

EDITORIAL

Role of contact tracing and prevention strategies in the interruption of leprosy transmission

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Summary The global prevalence of leprosy has declined from 5.2 million in the 1980s to 200,000 today.¹ However, the new case detection rate remains high: over the last 8 years, around 220,000–250,000 people have been diagnosed with leprosy each year. In June 2013, an international meeting was organised by the Novartis Foundation for Sustainable Development in Geneva, Switzerland,² with the objective of discussing the feasibility of interrupting the transmission of leprosy. The group of physicians, epidemiologists and public health professionals concluded that a successful programme would require early diagnosis and prompt multidrug therapy (MDT) for all patients, tracing and post-exposure prophylaxis (PEP) for contacts of patients newly diagnosed with leprosy, improvements in diagnostic tools, as well as strict epidemiological surveillance and response systems to monitor progress.

As a follow-up, a second expert group meeting was convened by the Novartis Foundation in January 2014 in Zurich, Switzerland, with the objective of reviewing the evidence for chemoprophylaxis in contacts and high-risk communities. The meeting also considered the definitions of ‘contacts’ and ‘contact tracing’, discussed alternative prophylaxis regimens, preliminary findings of operational pilot projects on PEP in Indonesia, as well as the development of diagnostic tools, and identified the priority questions for operational research in leprosy transmission.

The meeting outlined how contact tracing and chemoprophylaxis programmes can be implemented to interrupt leprosy transmission. The expert panel reached the following conclusions:

- Chemoprophylaxis with single-dose rifampicin (SDR) is efficacious in reducing the risk of developing leprosy, although the protective effect appears to be smaller in contacts closer to the index patient than in more distant contacts.³ SDR can be targeted to contacts or implemented as community mass prophylaxis in certain circumstances; the preferred approach depends on local factors, such as the case detection rate, the level of community stigma against leprosy, and the degree of access to healthcare for patients and contacts. Alternative prophylaxis regimens and the role of post-exposure immunoprophylaxis need to be further investigated.

- Contact tracing combined with PEP across very diverse settings offers protection rates similar to those reported in controlled trials. For high-incidence pockets ('hotspots') or remote or confined high-incidence populations ('hotpops'), blanket administration of PEP may be a better option.
- Implementation of contact-tracing programmes is feasible and cost-effective, particularly in high-risk groups, but it should be integrated into local healthcare services to ensure their long-term sustainability. Funding and support must be maintained after an initial pilot has finished. New programmes for contact tracing need effective surveillance systems to enable appropriate follow-up and outcome evaluation.
- The Novartis Foundation and Netherlands Leprosy Relief (NLR) are currently developing and implementing a large international programme to demonstrate the feasibility, acceptability, cost-effectiveness and real-world efficacy of PEP as a strategy to interrupt leprosy transmission, in six pilot projects in Asia, Africa and South America. These new pilot projects will be developed together with the local health authorities, healthcare workers, communities and patients, in order to create

Research priorities

The expert panel considered a number of research priorities regarding contact tracing and prophylactic treatment of contacts of patients newly diagnosed with leprosy:

- Does contact tracing combined with PEP with SDR reduce the incidence of leprosy in the general population, and, as such, interrupt transmission of the disease?
- What is the efficacy of alternative PEP regimens?
- When should PEP be used as a blanket approach, and when should it be targeted to contacts of newly diagnosed patients? Can a prevalence/case detection rate threshold be defined, above which mass administration of SDR would be preferable?
- Do different types of contact require different PEP regimens or interventions (e.g. higher or repeated dosing of rifampicin, longer-acting rifapentine, or a multidrug therapy for prevention in close contacts)?
- What would be an effective follow-up and management plan after PEP?
- Can specific biomarkers be identified that differentiate infected (asymptomatic) contacts from non-infected contacts?
- Can biomarkers be identified that predict progression to disease in infected individuals?
- Based on such biomarkers, can robust and reliable field-friendly diagnostic tests be developed to facilitate early diagnosis and appropriate targeting of treatment?
- Will immunoprophylaxis work synergistically with SDR in PEP?
- What are the limitations in sensitivity and specificity of seroconversion tests based on antigens such as PGL-I and LID-1? What is the ability of these tests to detect infection or predict the emergence of clinical symptoms?
- Do index patients, contacts and other stakeholders accept PEP with SDR, particularly in areas with a high level of leprosy-related stigma?
- Does the introduction of PEP affect the perception of leprosy in the community?

local ownership from the outset. The pilots should aim to be scalable and sustainable, and should therefore include an objective outcome assessment. Local ownership ensures that locally appropriate language and definitions of contacts are used in each of the pilots.

