Guidelines for the Diagnosis, Treatment and Prevention of Leprosy

World Health Organization

Guidelines for the diagnosis, treatment and prevention of leprosy

World Health Organization

Guidelines for the diagnosis, treatment and prevention of leprosy

ISBN: 978 92 9022 638 3

Suggested citation. Guidelines for the diagnosis, treatment and prevention of leprosy. New Delhi: World Health Organization, Regional Office for South-East Asia; 2017. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Sales, rights and licensing. To purchase WHO publications, see http://apps.who.int/bookorders. To submit requests for commercial use and queries on rights and licensing, see http://www.who.int/about/licensing.

Cover photos: Mr Masanori Matsuoka

Contents

Abbreviations and acronyms

BCG	bacille Calmette-Guérin
CI	confidence interval
COLEP	prospective sero-epidemiological study on contact transmission and chemoprophylaxis in leprosy
CRE	Office of Compliance, Risk Management and Ethics
DNA	deoxyribonucleic acid
DOI	Declaration of Interest
ELISA	enzyme-linked immunosorbent assay
EPI	Expanded Programme on Immunization
ERG	External Review Group
GDG	Guidelines Development Group
GLP	Global Leprosy Programme
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
GRC	Guidelines Review Committee
HIV	human immunodeficiency virus
IDRI	Infectious Disease Research Institute
ILEP	International Federation of Anti-Leprosy Associations
LPEP	Leprosy Post-Exposure Prophylaxis
LRI	Leprosy Research Initiative
MB	multibacillary
MDA	mass drug administration
MDT	multidrug therapy
NDO-LID	natural disaccharide octyl-leprosy IDRI diagnostic
NGO	nongovernmental organization
NTD	neglected tropical disease
PB	paucibacillary

PCR	polymerase chain reaction
PICO	population, intervention, comparator, outcome
PPV	positive predictive value
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCT	randomized controlled trial
RR	relative risk
RRR	relative risk reduction
SAGE	Strategic Advisory Group of Experts on Immunization
SDR	single-dose rifampicin
SOE	sum of errors
TB	tuberculosis
UMDT	uniform MDT
UN	United Nations
US$	United States dollar
WHO	World Health Organization

Acknowledgements

The development of these guidelines was coordinated by Laura Gillini, Medical Officer, Global Leprosy Programme (GLP) and supervised by Erwin Cooreman, GLP Team Leader.

The GLP would like to thank members of the Guidelines Development Group (GDG), members of the External Review Group (ERG), and World Health Organization (WHO) staff who contributed to the development of these guidelines as part of the Steering Group or as peer reviewers. The GLP appreciates the input provided by the national leprosy programmes of the following countries: Colombia, the Democratic Republic of the Congo, India, Morocco and the Philippines. The GLP is particularly grateful to the persons affected by leprosy who participated in focus group discussions in Colombia, Ghana, India and Nepal on diagnosis, treatment and contact screening.

The guidelines for the diagnosis, treatment and prevention of leprosy were developed with full funding support from The Nippon Foundation.

Contributors

These guidelines were a collaborative effort between the GDG, a methodologist, a systematic reviewer, ERG and the WHO Steering Group. The GDG and ERG included persons affected by leprosy. All contributors completed a WHO Declaration of Interest (DOI) form (summarized in Annex 1).

Guidelines Development Group

The GDG consisted of the following persons: Professor Jacques Grosset (Chair), Emeritus Professor of Medicine, Johns Hopkins University, he lives in France; Professor Marcos Boulos, University of Sao Paulo, Brazil; Professor Emmanuelle Cambau, University Paris Diderot, France; Professor Sang Nae Cho, Yonsei University College of Medicine, Republic of Korea; Professor Nilanthi R. da Silva, University of Kelaniya, Sri Lanka; Dr Sara Irène Eyangoh, Centre Pasteur du Cameroun, Cameroon; Dr Deanna Hagge, Anandabad Hospital, Nepal; Dr Marie Jocelyn Te, Regional Leprosy Control and Prevention Program, Ministry of Health, the Philippines; Dr Willem (Pim) Kuipers, International Federation of Anti-Leprosy Associations (ILEP), he lives in Australia; Dr Anil Kumar, National Leprosy Eradication Programme, Ministry of Health and Family Welfare, India; Professor Bhushan Kumar, Shalby Multispecialty Hospital, India; Professor Mourad Mokni, University of Tunis, Tunisia; Dr Indranil Mukhopadhyay, Public Health Foundation of India, India; Mr Vagavathali Narsappa, Association of People Affected by Leprosy, India; Professor Travis Porco, The Francis I. Proctor Foundation, Department of Epidemiology and Biostatistics and Department of Ophthalmology, University of California, United States of America; Dr Paul Saunderson, American Leprosy Missions, Chair ILEP Technical Commission, he lives in Norway; Dr Vineeta Shanker, Sasakawa-India Leprosy Foundation, India; Dr Cita Rosita Sigit Prakoeswa, Faculty of Medicine, Universitas Airlangga-Dr Soetomo Teaching Hospital, Indonesia; Professor W. Cairns Smith, Emeritus Professor of Epidemiology, School of Medicine and Dentistry, Aberdeen University, United Kingdom; Professor Marcos Virmond, Instituto Lauro de Souza Lima, Brazil; Dr Rie Yotsu, National Suruga Sanatorium, Japan.

