar will therefore be used as a baseline survey, randomization will only be done upon its completion.

**Participants**

Participants will be recruited from 48 villages on the Comoros (32 on Anjouan and 16 on Mohéli) and a number of villages yet to be determined in Miandrivazo district of Madagascar. Leprosy screening will be offered to both genders and all ages, if required treatment will be provided. PEP however will only be provided to those permanent residents aged two years or above who did not receive Rifampicin in the past two years. Another exclusion criterion is having cough of more than two weeks' duration (presumptive pulmonary tuberculosis).

**Randomization**

On Anjouan and Mohéli (Comoros) the randomization has been done at village level based on reported leprosy in- cidence in the years 2013–2017. Villages had been grouped by island in decreasing order of incidence in blocks of four. Within each block villages were randomly allocated to one of the four study arms in a mutually exclusive manner, using random numbers generated in Excel.
For Miandrivazo district (Madagascar) the randomization will be done at the end of the first year of 2019 after completion of the door-to-door active case detection carried out during the first year of the study. A number of high prevalence villages with a total population of ideally close to 20,000 will be selected, taking care of having a fourfold (e.g. 16 or 20). These will then be grouped into blocks of four based on prevalence and randomized over the four study arms within each block similarly to the procedure used on the Comoros.

**Outcome measures**
The principal outcome measure will be the leprosy incidence rates in each of the four study arms. The incidence rates in the Comoros will be measured between the first and the fourth door-to-door survey, while the incidence rates in Madagascar will be evaluated between the second and fourth survey round. The incidence rate ratios will then be calculated between the comparator arm (arm 1) and each of the intervention arms. In addition, the costs of screening and PEP provision in each of the four arms will be determined allowing to calculate a cost per leprosy case averted for each of the intervention arms with the comparator arm as baseline. Spatial clustering of leprosy at sub-village level will be assessed by comparing incidence rates within households of index cases and incidence among neighbourhood contacts at varying distances (< 25 m, 25– 50 m, 50–75 m and 75–100 m) to incidence rates among those living at more than 100 m from any index case.

**Intervention implementation and data collection**

Door-to-door screening will be conducted, covering all study villages once yearly for a total of four consecutive years. In addition to leprosy the study will focus on skin diseases. Treatment will be provided for common minor skin conditions such as fungal infections or scabies. Lep- rosy patients detected will be treated according to the guidelines from the national leprosy control program.
In each household screened, name, age and gender of each permanent household member will be recorded on a paper form during the visit. This form, of which one copy will be used per household, has a unique serial number. It has one line per person, each line with a space to sign for informed consent and a pre-printed unique barcode. These forms will be used to enter form serial number and name, age, gender and barcode of each individual in a database in MS Access. All other data will be recorded through an Android application made in Open Data Kit Collect (ODK). The serial number will be copied from the paper form into the app for each household, for each individual the corresponding barcode will be scanned. Apart from form serial number and barcodes, the app will also be used to record the date of visit, Global Positioning System (GPS) coordi- nates of the household, village name, and number of household members. For each household member we will record whether the person was present, whether the person has a history of leprosy, whether (s)he was examined and what was the result of the clinical exam. We will also record the presence or absence of a Bacille de Calmette Guérin (BCG) scar and ask for cough of more than two week's duration. These data are uploaded to a secure server whenever a village is completed. Names will not be recorded in the Android application but can be retrieved from the Access database if required based on the barcodes (e.g. for treatment of leprosy). Thus, exact records will be available on numbers of persons living in the households visited, numbers screened, numbers of cases identified and the date and location of screening activities.
Participants with cough for more than two weeks identified during surveys will have a sputum sample collected for tuberculosis screening. Those with confirmed tuberculosis will be treated according to the national tuberculosis guidelines.
Leprosy diagnosis will be clinical, based on the presence of three cardinal signs: patch with loss of sensation, en- larged peripheral nerves and/or slit-skin smear (SSS) positive for acid fast bacilli. All leprosy cases diagnosed will be verified by experienced leprosy national control program staff. If confirmed they will be treated according to WHO guidelines.
Conditional upon their informed consent, incident leprosy patients will be enrolled in a sub-study in which slit skin smears, nasal swabs and skin biopsies will be sampled. Biopsies will be subjected to quantitative polymerase chain reaction (qPCR) for Mycobacterium leprae.

In the framework of a sub-study, not part of this protocol, genotyping of bacillary DNA will be performed on all qPCR positive samples.
SDR-PEP will be provided to all household members in arms 2, 3 and 4 as soon as a new leprosy case is detected. Children below two years of age and persons having received Rifampicin within the last 24 months will be excluded. In Comoros, a new leprosy case is defined in the first round as a case arising after the 31st of December, 2017 (or after the 31st of December, 2018 in Madagascar), and in subsequent rounds as a case arising after the previous screening round.
In arms 3 and 4 PEP will also be provided to neighbourhood contacts living within 100 m of an index case. This will only be done once the entire village has been screened. Selection of the group of individuals living within 100 m of an incident case will be done after analysing cleaned data by the principal investigators in each island and the research coordinator at the Institute of Tropical Medicine, Antwerp. As explained earlier, in arm 4 non-household contacts living within 100 m of an index case are eligible for PEP only if they are positive to anti-PGL-I. In arm 3, if 50% or more of the population live within 100 m of an index case, the entire village will be considered eligible. This will be the case in arm 4 if 75% or more live within 100 m of an index case.
Detailed costs of screening and PEP implementation will be recorded for each study arm including direct costs for direct implementation, monitoring and support.

**Post exposure prophylaxis**
As post exposure prophylaxis we will use a single dose of Rifampicin, in accordance with the WHO guidelines. However, the dose used will be higher than the standard dose. Rifampicin has for decades been a core drug for the treatment of tuberculosis (TB). The dosage of 10 mg/kg recommended in the 1970s was established balancing concerns on toxicity and cost [8] However, this dose might not be optimal in terms of efficacy. A study using Rifampicin at 20 mg/kg daily in treatment of TB demonstrated a doubling in early bactericidal activity compared to the standard dose [9] In another TB study, two weeks of Rifampicin at a dose of 35 mg/kg was well tolerated without increase in toxicity [8] The recent study 'Optimization of the TB Treatment Regimen Cascade (OneRIF, Clinical- Trials.gov Identifier: NCT02153528)' documented no in- creased toxicity in 475 adults treated with Rifampicin at 20 mg/kg for six months as part of the treatment of drug-susceptible TB, compared to 468 adults that were treated with Rifampicin at 10 mg/kg.
There are also precedents of using Rifampicin at high doses for leprosy post-exposure prophylaxis and treatment. In the French Polynesia Rifampicin at 25 mg/kg was used as post-exposure prophylaxis [10–12]. Single dose of Rifampicin at 40 mg/kg was effective and safe for the treatment of PB cases with a negative bacillary index [13]. In the PEOPLE trial we therefore opted for Rifampicin in a single a dosage of 20 mg/kg, which we will refer to as 'Single Double Dose Rifampicin Post Exposure Prophylaxis' or 'SDDR-PEP'.
SDDR-PEP will be provided under supervision of a village health worker who will keep a record of each per- son eligible and whether or not this person has taken his dose. As higher Rifampicin dosage has been documented safe [8, 10–12], we will implement passive adverse events (AE) surveillance. An AE is defined as any unexpected event in a clinical investigation after administering a pharmaceutical product, it does not necessarily imply a causal relationship. A distinction will be made between AE's and serious AE's (SAE), the latter defined as an AE that provokes death or is life-threatening, requiring hospitalization or increase in duration of existing hospitalization, or results in permanent disability /incapacity or provokes a congenital anomaly/ birth defect. We will record all AE and SAE occurring within 72 h of Rifampicin administration and classify them according to severity and probable relationship to SDDR-PEP.

Also, health workers in charge of the selected villages will be informed about the PEOPLE trial and advised to report any AE or SAE. In case of SAE a specific template will be recorded and sent to pharmacovigilance unit of ITM within 24 h.
It has been documented that the risk of inducing Rifampicin resistance in undiagnosed TB or leprosy as a result of a single dose of Rifampicin is negligible [14]. Rifampicin resistance in TB can occur under monotherapy but that requires longer exposure [15]. In order to minimize the risk of Rifampicin resistance we will screen for TB and exclude all presumptive TB with cough of more than two weeks. Also, every person that has received Rifampicin within less than two years will be excluded from SDR-PEP. Finally, we will monitor Rifampicin resistance in leprosy through molecular testing on qPCR positive samples from leprosy cases.
Rifampicin interacts with drugs such as antiretrovirals (ARV) [16] that are known as inducer of a number of genes controlling drug metabolism and transport like cytochrome P450 isoenzymes and the drug efflux pump p-glycoprotein. Therefore, concentration of Rifampicin administered with ARV may decrease. As we are providing a single dose and given that the Rifampicin serum half-life is less than five hours such interaction effect can be considered negligible irrespective of the dosing [17].

**Rationale**

Effectiveness of PEP probably depends on the leprosy epidemiological burden, the type of contacts targeted and the type of PEP-regimen. Targeting household contacts only avoids issues of confidentiality but may lack effectiveness. Also targeting social contacts, as was done in the COLEP trial in Bangladesh, is probably more effective [6]. However, this approach may even not be effective in hyper endemic settings as suggested in a study performed in Indonesia [18].
Another important factor to consider is the regimen used. In the COLEP trial a 50–60% reduction in incidence was achieved after administering a single dose of Rifampicin at 10 mg/kg [6]. An expert committee convened in preparation of the PEP++ trial, which is to start soon, drafted a reinforced PEP regimen based on three monthly doses of Rifampicin plus Clarithromycin [19]. In the PEOPLE trial we choose to adopt a regimen that includes only one single dose of PEP for logistical and cost reasons.

**Data analysis**

For our main analysis we will fit a random effects Poisson model (or negative binomial if overdispersed) comparing incidence rates between the first and fourth survey round in arms 2, 3 and 4 with those of the comparator arm 1 (starting from the second survey round in Madagascar). As random effects we will use island (Anjouan, Mohéli or Madagascar), ‘block’, i.e. the groups of four villages arranged in order of incidence initially used in the randomization process and village. We will thus obtain incidence rate ratios between arm 1 and each of the other arms. Considering the fact that three comparisons will be performed, a p-value of 0.017 will be used as threshold of statistical significance.
Spatial clustering will be assessed by calculating for each individual the distance to the nearest leprosy affected household in the previous year [20]. Household coordinates will be plotted in Quantum GIS version 3.8 Zanzibar. We will then calculate the distance to the nearest index case household for each household using the distance matrix tool. As a next step subjects will be divided into six categories: household contacts, neighbours at less than 25 m and neighbourhood contacts be- tween 25 and 50 m, 50–75 m and 75–100 m and at more than 100 m. Incidence rate ratios for leprosy will be calculated with individuals living at more than 100 m as reference category and village as random effect.

Results of spatial analysis will be triangulated with results of phylogenetic of *M. leprae* clustering observed in the sub-study in which skin biopsy samples are collected from each consenting incident leprosy patient.
Both average cost per person screened for leprosy per island and the average cost per leprosy patient detected per study arm will be assessed. Cost data will be gathered throughout the study. All incremental costs will be calculated by using comparator arm as a baseline.

**Sample size**
The calculation of sample size is based on the primary objective and according to the methodology described by Hayes and Bennet for pair-matched randomized controlled trials [21]. The incidence rate in the comparator arm with no PEP will be compared to each of the three intervention arms. We assumed that the annual incidence rate in the comparator arm will be 1.5/1000, based on data from 48 villages on the Comoros for the years 2013 to 2017. We expected a reduction of the leprosy incidence of 50% in any of the intervention arms. As three comparisons will be made, we opted for a significance level of 0.017.
Based on data from the Comoros we calculated a coefficient of variation k between clusters of 0.29. With an aver- age cluster size of 2400, to achieve a power of 80%, we will need 13 clusters per study arm, i.e. 4* 31,200 participants. In order to compensate for inaccuracies in census data, as well as for absentees and non-responders, we decided to aim for 36,000 participants per study arm, i.e. 15% extra. Therefore, the total sample size is expected to be 124,000 and 20,000 to be recruited in the Comoros and in Madagascar respectively.

**Ethics**

The study will be carried out according to the principles stated in the Declaration of Helsinki, all applicable regulations and according to established international scientific standards. The choice of treatment for the leprosy patients will not depend on the results of the PEOPLE study, but on the current national leprosy guidelines.
The study has been approved by the 'Comité d'Éthique de la Recherche Biomédicale' (CERBM) in Madagascar and the 'Comité National d'Éthique pour les Sciences de la Vie et de la Santé' (CNESS) in the Comoros. Approval has also been obtained from the Institutional Review Board (IRB) of ITM given that ITM is the sponsor of this study. In addition, the study has been approved by the Ethics Committee (EC) of the University of Antwerp Hospital in Antwerp.
Prior to the start, this study has been included in the Clin- icaltrials.gov public registry (NCT03662022, on 7 September 2018, https://clinicaltrials.gov/ct2/show/NCT03662022).

**Discussion**

Although single-dose Rifampicin post-exposure prophylaxis has now been conditionally endorsed by WHO [5], a lot of debate remains. Some argue that SDR will mainly prevent paucibacillary leprosy which is less infectious or that SDR may just postpone new cases rather than preventing them. Others argue that SDR might eventually lead to resistance of M. leprae against Rifampicin [22]. The pivotal COLEP trial in Bangladesh did not provide any such indications. There was a clear incidence reduction of 50–60%, without any rebound after the intervention ended [6]. However, evidence from more than one site is required and other options of PEP need to be explored. As was explained earlier we do opt for a higher dose of Rifampicin, hoping the in- creased early bactericidal effect observed for M. tuberculosis will also apply to M. leprae.

The PEOPLE trial is the second major randomized controlled trial on post-exposure prophylaxis for leprosy after the COLEP trial. It is implemented against a background of very high leprosy incidence, which may have a major implication for effectiveness of PEP. The PEOPLE trial therefore includes two different approaches to PEP, targeting only household members and targeting entire communities. In addition, we will assess the feasibility and effectiveness of selecting neighbourhood contacts eligible for PEP based on presence of antibodies against M. leprae. Use of innovative digital tools for data collection and mapping allows geospatial patterns in leprosy transmission to be assessed, which can at a later stage be triangulated with results of phylogenetic clustering genotypes of *M. leprae* found in the patients. PCR results from the sub study will also allow the accuracy of diagnostic procedures to be validated.

Costing and cost-effectiveness are also part of the study. Thus, once completed we will be able to provide answers relevant for leprosy control programs concerned with questions on feasibility and cost of PEP implementation.

As a by-product of this study we are establishing a very well-characterized cohort of leprosy patients for which clinical information, samples and precise geographical location will be available. This cohort would allow other pertinent research questions to be answered such as risks for relapse and drug resistance [23].

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# 4 Exploring clustering of leprosy in the Comoros and Madagascar: A geospatial analysis

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**Abstract**

**Objectives**

To identify patterns of spatial clustering of leprosy.