- A test to identify subclinical disease and distinguish *M. leprae* exposure from infection would facilitate early and appropriate therapy (with PEP or MDT). The identification and validation of new, sensitive biomarkers for *M. leprae* infection and exposure may allow better targeting of PEP to those contacts at highest risk of developing leprosy.

Introduction

Early case detection and prompt treatment with multidrug therapy (MDT) are the cornerstones of the fight against leprosy. The use of MDT has reduced the global prevalence of leprosy from over 5.2 million people in the 1980s to 200,000 today¹ and 16 million patients have been treated with MDT. Novartis has provided the MDT drugs free of charge through the World Health Organization (WHO) since 2000.

The case detection rate for leprosy has plateaued at about 220,000–250,000 over the past 8 years,⁴ and the disease remains endemic in many countries in Africa, South America and Asia, but even countries with low endemicity may have localized high-burden pockets. As a result, it is urgent to design strategies that can interrupt disease transmission and curb the incidence again.

In June 2013, the Novartis Foundation for Sustainable Development and the World Health Organization (WHO)² organized an international expert meeting in Geneva, Switzerland, to discuss the feasibility of interrupting the transmission of leprosy and how this could be achieved.¹ An expert group of physicians, epidemiologists and public health professionals involved in leprosy and other disease control programmes concluded that a successful programme would require: (a) tracing of contacts of patients newly diagnosed with leprosy combined with post-exposure prophylaxis (PEP), (b) the development of diagnostic tools to identify those at risk of developing the disease, and (c) the use of epidemiological surveillance coupled to a strict response system, to enhance early diagnosis and prompt treatment of all patients with leprosy. The aim of this strategy is to demonstrate that the incidence of leprosy can be further reduced.

A second expert meeting was convened by the Novartis Foundation in January 2014 in Zurich, Switzerland, to review the evidence for chemoprophylaxis in contacts and high-risk communities, consider definitions of ‘contacts’ and ‘contact tracing’, explore alternative prophylactic regimens or methods, discuss the development of diagnostic tools and review the preliminary findings of operational pilot projects in implementing PEP. The expert group also aimed at identifying the remaining open questions for operational research in leprosy. The discussions formed the basis for the development of a series of pilot projects to assess the feasibility of interrupting leprosy transmission by performing contact tracing coupled to PEP in six countries in Asia, Africa and South America.

Review of the evidence for chemoprophylaxis in contacts and in high-risk communities.

SUMMARY OF THE EVIDENCE ON CHEMOPROPHYLAXIS AND IMMUNOPROPHYLAXIS IN LEPROSY

Contacts of patients who have been newly diagnosed with leprosy are at an increased risk of infection, and can be categorised by physical or social distance from the index patient (e.g. blood relative, household member, neighbour). Chemoprophylaxis with a single dose of rifampicin reduces the new case detection rate among contacts, as demonstrated by a randomized clinical trial from Bangladesh (the contact transmission and chemoprophylaxis in leprosy [COLEP] study).³

In the COLEP study (2002–2007), 21,711 contacts of 1037 index patients were randomized to either single-dose rifampicin (SDR; 600 mg) or placebo. SDR provided 57% protection after 2 years ($P = 0.0002$; number needed to treat [NNT] = 265).³ The protective effect was smaller among contacts who were closer to the index patient than among distant contacts. This difference may be due to a lower likelihood of infection among distant contacts, or due to repeat exposure of close contacts.

Another controlled study in Indonesia (2000–2003) included 3965 individuals from five islands endemic for leprosy; two doses of rifampicin (600 mg for adults, 300 mg for those aged 6–14 years) were given to contacts of patients (contact group), all eligible people (blanket group) or no one (control group). After 3 years of follow-up, a significant protective effect of rifampicin was observed in the blanket group only (75%, $P = 0.031$).⁵

Alternative regimens for PEP are also being evaluated; a combination of rifampicin, ofloxacin and minocycline (ROM) is currently being assessed in a clinical study in Brazil. In addition to chemoprophylaxis, immunoprophylaxis with BCG or with vaccines against *Mycobacterium leprae* may offer another option for preventing leprosy disease. A meta-analysis of studies found that BCG provides an overall protective effect against leprosy of 68% (95% CI: 56–80%) in contacts.⁶ However, evidence for the efficacy of revaccination with BCG remains unclear. It is currently being assessed in the MALTALep trial⁷ whether immunoprophylaxis with BCG is an efficacious adjuvant to chemoprophylaxis.