Methodologist

The methodologist was Professor Roger Chou, Department of Medical Informatics and Clinical Epidemiology and Department of Medicine, Oregon Health and Science University, United States of America.

Systematic reviewer

The systematic reviews of evidence for these guidelines were conducted by Dr Amudha Poobalan, Institute of Applied Health Sciences, School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, United Kingdom.

External Review Group

The ERG consisted of the following persons:

Dr Shengelia Bakhuti, Novartis Foundation, Switzerland; Dr Marivic F. Balagon, Leonard Wood Memorial Center for Tuberculosis and Leprosy Research, the Philippines; Dr Wim H. van Brakel, Netherlands Leprosy Relief, the Netherlands; Mrs Paula Soares Brandao, Panel of Women and Men Affected by Leprosy (ILEP), she lives in Brazil; Dr Hughes Davis, Novartis Global Drug Development, Switzerland; Mr Mathias Duck, Panel of Women and Men Affected by Leprosy (ILEP), he lives in Paraguay; Professor N.K. Ganguly, National Institute of Immunology, India; Professor Mohan D. Gupte, Chair Technical Advisory Group on Leprosy, India; Professor Eliane Ignotti, Mato Grosso State University, Brazil; Dr Herman-Joseph Kawuma, German Tuberculosis and Leprosy Relief Association, Uganda; Dr Ibtissam Khoudri, National Leprosy Programme, Ministry of Health, Morocco; Mrs Rachna Kumari, Panel of Women and Men Affected by Leprosy (ILEP), she lives in India; Dr Jean Norbert Mputu Luengu, National Leprosy Programme, Ministry of Health, Democratic Republic of the Congo; Professor Takahiro Nanri, Sasakawa Memorial Health Foundation, Japan; Mr Kofi Nyarko, Panel of Women and Men Affected by Leprosy (ILEP), he lives in Ghana; Professor Jan Hendrik Richardus, Erasmus Medical Center, Rotterdam University, the Netherlands; Mr Amar Bahadur Timalsina, Panel of Women and Men Affected by Leprosy (ILEP), he lives in Nepal; Dr Nestor Vera, National Leprosy Programme, Ministry of Health and Social Protection, Colombia; Professor Mitchell G. Weiss, Swiss Tropical and Public Health Institute and University of Basel, Switzerland.

WHO Steering Group

The WHO Steering Group included members with expertise in the areas of intellectual property, evaluation of essential medicines, management of neglected tropical diseases (NTDs), and gender, equity, and human rights. The members were:

Dr Erwin Cooreman, Chair, GLP, WHO Regional Office for South-East Asia

Dr Laura Gillini, GLP, WHO Regional Office for South-East Asia

Dr VRR Pemmaraju, GLP, WHO Regional Office for South-East Asia

Dr Manisha Shridar, Public Health, Innovation and Intellectual Property, WHO Regional Office for South-East Asia

Dr Klara Tisocki, Policy, Access and Use, WHO Regional Office for South-East Asia

Dr Md. Jamsheed Ahmed, Neglected Tropical Diseases, WHO Regional Office for South-East Asia

Dr Davison Munodawafa, Human Rights and Gender, WHO Regional Office for Africa

Dr Eduardo Calderon Pontaza, Human Rights, Office of Legal Counsel, Pan-American Health Organization/WHO Regional Office for the Americas

Mr Dimitry Esin, Neglected Tropical Diseases, WHO headquarters

Dr Linh Nguyen-Nhat, Global Tuberculosis Programme, WHO headquarters

Executive summary

Background

Leprosy is a disease that predominantly affects the skin and peripheral nerves, resulting in neuropathy and associated long-term consequences, including deformities and disabilities. The disease is associated with stigma, especially when deformities are present. Despite the elimination of leprosy as a public health problem (defined as achieving a point prevalence of below 1 per 10 000 population) globally in 2000 and at a national level in most countries by 2005, leprosy cases continue to occur. Over 200 000 new leprosy cases were reported in 2016. Therefore, guidance on early diagnosis and treatment of leprosy is essential for reducing the burden of this disease.