**Design**

We performed a baseline survey for a trial on post-exposure prophylaxis for leprosy in Comoros and Madagascar. We screened 64 villages, door-to-door, and recorded results of screening, demographic data and geographic coordinates. To identify clusters, we fitted a purely spatial Poisson model using Kulldorff's spatial scan statistic. We used a regular Poisson model to assess the risk of contracting leprosy at the individual level as a function of distance to the nearest known leprosy patient.

**Results**

We identified 455 leprosy patients; 200 (44.0%) belonged to 2735 households included in a cluster. Thirty-eight percent of leprosy patients versus 10% of the total population live 25 m from another leprosy patient. Risk ratios for being diagnosed with leprosy were 7.3, 2.4, 1.8, 1.4 and 1.7, for those at the same household, at 1–<25 m, 25–<50 m, 50–<75 m and 75–<100 m as/from a leprosy patient, respectively, compared to those living at ≥100 m.

**Conclusions**

We documented significant clustering of leprosy beyond household level, although 56% of cases were not part of a cluster. Control measures need to be extended beyond the household, and social networks should be further explored.

## Introduction

Leprosy is an ancient infectious disease caused by *Mycobacterium leprae*, a microorganism discovered by [1]. The main transmission route is probably airborne [2], with an incubation period ranging from 1–2 years to decades. When the disease is established, skin and nerve damage provoke the main symptoms. Immunological disturbances can trigger inflammatory episodes before, during and after treatment that can aggravate existing neuropathy or provoke new neuropathy [3]. Delay in diagnosis and treatment of leprosy and its complications can result in permanent deformities [4], which can cause social stigma [5].

Multidrug therapy (MDT) with rifampicin, clofazimine and dapsone, introduced in the 1980s, has proven highly effective [6, 7]. As a result, leprosy prevalence has dramatically decreased worldwide and in 2000, leprosy was declared eliminated as a public health problem. Elimination was defined as a global prevalence of less than 1 leprosy case per 10,000 population[8]. The impact on transmission, and by extension on the incidence of leprosy, has been less impressive. Since 2013, the annual number of new leprosy cases reported globally has persisted above 200 000, and the average incidence of leprosy in children has stagnated at close to 1 per 100 000 inhabitants [7]. These 2 indicators support evidence of uninterrupted transmission of M. leprae.

The Global Leprosy Strategy 2016–2020 aimed to reduce transmission, focusing on early diagnosis, especially in children, and targeting endemic communities through active case finding strategies [9]. In 2018 the World Health Organization endorsed preventive treatment for close contacts of patients in the form of single-dose rifampicin post-exposure prophylaxis (SDR-PEP)[10]. In Bangladesh, the pivotal COLEP trial had shown a 50%– 60% decrease in leprosy incidence when comparing contacts receiving SDR-PEP to contacts receiving a placebo [11, 12]. More recently, a modelling study in the context of the Indian health system predicted that SDR-PEP is a cost-effective intervention based on its ability to prevent disabilities [13]. Moreover, the feasibility of programmatic delivery of SDR-PEP has been demonstrated in 7 endemic countries in Asia, Africa and South America [14].

The Post ExpOsure Prophylaxis for LEprosy (PEOPLE) trial that commenced in late 2018 aims to gather further evidence for SDR- PEP and explore different modalities. The study is carried out in 64 villages in the Comoros and Madagascar, with 4 randomized study arms. Over 3 years (2 years in Madagascar), leprosy incidence in 3 intervention arms will be compared with that in the comparator arm without SDR-PEP (Arm 1). Modalities explored include provision of SDR-PEP to household contacts only (Arm 2), to all those living within 100 m of an index case (Arm 3), or to household contacts plus those living with 100 m of an index case and testing positive for antibodies directed against M. leprae-phenolic glycolipid-I (PGL-I), assessed by a rapid test that quantitatively detects immunoglobulin (IgM) antibodies against PGL-I in finger- stick blood (Arm 4) [15].

In this report, we analyse the baseline survey results, before SDR-PEP was provided, to assess patterns of spatial clustering of leprosy at household and individual level that may inform case- finding strategies.

## Methods

### Study design

As part of the baseline survey of the PEOPLE trial, we visited all households in 64 villages, 32 on Anjouan (Comoros), 16 on Mohéli (Comoros) and 16 in Miandrivazo district (Madagascar). All consenting household members were screened for leprosy and results were recorded, along with their leprosy history and basic demographic details, on smartphones,

using a custom-designed app in Open Data Kit (ODK) Collect. The app also enabled the recording of the geographic coordinates of each household visited. Thus, we developed a dataset containing records of 102 089 individuals, 57 619 on Anjouan, 21 982 on Mohéli and 22 488 in Miandrivazo, divided over 20 897 households. Median household size was 6 on Anjouan and Mohéli, with an interquartile range (IQR) of 4–8, and 5 in Miandrivazo (IQR 4–7). Among those surveyed, we found 455 (4.5 per 1000) prevalent leprosy cases, 346 (6.0 per 1000) on Anjouan, 39 (1.8 per 1000) on Mohéli, and 70 (3.1 per 1000) in Miandrivazo. We included cases already on treatment at the time of the survey and cases newly diagnosed during the survey. This dataset was used to explore the spatial clustering of leprosy.

**Study setting**

The Comoros is an archipelago located in the Indian Ocean, composed of 3 islands: the main island, Grand Comore, and two smaller islands, Anjouan and Mohéli. The country, with 832 000 inhabitants, is 1 of 23 high-priority countries for leprosy identified by the World Health Organization[7]. The leprosy burden is concentrated on Anjouan and Mohéli, whereas Grand Comore has only sporadic cases. In 2018, the leprosy case notification rates were 6.6 and 7.4 per 10 000 inhabitants, respectively, for Anjouan and Mohéli [16]. The Comoros is ranked 156 out of 189 countries on the human development index [17]. Over half of the population (55%) depend on agriculture but soil erosion makes production insufficient and fishing partially fills the food gaps [18]. In the latest national demographic survey, married women and men represent, respectively, 61% and 53% of the population that form nuclear families that include polygamic unions, which are more frequent in rural areas (20% versus 14% in urban areas).[19] Villages on the Comoros tend to be compact and well-delineated, with little open space inside village boundaries. Anjouan is the larger of the 2 leprosy endemic islands with a population of 332 466 on a land area of 424 km2, versus 52 360 population and a land area of 208 km2 for Mohéli. The population density on Anjouan is thus roughly 3 times higher than on Mohéli. This is further compounded by the fact that Anjouan has relatively little arable land because it is situated on a steep volcano. Most of the population therefore live in the coastal areas[20].

Both passive and active case finding strategies for leprosy are implemented. For over 10 years, leprosy elimination campaigns have been conducted regularly. During campaigns, the population is invited for screening for skin conditions in a defined location. Presumptive leprosy patients are examined by specialized staff and contact screening is done in the same place [21]. Throughout these campaigns, the proportion of new patients with visible deformities has been <3% [7] and the MDT completion rate for multi-bacillary cases [22] has been >90%, indicative of high-quality leprosy services. Nevertheless, the continued high incidence of leprosy and the high proportion of children (<15 years) among new cases (>30%) illustrates uninterrupted transmission.

Madagascar is a much larger country located in the Indian Ocean, just south-east of the Comoros, with a land area of approximately 592,800 km2. It is also included among the 23 high-priority countries for leprosy, notifying approximately 1500 leprosy cases per year for a total population of 26.2 million. The leprosy burden is distributed unevenly with high and low prevalence areas. The proportion of new patients presenting with visible deformities is close to 20% and the MDT completion rate in multibacillary cases is 76%; both indicators are explained by the limited geographical coverage of leprosy services. The proportion of children <15 years among new leprosy patients is 9%[7], though lower than on the Comoros, it still illustrates persistent transmission. The Madagascar National Leprosy Control Program implements passive and active case detection. Active case detection is guided at the regional level by endemicity, geographical accessibility and available means. On the human

development index Madagascar is ranked 164 out of 189 countries [17]. At a national level, 63.4% of the families are nuclear (65.8% and 54.3% in the rural and the urban areas, respectively). The study district of Miandrivazo is a poor rural district with a land area of 12 330 km2 and a population of 162 462. The study villages are situated 24–70 km from the district capital. They tend to be stretched out, consisting of multiple hamlets, and are often poorly accessible by road. Most villagers depend on agriculture for their livelihood, and raising livestock is another source of income [23].

**Sample size and statistical analysis**

The sample size was calculated for the primary objective of the PEOPLE trial described earlier, which compares the effectiveness and cost-effectiveness of 3 different modalities of providing SDR- PEP [24]. A total of 64 villages were selected, with an estimated population of approximately 140 000. The actual numbers of inhabitants in the villages were lower than these estimates and, as mentioned earlier, 102 089 participants were enrolled, among whom there were 455 active leprosy cases, either newly diagnosed during the survey or on treatment at that time.

Using the dataset described, we conducted 2 analyses. First, we used a collapsed dataset in which each household represented 1 observation with geographic coordinates, with the number of household members and leprosy cases as variables. This dataset was used to fit a purely spatial Poisson model using Kulldorff's spatial scan statistic to identify clusters of leprosy-affected households[25]. We used the software's default settings, i.e., circular clusters with a maximum size of 50% of the population. We retained only clusters that were statistically significant ($P < 0.05$) or borderline significant (0.05 s P s 0.10).

For the second analysis, we used individual data. Making use of the distance matrix module in QGIS[26], we determined for each individual the distance to the nearest other person who is a (prevalent) leprosy case. For individuals who were found to be leprosy cases themselves, this would be the distance to the nearest other leprosy case. Based on these distances, the study population was divided into 6 categories: 1. Household contacts of a leprosy patient; 2. Neighbours at <25 m of a leprosy patient; 3. Village contacts at 25–<50 m of a leprosy patient; 4. Village contacts at 50–<75 m of a leprosy patient; 5. Village contacts at 75–<100 m of a leprosy patient; 6. Those living at ≥100 m of a leprosy patient. These data were used to fit a Poisson model with prevalent leprosy as the outcome and distance category as the predictor. As a reference category, we used those living at ≥100 m from the nearest known other person with leprosy. To account for intracluster correlation, we added village of residence nested within island location to the model as a random effect. As a sensitivity analysis, not foreseen in the original statistical analysis plan, we repeated the analysis by site (Anjouan, Mohéli and Madagascar) and also after excluding villages with zero preva- lence.

**Results**

The 455 leprosy cases lived in 418 households. There was a single case in 382 households, 35 households had 2 cases, 1 household had 3 cases, and in the remaining 20 479 households, no prevalent leprosy cases were found.

Prevalence rates by village were 0.0–30.8 per 1000 with a median of 2.5 and IQR 0.99–5.0 per 1000. In 8 out of 64 villages, no active cases were found. Figure 1 shows the distribution of leprosy prevalence by village during the baseline survey.

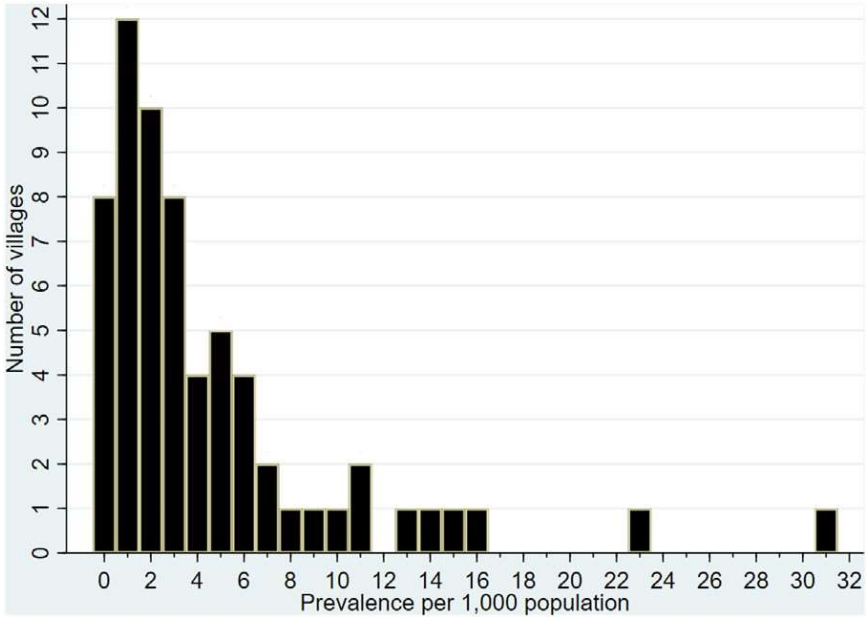


Figure 1. Distribution of leprosy prevalence per 1000 inhabitants, per village included in the survey, Comoros and Madagascar, 2019.
Among the 64 villages included in the study, there were 8 villages without leprosy cases. In the other 56 villages, the prevalence per 1000 population ranged between 1 in 12 villages to 31 in 1 village.

The Kulldorff's spatial scan statistic identified 4 statistically significant clusters on Anjouan, 1 significant and 1 borderline significant cluster on Mohéli, and 1 significant and 2 borderline significant clusters on Madagascar (Table 1). Of all 455 patients in the 3 sites, 200 (44.0%) belonged to a high prevalence cluster though 15 of those patients were part of borderline statistically significant clusters. An example of a cluster in the Comoros is shown in Figure 2 below.

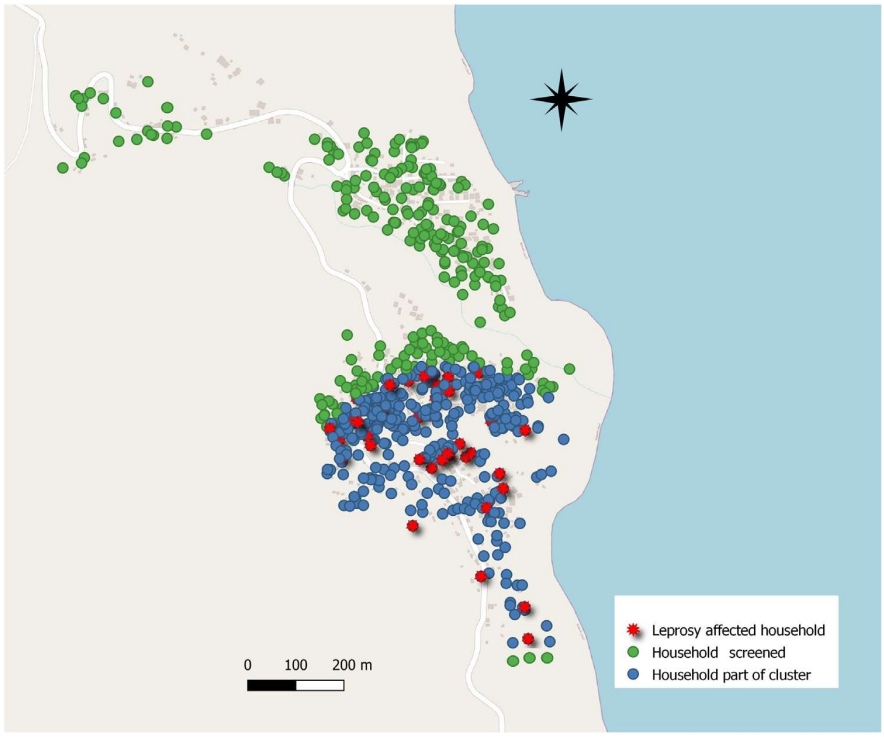


Figure 2. Clustering of leprosy cases in villages on Anjouan (with minimal adaptations to protect the privacy of participants).
The island of Anjouan had the highest proportion of leprosy cases belonging to significant clusters. In this example we illustrate the household screened in green, the household screened and part of a cluster in blue and the leprosy-affected households in red.