In certain settings, only 20–30% of new cases are detected among close household contacts. However, in low-endemic areas that proportion may be higher than in high-endemic areas, because of a lower risk of infection from other sources than the household contact. Given that currently the leprosy endemicity is relatively low globally, examination of contacts is likely to yield a higher proportion of the total new diagnoses nowadays than was previously observed.

An effective PEP strategy should consider not only the dosing strength, frequency and choice of the drug, but also the ideal number and type of contacts to be traced, examined and treated. Determining what constitutes an effective PEP strategy is therefore part of the international programme of six pilot projects currently being developed by the Novartis Foundation and NLR to assess the real-life efficiency of chemoprophylaxis in reducing leprosy transmission.

COMMUNITY MASS PROPHYLAXIS

Trials of dapsone have indicated that mass chemoprophylaxis can be efficacious in preventing leprosy in high-risk populations. These studies are now only of historical interest, given the need for dapsone to be taken for a long time to achieve protection.

Case studies from Micronesia, the Maldives, Indonesia and French Polynesia have shown that blanket treatment of a population with rifampicin or with ROM is feasible, and can reach a high coverage. These case studies showed that the NNT to prevent one case of leprosy depends on the protective effect of the prophylactic drug and the disease frequency, and that it is lower in high-endemicity areas. As a result, mass prophylaxis is therefore most efficient in high-risk or high-endemicity populations.⁸ Linking blanket prophylaxis for leprosy to mass drug administration programmes for other neglected tropical diseases may provide logistical advantages. It remains unproven whether mass revaccination with BCG can provide additional protection to blanket chemoprophylaxis in populations at high risk of leprosy.

RESULTS FROM MODELLING AND ECONOMIC EVALUATION ANALYSES

Findings from the SIMCOLEP study, a modelling analysis using data from the COLEP trial, suggest that the effectiveness of SDR depends on a broad range of factors, including the level of contact (e.g. household vs neighbour) and the BCG status.^{3,9,10} A micro-simulation model was used to predict the potential effect on the case detection rate of different leprosy interventions (such as SDR chemoprophylaxis or BCG infant vaccination on top of early diagnosis and prompt treatment of new patients with MDT).¹⁰ The results indicate that early diagnosis and treatment and BCG infant vaccination, have the greatest impact on case detection rates, and that SDR prophylaxis for household contacts can provide additional reductions. Notably, while SDR chemoprophylaxis was more effective in social contacts than in close contacts, interventions aimed at close (household) contacts may be more cost-effective as the NNT is smaller.⁹

Key points from presentations and discussions

- Chemoprophylaxis with SDR reduces the risk of developing leprosy.
- Chemoprophylaxis with various regimens can either be targeted to contacts or implemented as mass prophylaxis. The choice of approach should depend on local factors such the level of endemicity and case detection rates, as well as the degree of access to healthcare for patients and their contacts.
- Further research is needed to determine the effect of chemoprophylaxis with repeat doses of rifampicin, with other regimens (e.g. rifapentine or ROM), or in combination with BCG immunoprophylaxis.

Logistics – defining contacts, contact tracing and innovation

REVIEW OF THE WHO POSITION ON CHEMOPROPHYLAXIS

An update was presented on the International Leprosy Summit held in Bangkok in July 2013, as well as on the WHO global leprosy strategy (2011–2015)¹¹ and the WHO revision process for the next 5-year plan (2016–2020).

The Bangkok Summit emphasized the need to reinforce political commitment to eliminating leprosy and to focus on high endemic areas. The summit also highlighted the importance of reducing the incidence of patients with grade 2 deformities, involving communities in leprosy programmes, and adopting innovative approaches to early detection and treatment completion.

The current WHO position on chemoprophylaxis for contacts of newly diagnosed patients with leprosy is based on formal meetings by the WHO Technical Advisory Group (April 2009 and September 2011) and the WHO Expert Committee on Leprosy (October 2010).¹² These consultations concluded that: (a) contact tracing should remain a core part of the current WHO strategy, although further research is needed on the cost-effectiveness and logistics of its implementation; (b) contacts should be examined for leprosy, educated on the early signs of disease and considered for PEP with SDR, particularly in regions with high case detection rates; (c) factors such as resources, treatment contraindications and adverse reactions, as well as concerns about ethics and confidentiality, should always be considered when implementing a prophylaxis programme. However, implementation of these recommendations has remained generally poor.

Outstanding challenges identified for the 2016–2020 strategy include access to healthcare, early detection through self-reporting, empowerment of local stakeholders and training of healthcare workers.