On Anjouan, 173/346 leprosy patients (50%) were part of 4 high prevalence clusters, with statistically significant P-values of <0.01 and relative risks of 3.1–6.0. On Mohéli, 10/39 patients (24%) belonged to 2 high prevalence clusters, 1 statistically significant cluster that includes 8/39 cases (21%) with a prevalence rate ratio of 42.4 and $P < 0.0005$; the other 2 patients belong to a borderline significant cluster ($P = 0.088$) which is, in fact, a single household. In Madagascar, 17/70 patients (24%) were part of 3 high prevalence clusters, 1 small but statistically significant cluster comprising 4 patients ($P = 0.0045$) and 2 marginally significant clusters made up of 7 and 6 patients with P-values of 0.067 and 0.072, respectively. Details of the clusters are presented in Table 1.

Table 1. Characteristics of high prevalence clusters identified by Kulldorff's spatial scan statistic.

| Site | Cluster | Number of households | Cluster size (population) | Number of leprosy cases | Relative risk | *P*-value |
|---|---|---|---|---|---|---|
| Anjouan | 1 | 355 | 1688 | 47 | 5.2 | <0.0001 |
| | 2 | 1159 | 6159 | 93 | 3.1 | <0.0001 |
| | 3 | 91 | 464 | 16 | 6.0 | 0.0019 |
| | 4 | 113 | 592 | 17 | 5.0 | 0.0078 |
| Mohéli | 1 | 25 | 133 | 8 | 42.4 | <0.0001 |
| | 2 | 1 | 4 | 2 | 297.0 | 0.088 |
| Madagascar | 1 | 3 | 19 | 4 | 71.7 | 0.0045 |
| | 2 | 45 | 236 | 7 | 10.5 | 0.067 |
| | 3 | 32 | 160 | 6 | 13.1 | 0.072 |

In our second analysis, we found strong spatial clustering of leprosy based on the probability of being diagnosed with the disease as a function of geographical distance to the nearest other prevalent leprosy case at the time of the survey. In our model, controlling for intracluster correlation by using village of residence nested within island location as a random effect, and using those living at ≥100 m as a reference category, we observed prevalence rate ratios ranging from 7.5 for household members, 2.5 for neighbours within 25 m, decreasing to 1.8 for those living at 75–100 m, but all statistically significant. Details are shown in Table 2.

Table 2. Probability of being a leprosy patient as a function of distance to nearest index case random-effects model controlling for island and village of residence.

| Distance to index case | Population screened | Number of leprosy cases (%) | Adjusted prevalence rate ratio (95% CI) |
|---|---|---|---|
| Same household | 2159 | 73 (3.4) | 7.5 (5.2–10.8) |
| Neighbour contact at <25 m | 9448 | 98 (1.0) | 2.5 (1.8–3.5) |
| Neighbourhood contact at 25–<50 m | 13,645 | 91 (0.7) | 1.9 (1.4–2.7) |
| Neighbourhood contact at 50–<75 m | 11,255 | 52 (0.5) | 1.6 (1.1–2.3) |
| Neighbourhood contact at 75–<100 m | 8808 | 40 (0.5) | 1.8 (1.2–2.6) |
| Neighbourhood contact at ≥100 m | 56,774 | 101 (0.2) | Ref. |

We repeated the analysis for each island individually and found similar associations and gradients, details are shown in Table 3.

Table 3.Probability of being a leprosy patient as a function of distance to nearest index case random-effects model by island of residence, Anjouan, Mohéli, and Madagascar, 2019.

| Distance to | Prevalence rate ratio (95% CI) | | |
|---|---|---|---|
| Index case | Anjouan | Mohéli | Madagascar |
| Same household | 6.4 (4.0–10.1) | 32.8(12.6–85.3) | 9.7 (4.5–20.9) |
| Neighbour at <25 m | 2.4 (1.5–3.7) | 5.4 (1.9–15.8) | 2.1 (1.0–4.5) |
| Neighbourhood contact at 25–<50 m | 2.0 (1.3–3.1) | 2.0 (0.6–6.9) | 0.6 (0.2–1.8) |
| Neighbourhood contact at 50–<75 m | 1.8 (1.1–2.8) | [a]NA | 0.8 (0.3–2.2) |
| Neighbourhood contact at 75–<100 m | 1.6 (1.0–2.7) | 2.5 (0.8–7.5) | 1.8 (0.8–3.8) |
| Neighbourhood contact at ≥100 m | Ref. | Ref. | Ref. |

[a] There were no cases in this distanc band on Mohéli.

Due to the smaller sample size, the observed rates are less stable, but the general picture of associations and gradients observed remains unchanged. Excluding villages without cases had no significant impact either with prevalence rate ratios of 7.2 (95% CI 5.0–10-3), 2.4 (95% CI 1.7–3.4), 1.8 (95% CI 1.3–2.5), 1.5 (95% CI 1.0–2.1) and 1.7 (95% CI 1.1–2.4), respectively, for household contacts, neighbours at <25 m and neigbourhood contacts at 25–<50, 50–<75 and 75–<100 m distance, as compared with those living at 100 m.

**Discussion**

During our baseline survey in 64 villages on the Comoros and Madagascar, we found high leprosy prevalence and strong spatial clustering. The prevalence of leprosy at village-level exceeded 10 per 1000 population in 9 villages, including 1 in which >30 per 1000 had active leprosy. Among 455 leprosy patients, 200 (44%) were part of high-prevalence clusters. On Anjouan, where the prevalence is highest, these were most often large clusters extending across many households, even across villages. On Mohéli and in Madagascar clusters were smaller (2–8 patients). When considering the entire population in relation to the distance to the nearest index case, we found strong and highly significant associations. Compared with those living at 100 m from the nearest index case, the risk of leprosy was more than 7 times higher for household members. For neighbours at <25 m, the risk was 2–3 times higher. The association remained statistically significant up to 100 m.

Our findings are consistent with earlier results from Anjouan in which we assessed the probability of being diagnosed with leprosy as a function of distance to index cases of earlier years, during a door-to-door survey conducted in 4 villages in 2017[24, 27]. SDR-PEP had been provided in those villages in June 2015 to household contacts of leprosy patients diagnosed since the beginning of 2012. With those living at >75 m from the nearest index case (diagnosed between January 2012 and June 2015) as a reference, the highest risk measured by incidence rate ratio (IRR) of current leprosy (in 2017) was found among those residing in the same household (IRR 2.4, 95% CI 1.5–3.6) and a similar gradient with increasing distance was observed (IRR 1.8, 95% CI 1.3–2.5, IRR 1.2, 95% CI 0.8–1.7 and IRR 1.3, 95% CI 0.8–2.1 for those living at 1–25, 26–50 and 51–75 m, respectively) [24, 27]. The fact that SDR-PEP had been provided to close contacts of index cases may have obscured part of the association, especially among household contacts. In an earlier study in Indonesia[28] reported an incidence rate ratio of 9.4 for household contacts. Moet et al. emphasise the importance of contact-related factors such as the closeness and intensity of the contact and inherited susceptibility when considering who to screen for leprosy [29]. Similar conclusions as those presented by our study were drawn by Moura et al., highlighting the importance of extending contact screening beyond the household [30].

Although we found significant spatial clustering of leprosy, it is important to realize that 56% of cases identified in our surveys were sporadic cases, not belonging to any cluster. We also found that of 455 patients identified, 284 (62.4%) were living >25 m from the nearest other leprosy patient and would have been missed if we had limited screening to near neighbours around an index case. Even a cut-off of at 100 m would still have missed 22% of our patients. In another high endemicity setting, in Bihar, India, a study also found significant clustering among household members and neighbours living up to 25 m, with prevalence rate ratios of 6.3 (95% CI 1.9–21) and 3.6 (95% CI 1.3–10.2), respectively, when compared to those living at >100 m [31]. Here too, the majority of leprosy cases (75%) were at >25 m from the nearest index case.

Geographic proximity is an easy-to-apply criterion for active case finding but will not be sufficient to interrupt transmission of *M. leprae* when a substantial proportion of patients are not part of any spatial cluster. We will have to consider other contacts than just near neighbours. Moet et al. also refer to the 'stone in the pond' principle applied in tuberculosis, which aligns with our findings and those of van Beers et al., who emphasise the importance of contact [28, 29]. Social network analysis and genotyping of *M. leprae* can play important roles in further elucidating transmission and identifying those most at risk. In a study in Brazil, 66% of leprosy cases belonged to a household social network with 3 or more leprosy cases [32]. Our findings highlight the importance of redesigning active case finding strategies and targeting of post-exposure prophylaxis, taking into account the epidemiological burden and resources available. The tools used in this study (an app on a smartphone developed with open-access software) are well within reach of leprosy control programs. A shift away from paper-based systems could help to identify those most at risk more effectively.

Another area that should be explored is social network analysis. Although leprosy is a disease associated with social stigma, if all that is required from social contacts is to swallow one single dose of rifampicin to achieve a major reduction in risk, it is worthwhile trying to identify those contacts. In particular, this tracing would apply to contacts not living in the immediate surroundings of the index case.

As a limitation of our study, we acknowledge that despite the strong spatial correlations found, given the long incubation period of leprosy, it is highly likely that the source of the cases identified during our survey were patients that we did not consider as index cases because they were no longer on treatment when the survey took place.

Other neglected tropical diseases apply mass drug administration (MDA) for populations at high risk. However, this is harder to justify for a relatively rare disease like leprosy [33]. As time goes by, these MDA programs for once highly prevalent diseases are beginning to face similar challenges as in leprosy. If clusters of high endemicity could be clearly identified, strategies based on focused application of MDA could be considered. This was shown by Bakker et al. on small islands in Indonesia [34] and is the strategy currently piloted in the third arm of the PEOPLE trial. The use of digital technology can be very helpful in outlining such clusters. Similar technologies have also been applied for monitoring and reporting coverage of MDA for other neglected tropical diseases [35].

In conclusion, this study further supports the importance of expanding leprosy prevention and control activities beyond the household level. Focusing on those living within a 25 m perimeter of an index case is an efficient use of scarce resources but would miss a large proportion of cases. Additional criteria need to be developed and verified to identify those in need of screening and post-exposure prophylaxis, these could include social contacts. Digital tools can help in outlining high-risk areas, including in a programmatic context.

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# 5 High yield of retrospective active case finding for leprosy in Comoros

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**Abstract**

**Background**

The island of Anjouan, Comoros, is hyperendemic for leprosy with an annual incidence rate above 6 per 10.000 population in the last 15 years. During this period, the National Leprosy Programme (NLP) has been conducting so-called 'mini campaigns', inviting inhabitants of hyperendemic villages to a central location for screening of skin conditions. Also, household contacts of new leprosy cases diagnosed are either visited at their households by health staff or invited to the health facilities for leprosy screening. In this study, we report the yield of screening for leprosy among household contacts and neighbours by door-to-door screening in hyperendemic villages.

**Methodology**

Sixteen hyperendemic villages including houses of index cases registered since January 1st 2017 and before 1st December 2020 were included. A form with the list of households of index cases to be visited was created specifying the village, name age and gender of the index case. Additional forms were provided for the screening of neighbours. A customized open-source app allowed recording households geographic coordinates besides clinical and sociodemographic data of contacts screened.

**Results**

Between December 1st and December 17th, 131 out of 226 index case households aimed (58.8%) were visited, as well as 32 other nearby households. There were 945 persons recorded, 671 household contacts and 274 neighbourhood contacts. The median distance among index cases and non-household contacts was 98 meters (IQR 60-217). We examined 896 persons detecting 48(5.4%) leprosy cases. Among cases detected, 13(27.1%) had multibacillary (MB) leprosy, the median age was 18 years (IQR 8-34), 43% were below 15 years and two (4.2%) had visible deformities. The risk of contacts of developing leprosy was higher among 11 households linked to MB compared to one linked to a paucibacillary (PB) index case (OR 12.6, 95% CI 1.6-99.6). There were 12 new cases among 668 household contacts with a leprosy prevalence of 18.0 per 1,000 (95% CI 9.3-31.1). We found 30 new cases in neighbours and six additional cases were diagnosed between their households with a residual prevalence of 26.3 per 1,000 (95% CI 9.7-56.4).

**Discussion**

This screening campaign proved highly effective with a prevalence above 26‰ among household contacts. The contact screening should not be a one-off intervention but should be repeated some years later in high prevalence zones considering door-to-door visits for screening. The tools used are user-friendly and allow identification of high prevalence areas and can guide tailored screening.

## Introduction

Cavaliero and colleagues [1,2] describe a high yield of retrospective active case finding for leprosy in Cambodia, which has a fairly low level of endemicity. We conducted a comparable survey in high-prevalence villages on the island of Anjouan, Comoros, which is highly endemic for leprosy with an annual incidence rate of 550 per 1,000,000 population reported for 2019 [3]. Over the last 15 years, leprosy incidence on Anjouan has been consistently high, approximately 912 per 1,000,000 per year on average. For years, the National Leprosy Programme (NLP) has been conducting so-called "mini-campaigns" or "skin camps," based on the "camp approach" in which inhabitants of villages are invited for screening for all kinds of skin conditions in a central location [4]. Yet, when door-to-door screening was conducted in some of these villages served earlier with mini-campaigns, very high numbers of new leprosy cases were detected [5]. On Anjouan, in addition to mini-campaigns, household contacts of leprosy patients diagnosed are either visited in their homes by nurses trained in leprosy or invited to present to Primary Health Care (PHC) facilities for leprosy screening. In the ongoing PEP4LEP trial, conducted elsewhere, the effectiveness of the skin camp approach is being compared to self-presentation of contacts at health centers [6].

## The intervention

Whereas screening of household contacts is typically conducted soon after a leprosy patient has been newly diagnosed, we opted for screening household contacts of all patients diagnosed in the preceding 4-year period, i.e., since January 1, 2017. The villages selected were not included in the large ongoing PEOPLE trial on postexposure prophylaxis for leprosy, covering 32 of the most endemic villages on Anjouan, either because of their large population sizes or because at village level leprosy incidence was below average.[7] They were visited in December 2020. Under the coordination of the NLP, a sensitization session of community leaders was organized to enhance the acceptability of the screening. Prior to the visits, line listings were prepared by village of all leprosy patients registered since January 1, 2017. For each household to be visited, a form was created specifying the village, name, age, and gender of the index case and 15 lines to record contacts, 1 line per contact with a preprinted unique barcode. A customized app in Open Data Kit (ODK) was used for data collection. Besides sociodemographic and clinical data, the app allows recording the geographic coordinates of the household and scanning the barcodes and entering screening results for each individual. In total, 226 index case households were included, but additional forms were provided to screen and record results from surrounding households as deemed necessary by the field team and/or requested by the village members.

## Ethics statement

The NLP authorized the use of anonymized aggregated secondary data for retrospective analysis and publication. Additional approval for publication was obtained from the Institutional Review Board (IRB) of the Institute of Tropical Medicine (ITM), Antwerp (Approval number: 1541/21). Oral consent of participants was obtained as per guidelines that includes active case finding as routine programmatic activity. To avoid identification of affected households, a random error of 25 meters was added to the map shown in Fig 2.

## Results

Between December 1 and December 17, 2020, 133 out of 226 index case households listed (58.8%) were visited, as well as 32 other nearby households. Households not visited were

either absent or did not agree to screening. Most households (66.1%) were visited during the final 4 days of the survey. Over this period 945 persons were recorded: 671 household contacts and 274 neighborhood contacts. Out of those, 668 were screened, including 471 household contacts of index cases, among whom 12 new leprosy patients were diagnosed. A total of 32 neighborhood contacts screened were among those who spontaneously presented to the team because of skin lesions that were suspected to be leprosy. They were visited in their homes for further examination along with their household contacts. Thus, 30 new leprosy cases were identified among the self-presenting neighborhood contacts as well as 6 additional new cases among their household contacts (Fig 1).

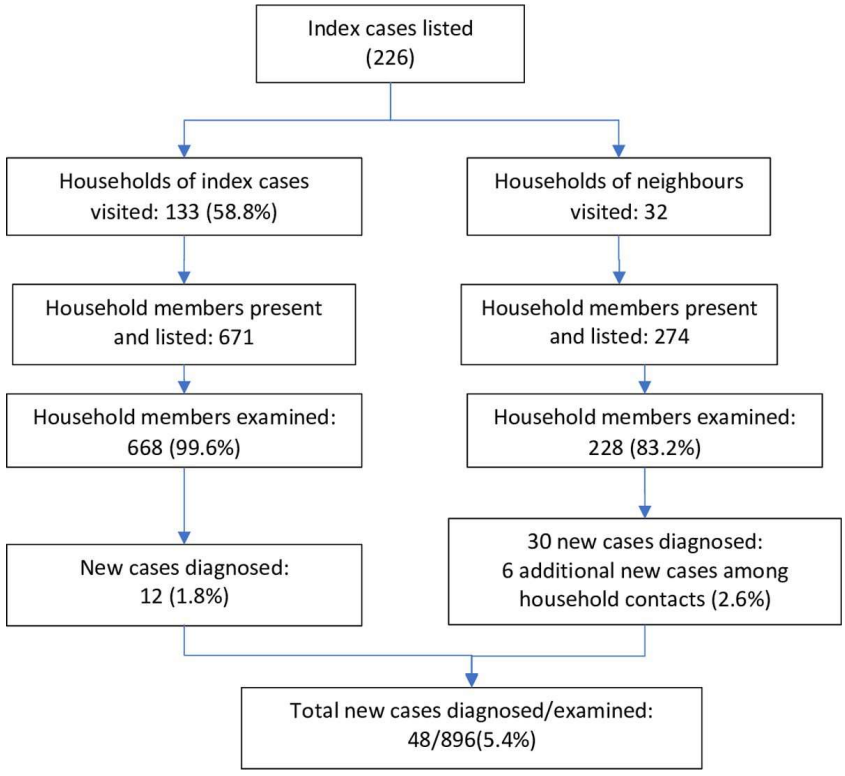


Fig 1. Flowchart of households screened for leprosy, Anjouan, December 2020.

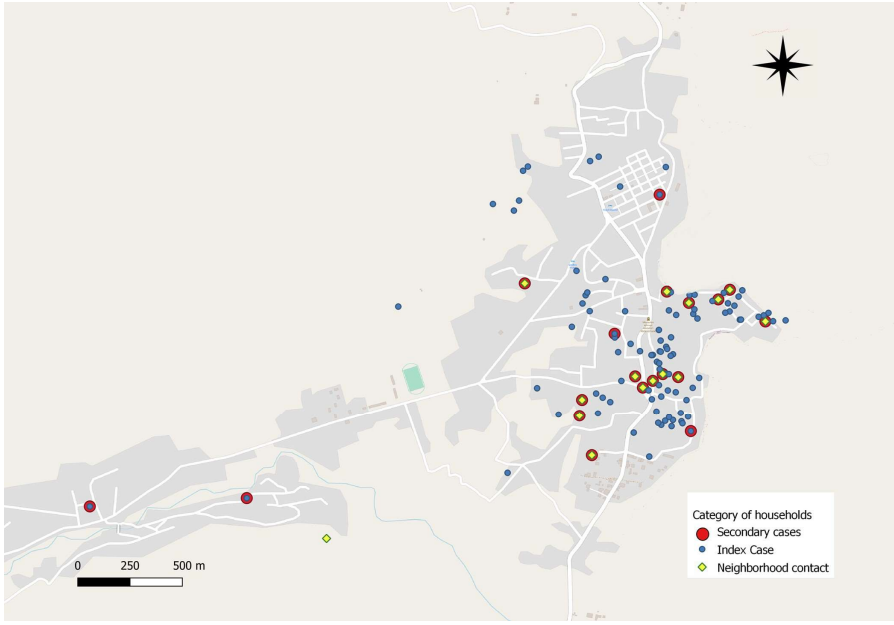


Fig 2. Map of a village with the households screened for leprosy (a random error of 25 meters was added to protect privacy of households screened). We used OpenStreetMap as a base layer for this map (https://www.openstreetmap.org/#map=8/50.510/4.475).

Altogether, 48 new leprosy patients were detected, all autochthonous. A total of 12 were detected among household contacts and the remaining 36 among neighborhood contacts. Of the 48 cases identified, 13 (27.1%) were multibacillary (MB) and 35(72.9%) were paucibacillary (PB). Median age was 18 years (IQR 8 to 34). A total of 19 (40%) were below 15 years of age, of those 7 were in the age category of 4 to 9 years, and the remainder were 10 to 15 years old.

None of the patients presented with grade 1 disability, but 2 (4.2%) had grade 2 disabilities. The median distance to index cases among non-household contacts was 98 meters (IQR 60 to 217 meters). Fig 2 below shows the distribution of households visited and cases identified for the largest village included in the survey.

Among the 133 index case households, 61 were households of PB cases and 72 belonged to MB cases. Out of 681 contacts recorded in those households, 252 out of 358 (70.4%) from PB households and 228 out of 323 (70.6%) from MB households were screened. In total, 11 out of 12 cases among household contacts were from MB households, and 1 was from a PB household (OR 12.6, 95% CI 1.6 to 99.6).

**Discussion**

This screening effort proved highly effective. Overall, the leprosy new case detection rate was 18.0 per 1,000 (95% CI 9.3 to 31.1) among 668 household contacts examined, most of whom

had already been visited previously, but longer ago. An additional 30 cases were found among persons presenting spontaneously, and upon screening 228 of their household contacts, 6 more cases were found, equivalent to a residual new case detection rate of 26.3 per 1,000 (95% CI 9.7 to 56.4). Being a contact of an MB index case was strongly associated with the probability of developing leprosy; this is similar to the findings in Bangladesh where household contacts of highly skin smear-positive index cases (MB patients) had more than 3 times higher risk of developing leprosy. [8]

This experience reinforces the notion that contact screening should not be a one-time effort but is worth repeating after some years, as was highlighted by Cavaliero and colleagues in a low-endemic context. In the largest village shown in Fig 2, leprosy cases are clearly clustered in the southeastern part of the village. In such high prevalence zones, even repeated (e.g., annual or biannual) door-to-door screening could be considered until clear signs of decline are demonstrated (e.g., until no more children are found among newly diagnosed leprosy cases). Since household contacts clearly are at extremely high risk, postexposure prophylaxis is strongly recommended [9]. In highly affected neighborhoods, even blanket coverage with postexposure prophylaxis should be considered [10]. The tools used allow to easily identify such high-risk areas and can guide further screening efforts, even under programmatic conditions.

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# 6 Less is more: Developing an approach for assessing clustering at the lower administrative boundaries that increases the yield of active screening for leprosy in Bihar, India

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**Abstract**

**Background**

In India, leprosy clusters at hamlet level but detailed information is lacking. We aim to identify high-incidence hamlets to be targeted for active screening and post-exposure prophylaxis.

**Methodology**

We paid home visits to a cohort of leprosy patients registered between April 1st, 2020, and March 31st, 2022. Patients were interviewed and household members were screened for leprosy. We used an open-source app(ODK) to collect data on patients' mobility, screening results of household members, and geographic coordinates of their households. Clustering was analysed with Kulldorff's spatial scan statistic(SaTScan). Outlines of hamlets and population estimates were obtained through an open-source high-resolution population density map(https://data.humdata.org), using kernel density estimation in QGIS, an open-source software.

**Results**

We enrolled 169 patients and screened 1,044 household contacts in Bisfi and Benipatti blocks of Bihar. Median number of years of residing in the village was 17, interquartile range (IQR)12-30. There were 11 new leprosy cases among 658 household contacts examined (167 per 10,000), of which seven had paucibacillary leprosy, one was a child under 14 years, and none had visible disabilities. We identified 739 hamlets with a total population of 802,788(median 163, IQR 65–774). There were five high-incidence clusters including 12% of the population and 46%(78/169) of the leprosy cases. One highly significant cluster with a relative risk (RR) of 4.7($p<0.0001$) included 32 hamlets and 27 cases in 33,609 population. A second highly significant cluster included 32 hamlets and 24 cases in 33,809 population with a RR of 4.1($p<0.001$). The third highly significant cluster included 16 hamlets and 17 cases in 19,659 population with a RR of 4.8($p<0.001$). High-risk clusters still need to be screened door-to-door.

**Conclusions**

We found a high yield of active household contact screening. Our tools for identifying high-incidence hamlets appear effective. Focusing labour-intensive interventions such as door-to-door screening on such hamlets could increase efficiency.

## Introduction

Leprosy is a complex infectious disease well known for centuries. *M. leprae* the pathogen that provokes leprosy, [1] multiplies in nerve and skin cells provoking skin lesions and neurological symptoms that vary from sensory loss, muscle weakness, and complete palsy, that later cause mutilations and deformities if not properly managed. The life-long disability associated with disfigurement is the main cause of stigma and discrimination. [2] This aspect, associated with the lack of diagnostic tests, limited access to proper and early care, and a long incubation period that could last decades, hinder the control of leprosy. The World Health Organization (WHO) concluded that the highly efficacious treatment with multidrug therapy (MDT) was insufficient to reduce the over 200,000 new cases annually that are notified for over a decade and recommends scaling up the preventive measures. [3] Based on the pivotal trial on chemoprophylaxis in leprosy (COLEP) in Bangladesh, the WHO recommends post-exposure pro- phylaxis with single-dose rifampicin (SDR-PEP) for healthy persons in contact with new leprosy cases. [4] Provision of SDR-PEP combined with active case finding and early care of leprosy is recognized as key for stopping transmission. Determining the population at risk for the provision of active case detection and SDR-PEP is key for planning programmatic implementation. [5] Although the programmatic implementation of SDR-PEP was successful in seven endemic countries, [6] the selection of those at higher risk and determining the operational areas for active case detection and SDR-PEP are lacking.

India is the country that notifies the largest number of new leprosy cases accounting for 60% worldwide and is recognized as one of the 23 WHO priority countries for leprosy control. [7] In 2019, Bihar was ranked fifth among 37 states of India, with 16,595 new leprosy cases reported, equivalent to an annual new case detection rate (ANCDR) of 1.31 cases per 10,000 population. Among these patients 1,694 (10.2%) were children and 458 (2.8%) had grade two disability (G2D), among the latter 15 were children. These indicators are higher compared to the national level in 2019, with an ANCDR of 0.81 per 10,000 population, 6.9% of children, and 2.4% G2D. [8] In recent years India implemented innovative active case-finding (ACF) strategies [9] and included SDR-PEP in the control strategy. These strategies require substantial support in terms of human and financial resources. Identifying people at high risk for enhancing effectiveness and rationalizing resources are key to sustaining these activities in the long run.

Leprosy is known to be distributed unevenly and to cluster [10,11], focusing on the lowest geographical unit at high risk is key in view of the limited resources available. [10]

In India, villages are comprised of small hamlets known as ‘Tola’, [11] that often share common sociodemographic characteristics such as caste or religion. [12] These hamlets are informal subdivisions within villages, and formal boundaries and population estimates are lacking. Most disease control programs, including the national leprosy eradication program (NLEP) record patients at the village level. Mapping leprosy patients at the household level and using GIS-based tools to outline hamlets has great potential in improving the targeting of control measures. [13]

In the present study, we aim to develop and pilot spatial methodologies to outline hamlets within villages and then identify clusters of hamlets with high leprosy incidence. As such, we aim to contribute to curbing transmission as targeted by the WHO Global Leprosy Strategy 2021–2030 [14] by providing useful information to the policymakers for efficient targeting of interventions such as ACF activities and SDR-PEP in leprosy endemic countries.

## Methods

### Ethics

Our study obtained ethical clearance from the Institutional Review Board (IRB) from the Institute of Tropical Medicine, Antwerp (Number 1182/17), the University of Antwerp (Number B300201733691), and the ethical board of the Krishna Institute of Medical Sciences, Andhra Pradesh, India (No number). All new leprosy patients and their household contacts that gave their consent were included in the study. For children participants, formal consent was obtained from the parent/guardian.

### Study design

This is a cross-sectional study, we recruited new leprosy cases diagnosed between April 1st, 2020 and March 31st, 2022 in two blocks of Madhubani District of Bihar State, India.

### Study setting

In 2021, the state of Bihar had an estimated population of 123,083,000 inhabitants with 1037 inhabitants per km2, ranked third among 37 states according to population density. [15] Around 80% of the population lives in rural areas, with an average household size of 4.8 members. Children under 15 years represent 36% and the sex ratio population is 1,009 females per 1,000 males. Around 60% of households are nuclear. The head of households are women in 23%. Concerning religion, 86% belong to Hinduism and 14% to the Muslim religion. Only 9% have water piped into the households, and 39% do not use any toilet facility. Most of the population lives from agriculture, with 39% of the population cultivating their land and 57% owning farm animals. [16]
Among the 38 districts of Bihar, we selected Madhubani which notifies around 800 new leprosy cases annually. Within Madhubani districts we selected the blocks of Benipatti and Bisfi, accounting for respectively 404,457 and 358,913 estimated inhabitants in 2021 distributed over 267 villages. [17] In the last decade, Benipatti and Bisfi had notified an annual average of 190 and 182 new leprosy cases per million inhabitants, among those child proportion and G2D proportion were 13% and 0.4% and 25% and 2% respectively for the two blocks. From 2012 to 2021, the average proportion of multibacillary (MB) and female cases was 39% and 48% in Benipatti compared to 36% and 54% in Bisfi.
The National Leprosy Eradication Programme (NLEP) in Bihar implements passive case finding at the Primary Health Care facilities where persons with skin lesions present themselves. In 2016, the NLEP started active leprosy case detection campaigns (LCDCs) where trained health staff with the involvement of Accredited Social Health Activists (ASHAs) con- ducted door-to-door leprosy screening in the households of villages ranked in leprosy high priority districts (defined as prevalence rate superior to one per 10,000 inhabitants in the last three years). [9] In Bihar, two rounds of the LCDCs were implemented. [18]

### Sample size

Out of 224 new leprosy patients reported in Bisfi and Benipatti over the study period (April 1st, 2020-March 31st, 2022), we aimed to enroll approximately 200. This would allow us to estimate any 50% proportion with a precision of ±7%.