REVIEW OF EXPERIENCES OF CONTACT TRACING AND PEP

Indonesia

At present, leprosy management in Indonesia includes contact tracing, with active screening among household and neighbour contacts usually within three months of index patient presentation. Success of the contact-tracing programme is assessed by monitoring the proportion of index patients who have had their contacts traced and examined (the index patient coverage, IPC), as well as the proportion of contacts of newly diagnosed patients who have been traced and examined (the contact examination coverage, CEC). The IPC for Indonesia was 24.7%; however, this varied considerably across regions (from 17% in South Sumatera to 100% in Banten). The national CEC was 17.6%, ranging from 1.4% in East Kalimantan to 100% in Banten. Across Indonesia, 29.8% of all new leprosy cases were found among contacts of index patients.

In 2012, a contact tracing and PEP programme was introduced in Sampang, East Java, supported by Netherlands Leprosy Relief (NLR). The programme has been implemented as a pilot for the first two years, and will be incorporated into routine leprosy services from the third year. Single-dose rifampicin (SDR) was provided to contacts of index patients, defined as household members, neighbours, or social contacts who had at least 20 hours of interaction per week. The programme aimed to trace and treat an average of 20 contacts per index patient. After potential contacts had been identified, health workers obtained informed consent from both the index patient and the contacts, conducted screening for leprosy, and administered chemoprophylaxis as appropriate. In 2013, two years after the start of the pilot in Sampang, the implementation of this intensified contact tracing and PEP programme had resulted in an IPC of 78%, with 95% of contacts having received chemoprophylaxis, showing that the initiative had been successful. The impact on the leprosy case detection rate will be evaluated at the end of the pilot period.

In East Java, intensive contact-tracing has been in use since 2004; however, in Sampang, it had not been fully implemented until the start of the chemoprophylaxis pilot in 2012. Between 2004 and 2011, the case detection rate in Sampang was relatively constant, at around 60/100,000. By 2013, the rate had declined slightly to 43/100,000; however, it is difficult to

determine whether this decline indicates a trend, and to what extent it can be attributed to the contact tracing and PEP rather than to the successful treatment of index patients.

Lessons from this project show that it is feasible to implement PEP as part of a routine health programme in which contact tracing is performed systematically. However, such programmes require ongoing policy support and supervision, strong local ownership and the continuous motivation of healthcare workers in the field. PEP intervention programmes in Indonesia were well received by all stakeholders and particularly by patients and their contacts, and contact examinations offered excellent opportunities to educate family members and increase leprosy awareness within the community. However, stigma was found to be a barrier to disclosing the disease to people beyond the household, and issues of informed consent and disclosure need careful consideration, as does training of involved staff.

Thailand

Contacts in Thailand are traced through annual examinations, patient check-ups during hospital visits, and, particularly in high-risk villages, Rapid Village Surveys. However, data from 2012 show that although 46% of newly diagnosed patients among household contacts had been identified through contact tracing, 50% were self-reported. Hence, there is a need to improve contact tracing, and public health strategies are now focusing on high-risk districts, the integration of contact examinations into routine home visits, disease investigations, and the use of incentives for case finding. The strategy also emphasises improved programme monitoring and supervision.

To assess the efficacy of PEP, a randomised, placebo-controlled trial with SDR was conducted among household, neighbouring and social contacts of leprosy index patients in communities in North East Thailand with high prevalence rates. The primary outcome measure was the development of clinical leprosy after 5 years. Contacts were most commonly classified as 'neighbours' (81%), followed by 'social contacts' (11%) and 'household contacts' (8%). After 5 years, the difference in case detection rate between the rifampicin and control groups was not statistically significant (relative risk 0.48 [95% CI: 0.18–1.27], $p = 0.105$), although this was similar to the difference observed in the COLEP trial. The result in the Thailand study was not statistically significant as the study was not powered to detect risk reductions of less than 50%, and as disease rates probably have been overestimated in the power calculations.

Based on these limited data, there are currently no plans for further implementation of SDR chemoprophylaxis in Thailand. However, contact tracing will be maintained for 10 years after the diagnosis of both paucibacillary (PB) and multibacillary leprosy (MB) patients.

Cambodia

The case detection rate for leprosy in Cambodia is relatively low, which led the National Leprosy Elimination programme to focus on tracing contacts of individuals who had been diagnosed with leprosy and had been successfully treated. Contact tracing was encouraged by and facilitated through a series of 'Contact Drives'. These included structured visits to households of former patients and their neighbouring contacts to provide leprosy examinations and health education. The Drives were managed by five national supervisors, overseeing 24 provincial supervisors, 77 district supervisors and 995 health centre staff. Previous contact tracing had been hindered by a lack of familiarity between health workers and patients; hence, the Drives also involved local village health support groups and village chiefs.