### Inclusion and exclusion criteria

We included all new leprosy patients diagnosed between April 1st, 2020 and March 31st, 2022 that accepted to be enrolled. We also included consenting permanent household members, including non-permanent, for screening for leprosy.

**Data collection**

We obtained a line listing of new leprosy patients diagnosed in both blocks during the study period. The index cases were visited following the order of registration in the leprosy register, if absent the next index case was visited. We developed one app for data collection using the open-source Open Data Kit (ODK) forms. This allowed collection of information about household contact screening, demographic data, results of screening, and household geographic coordinates. A second ODK app included a questionnaire about the mobility of leprosy cases.

**Data analysis**

Among new leprosy patients, we recorded the demographic and leprosy characteristics. We also recorded all permanent household members present at the visit and whether or not they were diagnosed with leprosy.
For outlining tolas and estimating their populations, we used population estimates from Humanitarian Data Exchange (HDX) which is an open-source platform for data sharing across crises and organizations managed by the United Nations Office for the Coordination of Humanitarian Affairs (UNOCHA). These population estimates are presented in raster files in Geotiff format, each raster point containing a value representing the estimated number of people. For India and Pakistan high resolution, Geotiff files are available with a pixel size of approximately 30 x 30 meters [19].
Then, using Quantum Geographic Information System (QGIS) 3, we downloaded from OpenStreetMap the outlines of Bisfi and Benipatti Blocks. [20] We overlaid them with the corresponding population layer ('poplation_20_lon_80_general-v1.5') downloaded from HDX. [19] We used the outlines of the two blocks as mask layer to clip the corresponding part of the population raster.
Next, we transformed this clip of the population raster file to vector points with UTM 45N as coordinate reference system (CRS) using the 'Raster pixels to points' module in the Toolbox of QGIS. The shapefile created has only one field, 'VALUE', which we reset to 1 by dividing it by itself. We then created a heatmap based on kernel density estimation with a radius of 100 meters (including 3–4 pixels) and a raster size of 10 meters. Raster size was based on the assumption that the total population of the two blocks of approximately 800,000 is spread out over a surface area of approximately 450 km2 of which approximately 20% is built-up area. Thus in the built-up area, there is approximately 1 person per 100 m2 on average. This heatmap was converted to a raster, using the 'Raster calculator' from the QGIS Toolbox, selecting pixels with a value > 1.
This raster was again converted to a vector layer using the 'Polygonize (raster to vector)' function from the 'raster' menu of QGIS. From this vector layer, we removed all records with a value of zero. These were again overlaid with the clipped population data ('population_20_-lon_80_general-v1.5'). We then applied the 'zonal statistics' option from the QGIS Toolbox to obtain population estimates for each hamlet. We removed hamlets with population estimates of less than 20. These we exported with CRS UTM 45N and added the row number as a unique ID variable for each hamlet.

As a next step, we plotted the household coordinates of all leprosy patients enrolled and used the 'count points in polygons' function in QGIS to determine the number of cases in each hamlet. We added the centroid of each hamlet making use of the 'geometry tools' in QGIS. Finally, we exported our map layer with hamlet ID, population, number of cases, and X and Y coordinates of the centroid to a CSV file that was used in a SaTScan analysis.
To identify clusters of high leprosy risk we used SaTScan v10 to calculate Kulldorff's spatial scan statistic, maximum cluster size was set to 5%, based on the assumption that clusters of more than 5% of the total population, i.e. > 40,000 are too large to conduct efficient interventions. As spatial window size, we opted for elliptic clusters and a minimum of 5 patients per cluster. [21]

## Results

### Characteristics of leprosy index cases

During the study period (April 1st, 2020 to March 31st, 2022), 224 new leprosy patients were notified in the two study blocks, of which we enrolled 169(76%). These include 78/130 (60%) from Benipatti and 91/94(97%) from Bisfi. Out of those 72 (43%) were detected through active case finding (ACF), 40 of those through the active screening campaigns by ASHAs. Age and gender distribution were comparable between the two blocks but the proportion of MB cases was highest in Benipatti (58% vs. 39%). Grade 2 disabilities (G2D) at time of diagnosis were more common in Benipatti (15%) than in Bisfi (5%). (Table 1)

Table 1. Demographic characteristics of index cases enrolled.

| **Block** | **Benipatti** | **(%)** | **Bisfi** | **(%)** |
|---|---|---|---|---|
| Children | 12 | (15%) | 12 | (13%) |
| Female | 38 | (49%) | 50 | (55%) |
| MB | 31 | (58%) | 44 | (39%) |
| G2D | 9 | (15%) | 4 | (5%) |
| **Total** | **78** | **(100%)** | **91** | **(100%)** |

The participation rate was better in Bisfi, reasons for not being enrolled in the study were: temporary migration, migration of female cases after marriage, address cannot be traced, death, and mobility restrictions because of the Covid-19 pandemic.

### Patterns of clustering of new leprosy cases

We identified 739 Tolas with a total population of 802,788. The median population per tola was 163, IQR (65–774) with a maximum population size of 45,954 and minimum population size of 29. Fig 1 below shows the tola's outline with a EarthExplorer image as background for part of the study area.

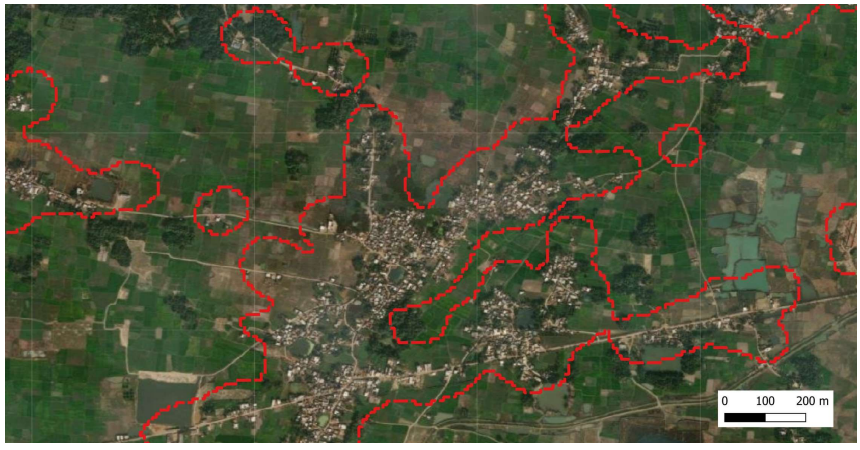


Fig 1. Tola's outlined shown against EarthExplorer background. We used United States Geological Survey (USGS) Map as a base layer for this map (http://www.usgs. gov).

Out of 169 cases included, 156 could be attributed to any of the hamlets, and 13 were outside the hamlets identified. Our SaTScan analysis identified five clusters with no overlap vary- ing in size from 6,324 to 31,809 population and including 78 of 156 cases. Relative risk ranged from 4.14 till 5.1, three clusters were statistically significant. Out of an estimated total population of 802,788, we thus were able to select a population of 98,623 (12%) in which 46% of reported cases had occurred. Details are shown in Table 2 below.

Table 2. Main clusters by Tolas in Bisfi and Benipatti, 2021–2022, India.

| Cluster | Number of locations | Cases | Population | [1]RR | P–value |
|---|---|---|---|---|---|
| 1 | 32 | 27 | 33,609 | 4.7 | <0.0001 |
| 2 | 32 | 24 | 33,809 | 4.1 | 0.0006 |
| 3 | 16 | 17 | 19,659 | 4.8 | 0.001 |
| 4 | 9 | 5 | 5,222 | 5.1 | 0.939 |
| 5 | 10 | 5 | 6,324 | 4.2 | 0.993 |
| All | 99 | 78 | 98,623 | | |

[1]RR = Relative risk

In Fig 2. We display the high-risk clusters identified.

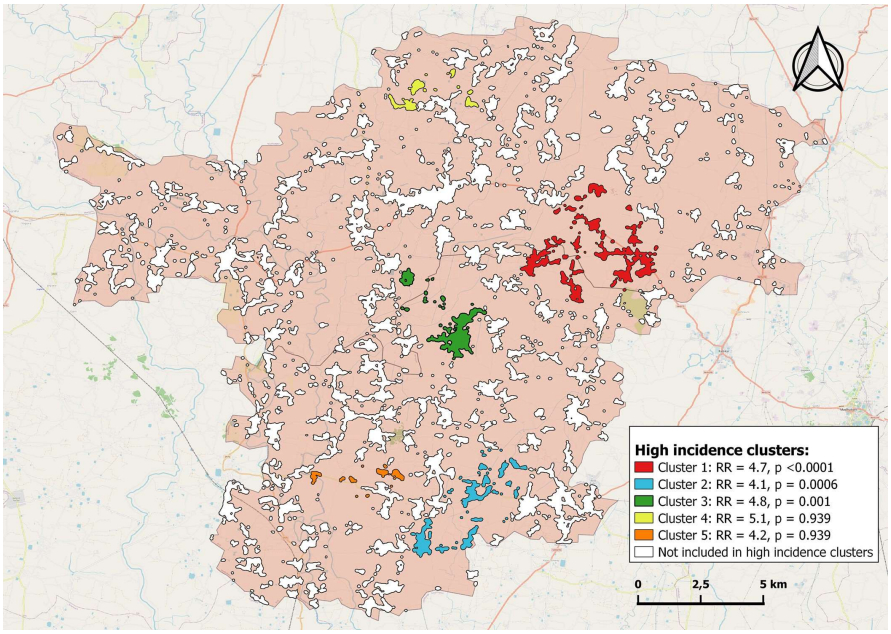


Fig 2. High incidence clusters identified, Benipatti and Bisfi, India, 2020–2022. We used OpenStreet Map as a base layer for this map (https://www. openstreetmap.org/#map=8/50.510/4.475).

Mobility characteristics of leprosy index cases

Most patients had been living in the same village for many years. The median number of years that the leprosy index cases resided in the same village was 17 (IQR 12–35) and 18 (IQR 12– 30) in Benipatti and Bisfi respectively. Only two leprosy index cases had been living in their village for one year and more than 80% had been living there for 11 years (Table 3).

**Table 3. Years of residence of leprosy index cases by block.**

| **Block** | **Benipatti** | | **Bisfi** | |
|---|---|---|---|---|
| **Years living in the village** | **n** | **(%)** | **n** | **(%)** |
| 1 year | 1 | (1%) | 1 | (1%) |
| 2–10 years | 14 | (18%) | 16 | (18%) |
| 11 years | 63 | (81%) | 74 | (81%) |
| **Total** | **78** | **(100%)** | **91** | **(100%)** |

Demographic characteristics of household contacts and results of screening for leprosy

Index cases enrolled were part of 172 households, accounting for 1,044 contacts listed, from which 663 (63.5%) were present. The median household size was 6 in Benipatti (IQR 5–7) and 7 (IQR 6–8) in Bisfi. We examined 99% of household contacts present at the time of visit (Table 4).

Table 4. Demographic characteristics and results of screening for leprosy among household contacts.

| Block | Benipatti | (%) | Bisfi | (%) |
|---|---|---|---|---|
| **Total listed** | **483** | **(100%)** | **561** | **(100%)** |
| Female | 222 | (46%) | 251 | (45%) |
| Children | 147 | (30%) | 186 | (33%) |
| Present at the visit | 330 | (68%) | 333 | (59%) |
| **Accepted examination** | **328** | **(99%)** | **330** | **(99%)** |
| Results of examination: | | | | |
| New case | 4 | (1.2%) | 7 | (2.1%) |
| Past leprosy or under treatment | 92 | (28%) | 97 | (29.4%) |
| No leprosy | 232 | (70.8%) | 226 | (68.5%) |

Among those, we found 11 (166 per 10,000) new leprosy cases belonging to nine households, and two households had two new leprosy cases. There were 7 PB (63%) cases, one child 14 years old (9%), and none had G2D.

## Discussion

We screened household contacts of 169 leprosy patients and identified 11 new cases among 663 persons screened, equivalent to a prevalence rate of 166 per 10,000. Making use of an innovative methodology we were able to outline 739 hamlets, part of the 267 villages in the two study blocks, and obtained population estimates for each. Plotting the geographic coordinates of leprosy index case households visited, we could identify five high-incidence clusters of which three were statistically significant. Focussing on the high-incidence clusters only would allow to select 12% of the population in which 46% of incident cases had occurred.

Our results illustrate once again that leprosy clusters at household level and that active screening of household contacts is highly efficient. Similar high yield of active screening of household contacts was reported from Comoros. [22] However, focusing only on household contacts will miss an important number of new leprosy cases as the increased risk of leprosy extends beyond households. [11] Using a GIS-based approach we were able to identify larger high-risk clusters beyond household level that would potentially benefit from measures such as active screening and post-exposure prophylaxis.

We also observed that in our study area mobility of leprosy patients is remarkably limited. The vast majority of patients interviewed (81%) had been living in their villages for more than 10 years. Taking into account also the long incubation period of leprosy, it may be worthwhile to consider not just current leprosy patients as index cases but also those detected in preceding years.

The methodology described allows to identify clusters of leprosy cases at a level below the village, which is the geographical unit most often recorded. It may be useful for other infectious diseases as well, such as visceral leishmaniasis and its sequel PKDL. [11,23] For leprosy, this approach contributes evidence to the Global Partnership for Zero Leprosy (GPZL) research question about the development of focused and adaptive sampling methods for efficient detection of local hot spots. [24] Other methods such as social network analysis can be further explored as addons in view of their usefulness observed in similar contexts. [25]

A potential limitation is a bias introduced by active case finding. If active case finding is focused on household contacts of leprosy patients or high-incidence tolas, new cases arising close to previous cases are more likely to be detected. This effect may even have been exacerbated by the Covid-19 pandemic that made passive case-finding services unavailable

for prolonged periods. However, in our study, most cases were identified passively, and most actively detected cases were identified in a survey by ASHAs, who are present in all villages and whose screening campaigns target entire districts. [18] Furthermore, despite the fact that screening of household contacts is recommended, we still identified a fairly large hidden prevalence within the households of index cases.
The methodology described relies on mapping at household level of leprosy index cases. This is certainly possible with the technology currently available to the vast majority of health workers. Mobile smartphones with GIS software are universally used and open-source software that allows mapping is widely available. Visiting the households of current and former leprosy patients is also highly valuable for the purpose of contact screening, as demonstrated again in this study.

## Conclusion

We have developed a method for outlining clusters of high leprosy incidence that warrants further exploration in other settings. The method is easy to apply and based on various open-source software. It does require mapping at household level of leprosy patients which should no longer be a major hurdle with the tools currently available. Thus we will be able to focus preventive activities such as ACF and PEP where they are most needed.

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# 7 General discussion

In this thesis, we studied interventions for curbing *M.leprae* transmission by the provision of post-exposure prophylaxis and active case detection (ACD) in WHO-priority countries (Comoros, India, and Madagascar). We implemented door-to-door screening for leprosy and used open-source tools for assessing clustering, including generating maps of hamlets as leprosy is known to be clustered at the lower administrative level. In Comoros, during door-to-door screening for leprosy, we also provided single double-dose rifampicin as chemoprophylaxis to different populations at risk. The efficacy of different modalities of provision of PEP will be assessed once the follow-up will be completed in 2023.

Active case detection needs a substantial amount of resources, and therefore a cost-efficient strategy will be needed to curb the transmission of *M.leprae*, including PEP with single-dose rifampicin (SDR). SDR PEP has proved moderately effective in the pivotal trial 'Contact Transmission and Chemoprophylaxis in Leprosy' (COLEP) conducted in Bangladesh, which documented a 57% reduction of leprosy incidence in contacts that received SDR PEP over the first two years of follow-up [1]. An earlier meta-analysis also found around 60% protection against leprosy for post-exposure prophylaxis with Dapsone or Acedapsone but this required several months of treatment. [2] In a study on three hyperendemic islands in Indonesia, a 75% reduction of leprosy was achieved on an island targeted with a blanket approach of two doses of SDR-PEP, compared to an island that had not received any PEP [3]. In the same study, SDR-PEP provided only to close contacts had no effect on incidence at the island level.

The reinforcement of the PEP regimen by combining rifampicin with other drugs or with immuno-modulators could increase its effectiveness [4]. A systematic review found a protective effect of 80% against leprosy of the combination of bacillus Calmette–Guérin (BCG) and SDR. [5] In Bangladesh, the MALTALEP trial (Order of Malta-Grants-for-Leprosy-Research) assessed the effectiveness of preventing leprosy in contacts vaccinated with BCG, followed by SDR provision 8-12 weeks later, compared to BCG vaccination only. The study showed that SDR after BCG vaccination resulted in a 42% reduction in the incidence of paucibacillary (PB) leprosy cases in the first year but that this effect disappears after two years of follow-up [6].

Identifying the type of contacts that could benefit most from PEP is key to enhancing its effectiveness and this may vary according to epidemiological contexts. In the COLEP trial, SDR was effective in preventing leprosy among close contacts, though in the earlier mentioned trial in Indonesia this was not the case [3]. In this hyperendemic setting, only blanket provision of PEP was effective. In Morocco, a low leprosy burden country, SDR-PEP was provided at the national level to all eligible household contacts and a 16% annual reduction of leprosy incidence was achieved from 2012 to 2017 [7].

Ahead of the WHO recommendation for SDR-PEP implementation, the Leprosy Post-Exposure Prophylaxis (LPEP) study assessed the feasibility of SDR-PEP under programmatic conditions and showed positive results in seven countries [8]. Another study in which the provision of PEP is combined with ACD is currently ongoing. In this trial called 'PEP4LEP', a comparison is made between skin camps to screen approximately 100 community contacts per leprosy patient, and health center-based screening in which a mobile health (mHealth) tool 'SkinApp' will support health workers' capacity for integrated skin screening. [9]

The 'PEP++ ' cluster-randomized controlled trial in India, Nepal, Brazil, and Indonesia will explore a new enhanced regimen of PEP with 3 doses of rifampicin 600 mg and clarithromycin 500 mg given at 4 weekly intervals, compared to SDR. The trial also explores

innovative ACD approaches, including context-specific community education materials to improve the perception and knowledge of leprosy and decrease stigma. Blanket preventive chemotherapy is provided in all villages and neighborhoods where clusters of leprosy patients are identified. [10] Both the 'PEP4LEP' and the 'PEP++' trials will enhance the capacity building of health staff, while the 'PEP++' trial will integrate mapping and community health education adapted to the settings.

The PEARL study (Pathway to the Elimination of Antibiotic Resistant and Latent tuberculosis in the Pacific) in Kiribati will study population-wide active screening for TB and leprosy, using chest X-Ray with computer-aided detection, tuberculin skin test, and Xpert MTB/RIF Ultra for TB screening. Those with latent TB infection will receive TB preventive therapy including rifampicin, or rifampicin or isoniazid, or rifapentine and isoniazid; those without TB or leprosy will receive SDR, and those with leprosy or TB confirmed will be treated according to the standards of care. [11]

We will now continue to discuss our findings and try to answer the research questions listed in chapter 1. We will discuss the strengths and limitations of the interventions we implemented, we will elaborate recommendations for policy and practice including future research, and we will draw conclusions based on our main findings.

## Main findings

### Research Question 1. What are the patterns of clustering of leprosy in Comoros and Madagascar?

In Comoros and Madagascar, during the baseline survey of the PEOPLE trial, we documented the spatial distribution of prevalent leprosy cases and assessed the risk of being diagnosed with leprosy as a function of distance to the nearest other person with leprosy.[12] We confirmed that the risk of contacts for contracting leprosy is higher for those living in the same households, this risk was also higher for neighbors up to 75 meters, compared to those living ≥100 meters of an index case. We had previously documented in four endemic villages in Anjouan that the risk for leprosy was statistically significantly increased up to 25 meters from an index case of the previous year, with a decreasing trend with increasing distance[13]. Our findings, support evidence that the risk of contracting leprosy at the household level is related to transmission [14]. However, the association between the risk of contracting leprosy and physical distance might be confounded by other factors such as genetic predisposition and belonging to the same social networks. [15] A study in Brazil documented the role of social networks in transmission and established clusters in places of co-residence but also at workplaces, therefore social networks should be also considered while assessing transmission and identifying the population at risk for active case detection and prevention activities. [16]

The clusters identified in the baseline survey of the PEOPLE trial included a relatively small population at risk (less than 10,000 in all clusters combined) and included approximately 50% of the total leprosy prevalent cases. [12] In total we had screened a population of 102,089, therefore focusing on clusters can increase efficiency for active case finding.

Later in 2020, in some highly endemic villages of Anjouan not included in the PEOPLE trial, we again documented clustering beyond the household level. [17]

For decades, Anjouan has been the leprosy high-burden island in Comoros with an annual average incidence rate of ≥ 500 new cases per million population. In Anjouan from the year 2000 onwards, the reported incidence is extremely high and transmission continues unabatedly as ≥30% of new cases are children.[18] Poverty in Anjouan is distributed rather homogenously, correlating with poor housing, malnutrition, and high population density. Situated on a steep volcano, only 30% of the land surface area is suitable for agriculture and housing. Children in Comoros are particularly at high risk as they share their rooms with two adults or four more children, [19] which increases the risk of contracting leprosy besides other risk factors present in the household (contact with an index case, malnutrition, poor hygiene, etc.). On the contrary, in the district of Miandrivazo in Madagascar, there is more heterogeneity in the distribution of households in rural areas with limited geographical access compared to urban areas. The characteristics of clusters found in Comoros and Madagascar can guide future strategies of control. As the resources for active case detection are limited, the focus could be on high-incidence clusters that include children for annual screening, until no more children are detected among new leprosy cases. In low-prevalence settings, the frequency of active case finding can be every two years looking for cost-efficiency as resources for conducting active case finding might be limited. In both high and low-endemic settings, post-exposure chemoprophylaxis can contribute to stopping the transmission of *M.leprae*. In high endemic settings, ACD and PEP provision to the entire village would be more efficient. [20] As we documented in Comoros,[17] in high endemic settings, contact screening should not be a one-off effort. It must be repeated until no more child cases are detected, targeting contacts of index cases diagnosed over the course of several years.

Another tool to improve cluster analysis is molecular epidemiology. In China, a study analyzed the relationship between clusters and genetics of *M.leprae* in endemic and non-endemic regions, concluding that the use of the variable number of tandem repeats (VNTR) combined with social and spatial network analysis, might increase the effectiveness of control measures in clusters. Whole Genome Sequencing (WGS) might increase the resolution of molecular epidemiology. [21] In a study in a high endemic setting in Brazil, genotyping identified *M.leprae* strains that were statistically significantly associated with positive bacterial index and knowing someone with leprosy in the same workplace. The two major clusters were present in poor neighborhoods and had a high incidence in children. [22]

### Research Question 2. What is the pattern of clustering and mobility of leprosy patients in Bihar, India?

In our study in Bihar (India), approximately 100,000 out of a total population of approximately 800,000 were living in high transmission clusters, these clusters included 35% of 224 leprosy prevalent cases identified. The approach used allowed us to split villages into smaller units, hamlets. Among the five clusters identified the average number of hamlets included was 20, ranging from 9 to 32 and the average population in the clusters was 19,725, ranging from 5,222 to 33,809. The average number of prevalent leprosy cases per cluster was 16, ranging from 5 to 27 and the relative risk in all clusters was above 4 and was statistically ($P < 0.001$) in three of the five clusters. Among 11 new cases found by active door-to-door screening, we found one child, illustrating recent transmission.

Concerning mobility, more than 80% resided in their respective village for more than 10 years. Therefore, in the rural context of Bihar mobility is unlikely to play a major role in the dissemination of transmission, and therefore active detection is justified in the clusters

identified. Our findings mirror the national trends of spatial heterogeneity in India that document the slow decline of transmission and highlight the importance of innovative active case detection. [23] Stopping active case detection in hyperendemic settings could lead to the artificial absence of clustering. [24]

### Research Question 3. How to build an approach for exploring clustering at the lower administrative levels in Bihar, India?

Studying clusters in smaller geographical units is key to increasing efficiency.
Using the principle of inclusion of open-source tools, we developed a methodology for exploring clustering at the lowest geographical level, the hamlet or 'tola'. The availability of maps at the lowest geographical level is an issue in many countries. Therefore, we used detailed satellite imagery available in a public repository (https://data.humdata.org). This allows outlining hamlets, based on kernel density estimations, and obtaining an estimate of their populations. This allowed us to document clustering at the lowest geographical level in India for the first time. Our methodology for outlining hamlets maps and estimating their populations is feasible and could be used for targeted active case detection and prevention activities in highly prevalent clusters. We do still need to validate this methodology in other settings but we expect it to be reproducible because such population rasters used are available for all countries from different sources.

In India, different active case detection interventions have been applied. These include 'Leprosy Case Detection Campaigns' (LCDC), 'Focused Leprosy Campaigns' (FLC), and a special plan for 'Hard To Reach Areas' (HTRA). LCDC started in 2016 in districts with a prevalence rate >1/10,000 population or G2D >3% in the two preceding years, where teams made up of health staff and community workers screened for leprosy door-to-door. FLC in low endemic districts was conducted if a single case of G2D was detected, including all households in villages or 300 households in urban areas, with 'Accredited Social Health Activists' (ASHA) or 'Multi-Purpose Workers' (MPH) to screen all residents for leprosy. HTRA defined areas where it is difficult to establish a good surveillance system. Customized ACD plans were prepared by a nodal person and teams were constituted including members of the community and health staff. These interventions unveiled hidden leprosy cases and over time decreased the proportion of G2D and children among new leprosy patients. [25]

These innovative ACD strategies combined with PEP will certainly contribute to the evidence of enhanced PEP provision and regimens and innovative ACD.

### Strengths and limitations

While estimating the association between distance and risk of leprosy among contacts and index cases, given the long incubation period of leprosy, the source of the cases identified during our survey may have included patients that were not considered index cases because they were no longer on treatment when the survey took place. However, this limitation may be overcome by repeating ACD in high-incidence clusters, as is also done in the PEOPLE trial where door-to-door screening is repeated on an annual basis. In a programmatic context, door-to-door screening of entire villages is not feasible as it requires a lot of resources, therefore cluster identification is crucial for a cost-effective ACD strategy until a clear indication of stopping transmission.

Cluster identification is based on the inclusion of the total number of cases in a specific geographical area. This does require mapping patients either at the household or (sub)village level, which is not routinely done at present. Mapping patients is possible though, and no longer needs to be costly thanks to technologies that have advanced and open-source tools available. Absenteeism during screening and refusals, as well as the long incubation period of leprosy, might contribute to the underestimation of the real number of new cases. Again, therefore repeated ACD is the most appropriate way to overcome these uncertainties.

The population estimates by satellite images we used for outlining the hamlets in Bihar might be inaccurate. However the same is true for available census data in many leprosy-endemic countries. The remote sensing estimates used will at least provide a proxy which could serve as a fair basis for planning activities.

For cluster analysis, we opted for Kulldorff's spatial scan statistic although there are other spatial methods described and cluster size will vary according to the method used. [26]

## Recommendations for policy and practice

Our findings demonstrated the importance of clustering analysis for efficiently targeting the ongoing transmission of *M.leprae* in highly endemic countries. Using an open-source app and software, we developed a tool for clustering analysis at the lowest geographical level that could be applied in other settings. Therefore, we recommend:

**To the national leprosy programs:**

- To include retrospective spatial analysis of the new cases detected in the preceding five years. This will allow the identification of clusters to be targeted in screening for leprosy.
- To include prospective mapping of new leprosy cases using smartphone apps or GPS loggers. This will help again in monitoring the progress of control and curbing transmission.
- To include spatial analysis for assessing access to services for people affected by leprosy care as Disability Prevention and Medical Rehabilitation and Community Based Rehabilitation.

**To ILEP (International Federation of Associations against Leprosy) and other technical partners including research institutions:**

- To support technically and financially the national leprosy programs in the integration of GIS as part of the programmatic tools for control and surveillance

**To the World Health Organization:**

- To integrate the lessons learned from spatial analysis research and programs best practice into recommendations for surveillance of transmission of *M.leprae* and post-elimination.

## Recommendations for future research

The results of the studies we published in the thesis are based on active case detection by door-to-door screening, spatial risk of developing leprosy, and clustering analysis. Other known methodologies not included i.e. the social network analysis, [27] genotyping of the

pathogen, [28] analysis of host genetics factors [29] and reservoirs.[30] The possible research questions can be studied:

- The correlation between spatial clustering with *M.leprae* genotyping
- The role of social networks in spatial and molecular clusters
- The role of genetics in high incidence clusters
- The land characteristics associated with the clustering of leprosy and the possible association with potential reservoirs
- The integration of sero-surveillance in highly prevalent clusters
- The integration of skin-neglected tropical diseases in active case detection and its contribution to the leprosy control

## Conclusion

Our findings highlighted the crucial role geographical information systems can play in the control of leprosy. We identified clustering beyond the household level, regardless of the provision of PEP. Therefore there is a need to explore the efficacy of adapted active case detection and PEP, including the monitoring of the success of control activities, and the surveillance in a post-elimination phase. Importantly, the tools we used are open-source and user-friendly, and the expertise we developed includes national leprosy programs, non-governmental organizations, and research institutions making them ready for scaling up in different prevalence settings while maximizing their cost-effectiveness.