Health centre staff and former patients were trained to recognize the signs of leprosy prior to the Drives. Particular discretion was used for the first Drive visit to reduce concerns and minimize stigma. Even though the contact tracing approach in Cambodia differed from that used in other programmes (in that contacts were traced for patients who had been diagnosed up to ten years earlier), the yield of the Drives in detecting new patients was close to 19/1,000 screened persons (unpublished data).

The main challenge of the national programme at present is to ensure that contact tracing continues after these Drives. Long-term financing, as well as recruitment and training of future contact tracing teams, are prerequisites for a sustainable programme to reduce the burden of leprosy in Cambodia.

Key points from presentations and discussions

- Contact tracing programmes, particularly in high-risk groups, are feasible, but their success depends on several factors.
 - Contact tracing needs to be integrated into the local health services or the national leprosy programme, or combined with other disease control programmes.
 - Community stigma and its ramifications should be taken into account. Funding and support must be sustainable.
 - Healthcare workers need to follow programme guidelines and keep accurate records; financial incentives may be an effective way to maintain engagement.
- Contact tracing and PEP in different settings may offer protection rates similar to those reported in randomized clinical trials, and may provide the greatest benefit in low-endemic countries. For high-incidence pockets ('hotspots') or populations ('hotpops'), a blanket approach to PEP may be more appropriate.
- Ethical questions around informed consent, the disclosure of index patients and the language used to describe leprosy remain a real concern, and should be considered in the planning of contact tracing and PEP activities.
 - Neighbourhood contacts may accept screening without knowing the identity of the index patient; introducing a method for self-screening could provide an alternative to disclosing patients' identities.
 - Leprosy may often be described using terms such as 'allergy' or 'skin condition'; therefore, to avoid ethical issues of misinformation, it is important that healthcare workers in leprosy programmes are briefed on the use of appropriate language.

LESSONS FOR CONTACT TRACING AND PEP FROM TUBERCULOSIS AND OTHER INFECTIOUS DISEASES

Experiences of PEP in the management of other infectious diseases may be of relevance to leprosy. For example, in the management of rabies, PEP with rabies immune globulin (RIG) is a safe and effective prophylactic treatment, and is given to individuals bitten by animals with a confirmed or suspected infection. Rabies is not thought to be transmissible between

humans, so PEP would not usually be given to contacts; however – because transmission is not biologically implausible – PEP with RIG is sometimes administered to high-risk contacts such as health professionals who care for patients with rabies (justified by the severe consequences of a rabies infection).

The eradication strategy for smallpox was modified when the incidence of the disease declined, and involved a switch from ‘mass campaigns’ to ‘surveillance and containment’. This is similar to the approach currently needed for leprosy. Smallpox outbreaks were contained by close monitoring of all households within a 2-mile radius around the infected household; in contrast, leprosy is much less infectious and therefore may not require such intensive monitoring. The smallpox vaccine was highly effective if administered up to three days after exposure, and even offered some protection up to seven days after exposure; for leprosy however, the administration of PEP may be less time-critical given the long incubation period.

Treatment of latent TB infections can also be informative for leprosy; combination therapy (with isoniazid, rifampicin and, occasionally, ethambutol) is commonly used as the preventive treatment regimen for TB. Importantly, effective prophylaxis for TB requires up to 6 months of prophylactic treatment.¹³ Alternative options to SDR for leprosy chemoprophylaxis, such as different rifampicin doses or longer regimens, may therefore be worth investigating.

For TB, the diagnostic thresholds for determining infection have shifted over time: tuberculin skin tests that were considered ‘indeterminate’ in the 1970s (5–9 mm lesions) are now considered ‘positive’ for household contacts or persons who are HIV-positive. When molecular tests to diagnose leprosy become widely available, they might also affect how different clinical subtypes are categorised.

Developing and piloting PEP – and research to improve it

ALTERNATIVE REGIMENS FOR POST-EXPOSURE CHEMOPROPHYLAXIS

Several commonly held assumptions about leprosy prophylaxis may need to be revised.¹³ Bacterial loads of viable *M. leprae* in subclinical cases and in patients with PB leprosy may be markedly higher than previously thought, and the incidence of spontaneous resolution of infections in endemic leprosy ‘hotspots’ may have been overestimated.¹³ In addition, although *M. leprae* resistance to rifampicin is minimal, repeat dosing may increase the likelihood of developing resistance. Hence, there may not be a single ‘ideal’ PEP regimen for leprosy, and other options (e.g. different drugs, doses, combinations or treatment durations) should be considered;¹³ this choice should be based on bacterial biology and drug pharmacology.