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## Summary

Leprosy or Hansen's disease is a complex ancient infectious disease, caused by *M.leprae* and *M.lepromatosis*. The most believed frequent mode of transmission is airborne and therefore those in close contact with a new leprosy case are at the most risk of developing the disease although this depends on immunity heterogeneity. Despite leprosy has been the first infectious disease where the pathogen agent was identified, research and development have failed in the creation of reliable diagnostic tests for infection and disease. Therefore, the World Health Organization (WHO) recommends clinical cardinal signs and the ancient slit skin smear (SSS) for the diagnosis of the disease, and no diagnostic test for diagnosis of infection is currently recommended. Both clinical and laboratory skills and expertise are key for ensuring the reliability of diagnosis, which is dwindling due to the sustained decrease of leprosy prevalence worldwide. Nevertheless, the incidence has plateaued in the last decade around 200,000 new cases at the global scale and the highly effective treatment with multidrug therapy (MDT) has been insufficient to stop transmission. In 2018, the WHO has recommend single-dose rifampicin (SDR) as post-exposure prophylaxis (PEP) for the contacts of new leprosy patients without signs of leprosy disease. The protection of PEP is around 60% and is based on the pivotal COLEP trial in Bangladesh. The Leprosy post-exposure prophylaxis with single-dose rifampicin (LPEP) study has documented the feasibility of PEP under programmatic conditions, and there is also evidence that PEP is cost-effective. Nevertheless, operational challenges for the most cost-effective approach to the provision of PEP for the high-risk population without causing harm to the persons eligible for SDR, and avoiding the increase of prevalence of rifampicin resistance, remain.

In this Ph.D., we developed and estimated the effectiveness of innovative active case detection strategies based on Geographic Information Systems-based (GIS-based) technologies for stopping transmission of *M. leprae* in high-priority countries i.e. Comoros, India, and Madagascar.
Using GIS-based technologies, we studied highly prevalent clusters in Comoros and Madagascar. Clustering analysis was nested in a larger ongoing trial on post-exposure prophylaxis (PEP) for leprosy (the PEOPLE trial), where detailed mapping of entire village populations, including leprosy patients, was necessary for assessing different modalities for PEP. In India, we assessed the clustering of leprosy and mobility of leprosy patients, to identify highly prevalent clusters at the hamlet level. For this purpose, we developed a methodology to outline hamlets maps including their population to assess clustering for targeted active case detection strategies coupled with prevention activities.

The following research questions were answered:

1. What are the patterns of clustering of leprosy in Comoros and Madagascar?
2. What is the pattern of clustering and mobility of leprosy patients in Bihar, India?
3. How to build an approach for exploring clustering at the lower administrative levels in Bihar, India?

We discussed the latest evidence of the natural history of leprosy and the most recent control strategies in Chapter 1.

In chapter 2, we analyzed door-to-door screening for leprosy in four endemic villages of Comoros that received SDR-PEP and we calculated the spatial risk of contracting leprosy for contacts including the protective effect of SDR-PEP for those who received it. We found 114

new cases among 5760 contacts screened (2.0% prevalence), in addition to the 39 cases detected in the two preceding years. There were statistically significant associations of incident leprosy with physical distance to index cases ranging from 2.4 (95% confidence interval (95% CI) 1.5–3.6) for household contacts to 1.8 (95% CI 1.3–2.5) for those living at 1–25 m, compared to individuals living at ≥75 m. The effect of SDR-PEP appeared protective but did not reach statistical significance due to the low numbers, with an incidence rate ratio (IRR) of 0.6 (95% CI 0.3–1.2) overall, and 0.5 (95% CI 0.2–1.3) when only household contacts were included. We concluded that this pilot survey unveiled an increased risk of leprosy in contacts beyond the household, reinforcing the need for a wider circle should be considered for chemoprophylaxis. Also, baseline surveys and extended contact definitions are essential for improving SDR-PEP effectiveness.

Chapter 3, describes the protocol of Post ExpOsure Prophylaxis for Leprosy in the Comoros and Madagascar (PEOPLE), a cluster-randomized trial to assess the effectiveness of three modalities of implementing PEP. In the PEOPLE trial, four annual door-to-door surveys will be performed in four arms. All consenting permanent residents will be screened for leprosy. Leprosy patients will be treated according to international guidelines and eligible contacts will be provided with SDR-PEP. Arm-1 is the comparator where no PEP will be provided. In arms 2, 3, and 4, SDR-PEP will be administered at a double dose (20 mg/kg) to eligible contacts aged two years and above. In arm 2, all household members of incident leprosy patients are eligible. In arm 3, not only household members but also neighborhood contacts living within 100-m of an incident case are eligible. In arm 4, such neighborhood contacts are only eligible if they test positive for anti-PGL-I, a serological marker. Incidence rate ratios calculated between the comparator arm 1 and each of the intervention arms will constitute the primary outcome. The PEOPLE trial will assess the effectiveness of PEP in a high-incidence setting of three different approaches and will identify who benefits most from PEP. Final results are expected in 2023.

In chapter 4, we describe the findings of the baseline survey of the first year of the PEOPLE trial in Comoros and Madagascar. We also assessed clustering at the village level fitting a purely spatial Poisson model by Kulldorff's spatial statistic and measured the distance risk of contact to the nearest leprosy patient. There were 455 leprosy patients; 200 (44.0%) belonged to 2735 households included in a cluster. Thirty-eight percent of leprosy patients versus 10% of the total population live 25 m from another leprosy patient. Risk ratios for being diagnosed with leprosy were 7.3, 2.4, 1.8, 1.4, and 1.7, for those in the same household, at 1–<25 m, 25–<50 m, 50–<75 m, and 75–<100 m as/from a leprosy patient, respectively, compared to those living at ≥100 m. We concluded that due to the significant clustering of leprosy beyond the household level, control measures need to be extended beyond the household, and social networks should be further explored.

Chapter 5, describes active case finding of household members of new cases detected in the preceding four years (2017-2020) in 32 villages not included in the PEOPLE trial in Anjouan, Comoros. Some neighbors requested to be screened for leprosy. We screened 131 out of 226 index case households aimed (58.8%), and 32 other nearby households. There were 945 persons recorded, 671 household contacts, and 274 neighborhood contacts. We examined 896 persons detecting 48(5.4%) leprosy cases. Among cases detected, 13(27.1%) had multibacillary (MB) leprosy, the median age was 18 years (IQR 8-34), 43% were below 15 years and two (4.2%) had visible deformities. The risk of contacts of developing leprosy was higher among 11 households linked to MB compared to one linked to a paucibacillary (PB) index case (OR 12.6, 95% CI 1.6-99.6). There were 12 new cases among 668 household

contacts with a leprosy prevalence of 18.0 per 1,000 (95% CI 9.3-31.1). We found 30 new cases in neighbors and six additional cases were diagnosed between their households with a residual prevalence of 26.3 per 1,000 (95% CI 9.7-56.4). We found a high prevalence above 26‰ among household contacts. We concluded that contact screening should not be a one-off intervention but should be repeated some years later in high-prevalence zones considering door-to-door visits for screening. The tools used are user-friendly and allow the identification of high-prevalence areas and can guide tailored screening.

In chapter 6, we document the mobility of new leprosy cases in two endemic blocks of the State of Bihar, India. We also screened household contacts for leprosy. Finally, we developed a GIS-based system to outline the lowest administrative level (hamlets known as Tola) including its population for assessing clustering. We visited 169 patients and screened 1,044 household contacts in Bisfi and Benipatti blocks in the state of Bihar. Median number of years of residing in the village was 17, interquartile range (IQR)12-30. We found 11 new leprosy cases among 658 household contacts examined (167 per 10,000), of which seven had paucibacillary leprosy, one was a child under 14 years, and none had visible disabilities. We identified 739 hamlets with a total population of 802,788(median 163, IQR 65–774). There were five high-incidence clusters at the hamlet level including 12% of the population and 46%(78/169) of the leprosy cases. One highly significant cluster with a relative risk (RR) of 4.7($p<0.0001$) included 32 hamlets and 27 cases in 33,609 population. A second highly significant cluster included 32 hamlets and 24 cases in 33,809 population with a RR of 4.1($p<0.001$). The third highly significant cluster included 16 hamlets and 17 cases in 19,659 population with a RR of 4.8($p<0.001$). There was a high yield of active household contact screening. We concluded that our tools for identifying high-incidence hamlets could be effective and need to be assessed in the field for increasing the efficiency of active case detection.

**Recommendations for policy and practice**

GIS-based tools increase efficiency when targeting active case detection in highly prevalent clusters where there is ongoing transmission of *M.leprae*. We also developed a tool for clustering analysis at the lowest geographical level that could be applied in other settings. Therefore, we recommend:

**To the national leprosy programs:**

- Including retrospective spatial analysis of the new cases detected in the preceding five years for targeted active case detection for leprosy.
- Including prospective mapping of new leprosy cases using smartphone apps or GPS loggers for monitoring the progress of control and curbing transmission.
- Including spatial analysis for assessing access to services for people affected by leprosy care as Disability Prevention and Medical Rehabilitation and Community Based Rehabilitation.

**To ILEP (International Federation of Associations against Leprosy) and other technical partners including research institutions:**

- Ensuring continuous support technically and financially the national leprosy programs in the integration of GIS as part of leprosy control and surveillance

**To the World Health Organization:**

- Integrating the lessons learned from spatial analysis research and programs best practice into recommendations for surveillance of transmission of *M.leprae* and post-elimination phase.

## Recommendations for future research

In this thesis, we published the results of active case detection by door-to-door screening, spatial risk of developing leprosy, and clustering analysis. Other known methodologies not included i.e. the social network analysis, genotyping of the pathogen, analysis of host genetics factors, and reservoirs. Therefore, the possible research questions that can be studied are:

- The correlation between spatial clustering with *M.leprae* genotyping
- The role of social networks in spatial and molecular clusters
- The role of genetics in high incidence clusters
- The land characteristics associated with the clustering of leprosy and the possible association with potential reservoirs
- The integration of sero-surveillance in highly prevalent clusters
- The integration of skin-neglected tropical diseases in active case detection and its contribution to the leprosy control

## Conclusion

Our findings highlighted the crucial role of geographical information systems in the control of leprosy while ensuring rational and efficient use of resources. As clustering is beyond the household level, regardless of the provision of PEP, there is a need 1) to explore the efficacy of adapted active case detection and PEP, 2) to monitor the success of control activities, and 3) to ensure surveillance in a post-elimination phase. All the tools we used are open-source and user-friendly, and the expertise we developed includes multidisciplinary partners i.e. the national leprosy programs, non-governmental organizations, and research institutions making them ready for scaling up in different leprosy prevalence settings while maximizing their cost-effectiveness.

## Samenvatting

Lepra of de ziekte van Hansen is een complexe infectieziekte, bekend sinds de oudheid, veroorzaakt door *M.leprae* en *M.lepromatosis*. De meest waarschijnlijke wijze van overdracht is via de lucht en daarom lopen degenen die in nauw contact komen met een onbehandelde leprapatiënt het meeste risico om de ziekte te krijgen, hoewel dit afhangt van de immuniteit die zeer heterogeen is. Hoewel lepra de eerste infectieziekte was waarvan de ziekteverwekker werd geïdentificeerd, zijn onderzoek en ontwikkeling er niet in geslaagd betrouwbare diagnostische tests voor infectie en ziekte te ontwikkelen. Daarom adviseert de Wereldgezondheidsorganisatie (WHO) voor de diagnose van de ziekte nog altijd te vertrouwen op klinische kardinale tekenen en het aloude huidincisie-uitstrijkje (SSS), en wordt momenteel geen diagnostische test aanbevolen om de infectie vast te stellen. Zowel klinische als laboratoriumvaardigheden en expertise zijn essentieel om de betrouwbaarheid van de diagnose te waarborgen, die betrouwbaarheid neemt af door de aanhoudende daling van de lepraprevalentie wereldwijd. Niettemin is de incidentie de afgelopen tien jaar wereldwijd gestagneerd rond de 200.000 nieuwe gevallen per jaar en is de zeer effectieve behandeling met multi-geneesmiddeltherapie (MDT) onvoldoende geweest om de transmissie te stoppen. In 2018 heeft de WHO een éénmalige dosis rifampicine (single-dose rifampicine of SDR) aanbevolen als post-expositie profylaxe (PEP) voor de contacten van nieuwe leprapatiënten die zelf nog zonder klinische tekenen van lepra zijn. De bescherming van PEP bedraagt ongeveer 60%, een schatting gebaseerd op de baanbrekende COLEP-studie in Bangladesh. De 'Leprosy post-exposure prophylaxis with single-dose rifampicin' (LPEP) studie heeft de haalbaarheid van PEP onder programmatische omstandigheden gedocumenteerd en er zijn ook aanwijzingen dat PEP kosteneffectief is. Niettemin blijven er operationele uitdagingen voor de meest kosteneffectieve aanpak van de verstrekking van PEP aan hoogrisicopopulaties, met de bedoeling geen schade te berokkenen aan de personen die voor SDR in aanmerking komen, en toename van de prevalentie van rifampicineresistentie te vermijden.

In dit doctoraat hebben we innovatieve, op geografische informatiesystemen (GIS) gebaseerde strategieën ontwikkeld en getest voor de actieve opsporing van leprapatiënten om de overdracht van *M. leprae te* stoppen in landen met een hoge prioriteit, namelijk de Comoren, India en Madagaskar. Met behulp van GIS-gebaseerde technologieën bestudeerden we clusters van hoge prevalentie in de Comoren en Madagaskar. De clusteringanalyse was ingebed in een groter lopend onderzoek naar postexpositieprofylaxe (PEP) voor lepra (de PEOPLE-studie), waarbij het gedetailleerd in kaart brengen van hele dorpspopulaties, inclusief leprapatiënten, noodzakelijk was voor het beoordelen van verschillende modaliteiten van PEP. In India beoordeelden wij de clustering van lepra en de mobiliteit van leprapatiënten, om hoog-prevalente clusters op gehuchtniveau te identificeren. Daartoe ontwikkelden wij een methode om kaarten te maken van gehuchten, inclusief een schatting van hun bevolkingsaantallen, om de clustering te beoordelen voor gerichte actieve screeningstrategieën, gekoppeld aan preventieactiviteiten.

De volgende onderzoeksvragen werden beantwoord:

- Wat zijn de patronen van clustering van lepra op de Comoren en Madagaskar?
- Wat is het patroon van clustering en mobiliteit van leprapatiënten in Bihar, India?
- Hoe kan een aanpak worden ontwikkeld om clustering op de lagere bestuursniveaus in Bihar, India, te onderzoeken?

In hoofdstuk 1 hebben wij de meest recente gegevens over de natuurlijke geschiedenis van lepra en de meest recente bestrijdingsstrategieën besproken.

In hoofdstuk 2 analyseerden we huis-aan-huis screening op lepra in vier endemische dorpen op de Comoren die PEP op basis van een éénmalige dosis rifampicine (SDR-PEP) ontvingen en berekenden we het risico op lepra voor contacten in functie van afstand, inclusief het beschermende effect van SDR-PEP voor degenen die het ontvingen. We vonden 114 nieuwe gevallen onder 5760 gescreende contacten (2,0% prevalentie), naast de 39 gevallen die in de twee voorgaande jaren waren ontdekt. Er waren statistisch significante associaties van incidente lepra met fysieke afstand tot indexgevallen, variërend van 2,4 (95% betrouwbaarheidsinterval (95% CI) 1,5-3,6) voor huishoudcontacten tot 1,8 (95% CI 1,3-2,5) voor degenen die op 1-25 m woonden, vergeleken met personen die op ≥75 m woonden. Het effect van SDR-PEP leek beschermend, maar bereikte geen statistische significantie vanwege de lage aantallen, met een incidentieratio (IRR) van 0,6 (95% CI 0,3-1,2) in totaal, en 0,5 (95% CI 0,2-1,3) wanneer alleen huishoudelijke contacten werden meegerekend. Wij concludeerden dat dit proefonderzoek een verhoogd risico op lepra onthulde ook bij contacten buiten het huishouden, wat de noodzaak versterkt om een bredere kring te overwegen voor postexpositieprofylaxe. Ook zijn nulmetingen en uitgebreide contactdefinities essentieel voor het verbeteren van de effectiviteit van SDR-PEP.