Reliable laboratory assays are essential to identify and assess alternative drugs and regimens that are efficacious against *M. leprae*.¹⁴ For example, Davis and colleagues (2013) assessed the viability of *M. leprae* by measuring the expression levels of two genes (*esxA* and *hsp18*) via quantitative reverse transcription–polymerase chain reaction (RT–PCR).¹⁴ The test, which was validated using conventional assays (testing respiration and membrane integrity), measured the viability of *M. leprae* from tissue samples without the need for bacterial isolation or immediate processing; this makes the RT–PCR assay potentially applicable to *in vivo* drug testing and use in the field for assessing the viability of *M. leprae*.¹⁴ The assay was also used to test the effects of treatment with rifampicin and rifapentine (each

at 10 mg/kg for 1, 5 or 20 daily doses) in mice infected with *M. leprae*. Rifapentine significantly reduced bacterial viability after five doses, whereas rifampicin required up to 20 doses for the same efficacy. Neither drug was effective after a single dose.¹⁴

DEVELOPING NEW IMMUNOPROPHYLAXIS TOOLS

Immunoprophylaxis with BCG has been shown to be efficacious against leprosy,^{6,15} and additional vaccines are in development. The safety and efficacy of the novel leprosy vaccine, LepVax, have been demonstrated in an armadillo disease model. Animals were inoculated with *M. leprae*, and were given LepVax (n = 8), BCG (n = 6) or no vaccine (control; n = 7) 1 month later. After 9 months, the incidence of nerve damage was markedly lower in LepVax-vaccinated animals (13%) than in BCG-vaccinated animals (66%) or controls (88%).

HUMORAL-MEDIATED-IMMUNITY-BASED DIAGNOSTIC TESTS

In order to facilitate early and appropriate treatment with MDT or PEP, diagnostic tests need to detect early-stage disease, be simple to perform, and provide objective results. NDO-LID[®] (OrangeLife, Rio de Janeiro, Brazil) is a new test that has recently become available; it detects antibodies against ND-O (a mimetic of *M. leprae* phenolic glycolipid I [PGL-I]) and LID-1 (leprosy IDRI diagnostic).^{16,17} Another new test is Leprosy Detect[™] fast ELISA (InBios, Seattle, WA, USA), which is based on complementary detection of antibodies and can provide results in two hours.¹⁸ In addition, leprosy-specific T-cell assays based on whole-blood samples or skin tests are currently being developed by the Infectious Disease Research Institute (Seattle, WA, USA) and will enter evaluation in 2014.¹⁹

A recent study has also suggested that the detection of antibodies against PGL-I may identify individuals with subclinical infections who are at an increased risk of developing symptomatic leprosy. This study from Rio de Janeiro, Brazil, assessed BCG vaccination status and seropositivity for PGL-I among 2135 contacts of people with leprosy.²⁰ Individuals who tested positive for the presence of PGL-I antibodies were at a 3.2-fold (95% CI: 1.6–6.1) greater risk of developing leprosy than those who tested negative for the antibodies. Testing positive for PGL-I may therefore be a marker of infection, and seropositive individuals could be targeted for PEP.²⁰ One suitable measure to quantify infection risk may be the seroconversion rate (i.e. the proportion of contact persons who initially tested negative for PGL-I, but had a positive result in a later follow-up).

CELLULAR-MEDIATED-IMMUNITY-BASED DIAGNOSTIC TESTS TO TARGET PEP

Currently available diagnostic tests cannot distinguish people with *M. leprae* infection (i.e. those who may develop symptoms and could benefit from MDT) from contacts of patients with leprosy (i.e. those who have been exposed to *M. leprae* and are at an increased risk of infection, and could benefit from PEP) and individuals who have not been exposed to *M. leprae* or have cleared the mycobacteria efficiently without the occurrence of infection (i.e. those who are not infected and do not require preventive treatment). Thus, there is a clear need to develop a robust, field-friendly diagnostic assay to enable health workers to target treatment appropriately.

The leprosy disease spectrum is determined by both cellular-mediated immunity (CMI) and humoral-mediated immunity (HMI) against *M. leprae*. Hence, tests that should

simultaneously detect biomarkers for both types of immune response.²¹ A field-friendly version of such a test (based on up-converting phosphor [UCP] lateral flow strips with a long shelf-life), developed by Leiden University, is currently being evaluated at multiple field sites.²² The assay is suitable for multiplex detection of different cytokines, and can be combined with antibody-detection tests (i.e. antibodies against PGL-I) to detect both CMI and HMI responses to *M. leprae*.²² Moreover, point-of-care test formats with short test-to-result times are also in development.

Geluk and colleagues recently described a novel CMI-based whole-blood assay that measures interferon- γ (IFN- γ and/or IP-10) levels in response to *M. leprae*-unique antigens (including ML2478). The assay can accurately detect the extent of *M. leprae* exposure along a proximity gradient in healthy individuals in areas of high or low leprosy endemicity.²³ These data suggest that measuring IFN- γ /IP-10 levels (in response to *M. leprae*-unique proteins) may be a useful tool to identify individuals who have been significantly exposed to *M. leprae*, and who are therefore at risk of infection and subsequently transmitting the disease.²³ To distinguish further between exposed (but protected) individuals and patients in highly endemic areas, an additional test could be developed based on a panel of biomarkers: IL-1 β , MCP-1 and MIP-1 β . These and other biomarkers are currently being evaluated in longitudinal studies among contacts, to assess the predictive value when testing for leprosy infection.²³ In addition, measuring IFN- γ /IP-10 levels also provides a test to assess the effect of treatment.

Key points from presentations and discussions

- PEP with SDR is efficacious in the prevention of leprosy; however, alternative regimens (including higher or multiple doses of rifampicin, different drug regimens or combination therapies) should be considered for further study.
- Treatment selection and implementation would benefit from new tests that can diagnose sub-clinical leprosy and distinguish between infected contacts and non-infected individuals
- New diagnostic tests that can simultaneously detect biomarkers specific for both CMI and HMI responses are currently under development; ideally the biomarkers with the best predictive value for developing leprosy disease should be selected for inclusion in a field friendly test.
- It might be useful to test contact persons on their PGL-I status (given the increased risk to develop leprosy in positive persons), and direct PEP towards the PGL-I positives.

THE MALTALEP TRIAL: CHEMOPROPHYLAXIS AND BCG

The ongoing MALTALEP trial is designed to assess the effectiveness of SDR combined with BCG in contacts of patients newly diagnosed with leprosy. This 3-year trial aims to randomize a total of approximately 20,000 contacts from 1300 index patients with leprosy (about 15 contacts per index patient) to either BCG alone or BCG + SDR (10,000 contacts per study arm); the primary outcome is the number of new leprosy diagnoses after 1 or 2 years. BCG will be given 6 weeks after the index patient has started MDT; SDR will be given 8 weeks after BCG to those in the BCG + SDR arm.

It is hypothesized that the effects of treatment with BCG and SDR may be additive, and that the combined effect may be longer-lasting than SDR alone. Recruitment for this trial will finish in 2014, and patients will be followed up for 2 years.⁷

SURVEILLANCE AND RESPONSE SYSTEMS FOR PEP

Surveillance of patient-level data is essential for measuring the success of an intervention and tailoring the response to local requirements. Potential surveillance tools include chemoprophylaxis modelling, geographical information systems, spatial modelling (to define hotspots) and electronic data recording and storage systems; the involvement of a cultural anthropologist may be necessary to ensure that the chosen methods are acceptable for the study population. Each national program should define the response procedures that will be introduced in the surveillance system; for example, this could include contact-tracing within 3 months of diagnosis of the index patient, with PEP administered onsite during the contact visit.

EpiAnywhere is a public health surveillance platform that can be used to record patient data, identify existing cases and produce reports, and provide access to manuals and training materials. It is a broader, expanded version of TBAnywhere.net (jointly developed by JBS International Inc., MD, USA, and Looking Glass Analytics, WA, USA) that was developed with funding from the Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA. The CDC also guided the implementation of a Hansen's Disease surveillance module within the EpiAnywhere platform. Advantages of such a web-based platform include adaptability for other programme needs (e.g. prophylaxis), central data storage, improved contact tracing and follow-up, ease of reporting and timely evaluation of the impact of interventions.

Key points from presentations and discussions

- Effective surveillance and response systems for leprosy are essential for contact tracing, follow-up and outcome evaluation.
- The BCG vaccine remains a key element in the leprosy elimination strategy, and additional, leprosy-specific vaccines are in development. If the new TB vaccines currently in development are to replace BCG (which seems unlikely at the moment), then it will be important that these are also evaluated for their preventive effect on leprosy.

Discussion

A large international programme of pilot projects is currently being developed by the Novartis Foundation and NLR, in collaboration with several national leprosy programmes and other partners of the International Federation of Leprosy Associations (ILEP), to assess the effect of chemoprophylaxis on the transmission of leprosy. The pilots are designed to demonstrate the feasibility, acceptability, cost-effectiveness and real-world efficacy of contact tracing and PEP as a strategy to interrupt leprosy transmission. The projects are also intended to facilitate the integration of chemoprophylaxis experiences into national programmes and guidelines, provide a toolkit for contact management and PEP, create

locally adaptable surveillance and response systems for PEP, and demonstrate the cost-effectiveness of chemoprophylaxis.