Hoofdstuk 3 beschrijft het protocol van 'Post ExpOsure Prophylaxis for Leprosy in the Comoros and Madagascar' (PEOPLE), een cluster-gerandomiseerde trial om de effectiviteit van drie modaliteiten voor het uitvoeren van PEP te beoordelen. In de PEOPLE-studie zullen vier jaarlijkse huis-aan-huis onderzoeken worden uitgevoerd in vier armen. Alle instemmende permanente bewoners zullen worden gescreend op lepra. Leprapatiënten zullen worden behandeld volgens internationale richtlijnen en in aanmerking komende contacten zullen SDR-PEP krijgen. Arm-1 is de vergelijkingsarm waar geen PEP zal worden verstrekt. In de armen 2, 3 en 4 zal SDR-PEP in een dubbele dosis (20 mg/kg) worden toegediend aan in aanmerking komende contacten van twee jaar en ouder. In arm 2 komen alle leden van het huishouden van incidente leprapatiënten in aanmerking. In arm 3 komen niet alleen leden van het huishouden maar ook buurtcontacten die binnen een straal van 100 m van een incidente patiënt wonen, in aanmerking. In arm 4 komen dergelijke buurtcontacten alleen in aanmerking als zij positief testen op anti-PGL-I, een serologische marker. De primaire uitkomst is de incidentieratio tussen de vergelijkingsarm 1 en elk van de interventiearmen. De PEOPLE-studie zal de doeltreffendheid van drie verschillende benaderingen van PEP in een setting met hoge incidentie beoordelen en zal vaststellen wie het meeste baat heeft bij PEP. De eindresultaten worden in 2023 verwacht.[2]

In hoofdstuk 4 beschrijven we de bevindingen van de nulmeting van het eerste jaar van de PEOPLE-studie in de Comoren en Madagaskar. We beoordeelden ook de clustering op dorpsniveau door een ruimtelijk Poisson-model toe te passen met behulp van de ruimtelijke statistiek van Kulldorff en het risico op lepra te berekenen in functie van afstand tot de dichtstbijzijnde leprapatiënt. Er waren 455 leprapatiënten; 200 (44,0%) behoorden tot 2735 huishoudens in een cluster. Achtendertig procent van de leprapatiënten versus 10% van de totale bevolking woont binnen de 25 meter van een (andere) leprapatiënt. Risicoratio's voor de diagnose lepra waren 7,3, 2,4, 1,8, 1,4, en 1,7, voor degenen in hetzelfde huishouden, op respectievelijk 1-<25 m, 25-<50 m, 50-<75 m, en 75-<100 m van een leprapatiënt, vergeleken met degenen die op ≥100 m woonden. Wij concludeerden dat wegens de significante clustering van lepra buiten het niveau van het huishouden, controlemaatregelen moeten

worden uitgebreid tot buiten het huishouden, en sociale netwerken verder moeten worden onderzocht.

Hoofdstuk 5, beschrijft het actief screenen van huishoudcontacten van nieuwe gevallen die in de voorgaande vier jaar (2017-2020) zijn ontdekt in 32 dorpen die niet zijn opgenomen in de PEOPLE-studie in Anjouan, Comoren. Ook sommige buren vroegen om gescreend te worden op lepra. We screenden 131 van de 226 beoogde indexgevalhuishoudens (58,8%), en 32 andere nabijgelegen huishoudens. Er werden 945 personen geregistreerd, 671 huishoudelijke contacten en 274 buurtcontacten. We onderzochten 896 personen en vonden 48 nieuwe lepragevallen (5,4%) . Onder de opgespoorde gevallen hadden 13 (27,1%) multibacillaire (MB) lepra, de mediane leeftijd was 18 jaar (IQR 8-34), 43% was jonger dan 15 jaar en twee (4,2%) hadden zichtbare misvormingen. Het risico van contacten om lepra te ontwikkelen was hoger bij 11 huishoudens gelinkt aan MB patiënten in vergelijking met één huishouden gelinkt aan een paucibacillair (PB) indexgeval (OR 12,6, 95% CI 1,6-99,6). Er waren 12 nieuwe gevallen onder 668 huishoudelijke contacten met een lepraprevalentie van 18,0 per 1.000 (95% CI 9,3-31,1). We vonden 30 nieuwe gevallen bij buren en zes extra gevallen werden gediagnosticeerd in hun huishoudens met een restprevalentie van 26,3 per 1.000 (95% CI 9,7-56,4). Wij vonden een hoge prevalentie, boven de 26‰, onder contacten in het huishouden. Wij concludeerden dat contactscreening geen eenmalige interventie moet zijn, maar enkele jaren later moet worden herhaald in gebieden met een hoge prevalentie, waarbij huis-aan-huis bezoeken voor screening moeten worden overwogen. De gebruikte instrumenten zijn gebruiksvriendelijk en maken het mogelijk gebieden met een hoge prevalentie te identificeren en kunnen als leidraad dienen voor gerichte actieve screening.

In hoofdstuk 6 documenteren we de mobiliteit van nieuwe lepragevallen in twee endemische sub-districten van de staat Bihar, India. Ook screenden we contacten in huishoudens op lepra. Ten slotte ontwikkelden we een op GIS gebaseerd systeem om het laagste administratieve niveau (gehuchten, ter plaatse bekend als 'Tola') in kaart te brengen, inclusief de geschatte bevolkingsaantallen, om clustering te beoordelen. We bezochten 169 patiënten en onderzochten 1.044 huishoudelijke contacten in Bisfi en Benipatti sub-districten in de staat Bihar. De mediaan van het aantal jaren dat men in het dorp woonde was 17, interkwartiel bereik (IQR) 12-30. Wij vonden 11 nieuwe lepragevallen onder 658 onderzochte huishoudcontacten (167 per 10.000), waarvan zeven met paucibacillaire lepra, één onder kinderen jonger dan 14 jaar, en geen enkele met zichtbare afwijkingen. We identificeerden 739 gehuchten met een totale bevolking van 802.788 (mediaan 163, IQR 65-774). Er waren vijf clusters met hoge incidentie op gehuchtsniveau die 12% van de bevolking en 46% (78/169) van de lepragevallen omvatten. Eén zeer significante cluster met een relatief risico (RR) van 4,7 ($p<0,0001$) omvatte 32 gehuchten en 27 gevallen op 33.609 inwoners. Een tweede zeer significante cluster omvatte 32 gehuchten en 24 gevallen in 33.809 inwoners met een RR van 4,1($p<0,001$). Het derde zeer significante cluster omvatte 16 gehuchten en 17 gevallen in 19.659 inwoners met een RR van 4,8($p<0,001$). Er was een hoog rendement van actieve screening van huishoudelijke contacten. Wij concludeerden dat onze instrumenten voor het identificeren van gehuchten met een hoge incidentie effectief zouden kunnen zijn en in het veld moeten worden beoordeeld om de efficiëntie van actieve opsporing van lepra te vergroten.

**Aanbevelingen voor beleid en praktijk**

Op GIS gebaseerde hulpmiddelen verhogen de efficiëntie bij de actieve opsporing van lepra in zeer prevalente clusters waar overdracht van *M.leprae* nog altijd gaande is. Wij hebben ook

een instrument ontwikkeld voor clusteringanalyse op het laagste geografische niveau dat in andere settings kan worden toegepast. Daarom bevelen wij aan:

**Aan de nationale lepra-programma's:**

- Includeren van retrospectieve ruimtelijke analyse van de nieuwe gevallen die in de voorgaande vijf jaar zijn ontdekt voor gerichte actieve opsporing van lepra.
- Includeren van het prospectief in kaart brengen van nieuwe lepragevallen met behulp van smartphone-apps of gps-loggers om de voortgang van de bestrijding en het terugdringen van de transmissie op te volgen.
- Includeren van ruimtelijke analyse voor de beoordeling van de toegang tot diensten voor mensen die getroffen zijn door lepra, zoals diensten voor preventie van handicaps, voor medische revalidatie en gemeenschapsdiensten voor revalidatie.

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- Zorgen voor continue technische en financiële ondersteuning van de nationale lepraprogramma's bij de integratie van GIS als onderdeel van leprabestrijding en -epidemiologische opvolging.

**Aan de Wereldgezondheidsorganisatie:**

- Integratie van de lessen die zijn getrokken uit onderzoek naar ruimtelijke analyse en de beste praktijken van programma's in aanbevelingen voor epidemiologische opvolging van transmissie *M.leprae*, ook in de fase na de uitroeiing.

**Aanbevelingen voor toekomstig onderzoek**

In dit proefschrift publiceerden wij de resultaten van actieve huis-aan-huis screening, ruimtelijk risico op het ontwikkelen van lepra, en clustering analyse. Andere bekende methodologieën zijn niet opgenomen, namelijk de sociale netwerkanalyse, genotypering van de ziekteverwekker, analyse van gastheer-genetische factoren, en reservoirs. Daarom zijn de mogelijke onderzoeksvragen die nog bestudeerd kunnen worden:

- De correlatie tussen ruimtelijke clustering en *M.leprae* genotypering
- De rol van sociale netwerken in ruimtelijke en moleculaire clusters
- De rol van genetica in hoge incidentieclusters
- De landkenmerken die verband houden met de clustering van lepra en de mogelijke associatie met potentiële reservoirs
- De integratie van serologische surveillance in zeer prevalente clusters
- De integratie van verwaarloosde tropische huidziekten in de actieve screening en de bijdrage daarvan aan de bestrijding van lepra

**Conclusie**

Onze bevindingen benadrukten de cruciale rol van geografische informatiesystemen bij de bestrijding van lepra en zorgden voor een rationeel en efficiënt gebruik van middelen. Aangezien clustering verder gaat dan het niveau van het huishouden, ongeacht de verstrekking van PEP, is er behoefte 1) aan onderzoek naar de doeltreffendheid van aangepaste actieve screening en PEP, 2) aan het opvolgen van het succes van controleactiviteiten, en 3) aan epidemiologische surveillance in een post-eliminatiefase. Alle

door ons gebruikte instrumenten zijn open-source en gebruiksvriendelijk, en in de door ons ontwikkelde expertise zijn multidisciplinaire partners betrokken, d.w.z. de nationale lepraprogramma's, niet-gouvernementele organisaties en onderzoeksinstellingen, waardoor ze klaar zijn voor opschaling in verschillende settings waar lepra voorkomt, terwijl ze maximaal kosteneffectief zijn.

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## Curriculum Vitae

After completing his studies in Medicine in 1999 at Universidad Mayor de San Simón, Cochabamba – Bolivia where he was born, his career started in 2000 as a leishmaniasis research assistant in Cochabamba. Then, from 2002-2003, he followed the Master of Science in Public Health (MPH) training course at the Institute of Tropical Medicine (ITM), Antwerp - Belgium. Later, in Burundi, he acted as medical advisor of the national TB and leprosy program and Damien Foundation representative from 2004-2008. In Navarre Spain, he was trained as a community and family medicine specialist and worked as a general practitioner (2008-2012). Next, from 2012-2013, he worked in the coordination team of the MPH at the ITM, Antwerp - Belgium. From 2013-2015, based in Guinea he acted as medical advisor of the national TB program and representative of Damien Foundation. Since September 2015, he works as a medical advisor and research coordinator at Damien Foundation Headquarters in Brussels, Belgium.

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18. Decroo, T., K. Jai, M. Aung, M. A. Hossain, M. Gumusboga, **N. Ortuno-Gutierrez**, B. Catherine, D. Jong and A. Van Deun (2021). "Bedaquiline can act as core drug in a standardized treatment regimen for fluoroquinolone-resistant rifampicin-resistant tuberculosis." European Respiratory Journal: 2102124.
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20. Souleymane, M. B., T. Decroo, S. Mamadou, A. Soumana, I. M. Lawan, A. Gagara-Issoufou, E. Adehossi, **N. Ortuno-Gutierrez**, L. Lynen, L. Rigouts, B. C. de Jong, A. Van Deun and A. Piubello (2022). "Definitive outcomes in patients with rifampicin-resistant tuberculosis treated in Niger from 2012 to 2019: A retrospective cohort study." Int Health.
21. **Ortuño-Gutiérrez, N**., A. Mzembaba, A. Baco, S. M. Braet, A. Younoussa, Z. Salim, M. Amidy, S. Grillone, A. Said, B. C. de Jong, J. H. Richardus and E. Hasker (2022). "High yield of retrospective active case finding for leprosy in Comoros." PLOS Neglected Tropical Diseases 16(3): e0010158.
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| Description | Organizer | EC |
|---|---|---|
| **Required** | | |
| ESHPM - Attending a conference (with or without a poster presentation) (2016) | 19 International Leprosy Conference | 1.00 |
| ESHPM - Attending a conference (with or without a poster presentation) (2017) | The Union | 1.00 |
| ESHPM - Attending a conference (with or without a poster presentation) (2017) | 10th European Congress on Tropical Medicine and International Health | 1.00 |
| Clinical decision making for drug-resistant tuberculosis (2018) | The Institute of Tropical Medicine, Atwerp | 5.00 |
| ESHPM - Attending a conference (with or without a poster presentation) (2018) | The Union | 1.00 |
| ESHPM - Attending a conference (with or without a poster presentation) (2019) | International Leprosy Association | 1.00 |
| ESHPM - Attending a conference (with or without a poster presentation) (2019) | The Union | 1.00 |
| ESHPM - Attending a conference (with or without a poster presentation) (2020) | The Union | 1.00 |
| ESHPM - Attending a conference (with or without a poster presentation) (2021) | The Union | 1.00 |
| **Optional** | | |
| Operational research training Central African Tuberculosis Network (CARN), (2018) | CARN | 2.00 |
| Operational research training Central African Tuberculosis Network (CARN), (2019) | CARN | 2.00 |
| Structured Operational Research and Training Initiative (SORT IT) (2019) | WHO Special Programme for Research and Training in Tropical Diseases | 2.00 |
| Operational research training Central African Tuberculosis Network (CARN), (2019) | CARN | 2.00 |
| Structured Operational Research and Training Initiative (SORT IT) (2021) | WHO Special Programme for Research and Training in Tropical Diseases | 2.00 |
| Operational research training Central African Tuberculosis Network (CARN), (2021) | CARN | 2.00 |
| Structured Operational Research and Training Initiative (SORT IT) (2021) | WHO Special Programme for Research and Training in Tropical Diseases | 2.00 |
| Structured Operational Research and Training Initiative (SORT IT) (2021) | WHO Special Programme for Research and Training in Tropical Diseases | 2.00 |
| Structured Operational Research and Training Initiative (SORT IT) (2022) | WHO Special Programme for Research and Training in Tropical Diseases | 2.00 |
| | | ------ + |
| Total EC | | 31.00 |