Starting in 2014, the pilot projects will be conducted in six countries (in Asia, Africa and Latin America) in regions with relatively high leprosy endemicity where contact tracing programmes and health information systems are functioning. The pilots also require upfront endorsement of and support by national health programmes and local partners in the ILEP. Epidemiological surveillance and health economics research will be designed and coordinated by the Erasmus Medical Center Rotterdam, Netherlands.

The expert panel identified a number of operational considerations for the design of new contact tracing and PEP pilot projects. Local ownership should be established from the outset by developing partnerships with local health authorities, healthcare workers, communities and patients, to guarantee long term sustainability. The use of locally appropriate definitions of contacts and the objective measuring of outcomes are also essential prerequisites for such projects.

Several recommendations were suggested to ensure the long-term sustainability of new projects. Integrating pilots into existing local health services and coupling them to other disease control programmes would allow the alignment of factors such as logistics and financial management, and minimise disruption when the pilot project transitions to a full programme. Operational simplicity, such as tracing a manageable number of contacts per index patient and choosing a realistic number of years for contact follow-up, is also important; however, specific 'targets', such as the number of contacts to be traced, should be set with care to avoid encouraging a 'target-chasing' culture among healthcare workers. Efficiency could be encouraged by considering the optimal time of the day and seasonal migration patterns for the timing of home visits for contact tracing and follow-up, and potentially by offering financial incentives to encourage patient participation, e.g. to compensate for time lost at work. The implementation of contact tracing requires clear and useable definitions of who the 'contact persons' are (e.g. 'household', 'neighbour' and 'social' contacts); however, these definitions are likely to vary by country, region and culture. Hence, local ownership is the best way to ensure the use of appropriate definitions and language.

The overall aim and outcome of the pilot projects should be the development of a toolkit of approaches for contact management and chemoprophylaxis that can be adapted for local and global use.

Other recommendations for the pilots are to use modelling analyses to calculate targets such as the proportion of contacts to be reached for a given reduction in incidence (case detection rate), and to conduct projects across a diverse range of settings (e.g. rural versus urban; highly endemic or with pockets of high endemicity). On the other hand, new projects should also consider including self-screening opportunities possibly involving schools (based on experience with projects in Brazil), and should recognise and address ethical problems around disclosure of the index patient and stigma.

Finally, the success of the pilots needs to be evaluated through appropriate outcome measurements. Appropriate indicators are: (a) the yield of newly diagnosed patients identified by contact tracing, (b) the cost per new case identified or prevented, or (c) changes in the perception of leprosy and of leprosy-related stigma. Outcome measures need to be collected using suitable information surveillance systems, and results should first be communicated locally.

Overall, the pilots need to include proper data collection to answer the question as to whether PEP reduces the incidence of leprosy in the pilot region population.

Other remaining research questions with regard to leprosy transmission should however be addressed in randomised controlled trials:

- What is the efficacy of alternative PEP regimens?
- When should PEP be used as a blanket approach, and when should it be targeted to contacts of newly diagnosed patients? Can a prevalence/case detection rate threshold be defined, above which mass administration of SDR would be preferable?
- Do different types of contact require different PEP regimens or interventions (e.g. higher or repeated dosing of rifampicin, or longer-acting rifapentine for prevention in close contacts)?
- Will immunoprophylaxis work synergistically with SDR in PEP (currently investigated in the MALTALEP trial)?

Other operational research priorities and questions that can be answered in the pilots are:

- What would be an effective follow-up and management plan after PEP?
- What are the limitations in sensitivity and specificity of seroconversion tests based on antigens such as PGL-I and LID-1? What is the ability of these tests to detect infection and predict the emergence of clinical symptoms?
- Do index patients, contacts and other stakeholders accept PEP with SDR, particularly in areas with a high level of leprosy-related stigma?
- Does the introduction of PEP affect the perception of leprosy in the community?

And on the other hand, it is essential that longitudinal studies further evaluate whether:

- Specific biomarkers can be identified that differentiate infected (asymptomatic) contacts from non-infected (but exposed) contacts?
- Biomarkers can be identified that predict progression to disease in infected individuals?
- And based on such biomarkers, whether robust and reliable field-friendly diagnostic tests can be developed to facilitate early diagnosis and appropriate targeting of treatment?

Developing new diagnostic tests and rigorous research programmes will assist national programmes in carrying out their tasks more effectively, and thus reduce the global burden of leprosy.

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