Leprosy is classified as paucibacillary (PB) or multibacillary (MB), based on the number of skin lesions, presence of nerve involvement and identification of bacilli on slit-skin smear. The standard treatment for leprosy involves the use of multiple (two or three) drugs; the duration of treatment, dose and number of antibiotics depend on the type of leprosy (PB or MB) and age of the patient (adult or child). Strategies to prevent leprosy include vaccination or use of prophylactic antibiotics among persons with exposure.

Rationale and methods

The purpose of these WHO guidelines is to provide evidence-based recommendations on the diagnosis, treatment and prevention of leprosy, utilizing WHO guideline development methods based on the GRADE[1] process. Previous leprosy guidance documents were developed through Expert Committee meeting reports and/or through other technical documents, without a formal guideline development process. For prevention of leprosy, these guidelines focus on the use of antibiotics (chemoprophylaxis). Although vaccinations could prevent leprosy, WHO regulations require that the Strategic Advisory Group of Experts on Immunization (SAGE) formulate all vaccination (immunoprophylaxis) recommendations. Therefore, the Guidelines Development Group (GDG) reviewed evidence on vaccinations but did not formulate recommendations; rather, findings on vaccinations were shared with the SAGE *bacille Calmette-Guérin* (BCG) working group to help inform its recommendations.

The primary audience for these WHO guidelines includes persons involved in leprosy policy formulation and clinicians who manage leprosy, particularly in low- and middle-income countries.

1 GRADE: Grading of Recommendations Assessment, Development and Evaluation

These guidelines were developed in accordance with procedures established by the WHO Guidelines Review Committee (GRC). The scope of the guidelines and associated systematic reviews was determined in October 2016. Systematic reviews were commissioned to address the key questions developed in the scoping process on diagnosis, treatment and prevention of leprosy. Recommendations were formulated by a regionally representative and multidisciplinary GDG at a meeting held in May 2017 and in a subsequent meeting in October 2017 held upon availability of additional evidence. The GRADE approach was used to formulate and categorize the strength of recommendations (strong or conditional), and was adapted for questions related to diagnostic tests. GRADE includes an assessment of the quality of evidence (high, moderate, low or very low), consideration of the overall balance of benefits to harms (at individual and population levels), patient/health worker values and preferences, resource use, effects on equity, cost–effectiveness and consideration of feasibility and effectiveness across a variety of settings, including resource-limited settings and those in which access to laboratory infrastructure and specialized tests is limited. There was no evidence on benefits and harms of treatment for drug-resistant leprosy; therefore, recommendations for this topic were based on expert opinion. The process also identified other key research gaps to help inform the future research agenda for leprosy. These guidelines do not address the programmatic aspects of leprosy management, which is covered by the WHO *Global Leprosy Strategy 2016–2020 "Accelerating towards a leprosy-free world"* and its accompanying *Operational Manual* and *Monitoring and Evaluation Guide*.

Summary of recommendations

Table 1 summarizes the recommendations on diagnosis, treatment and prevention of leprosy with antibiotics (chemoprophylaxis).

Diagnosis of leprosy

The guidelines recommend no additional tests in addition to standard methods for diagnosis of leprosy: the diagnosis of leprosy remains based on the presence of at least one of three cardinal signs: (i) definite loss of sensation in a pale (hypopigmented) or reddish skin patch; (ii) thickened or enlarged peripheral nerve with loss of sensation and/or weakness of the muscles supplied by that nerve; or (iii) presence of acid-fast bacilli in a slit-skin smear. The clinical diagnosis of early leprosy and PB leprosy can be a challenge. Therefore, a number of serological and other laboratory assays have been developed to supplement clinical diagnostic methods. However, enzyme-linked immunosorbent assays (ELISA) and lateral flow assays are associated with low diagnostic accuracy for PB leprosy. Although some polymerase chain reaction (PCR)-based assays are associated with higher diagnostic accuracy, they lack standardization, are not commercially available, and would be difficult to perform in most primary health-care settings.

The guidelines also do not recommend any test for the diagnosis of leprosy in asymptomatic contacts. The predictive accuracy of diagnostic tests for identifying persons who will develop leprosy is low, with poor positive predictive values.

Treatment of leprosy

The guidelines recommend a 3-drug regimen of rifampicin, dapsone and clofazimine for all leprosy patients, with a duration of treatment of 6 months for PB leprosy and 12 months for MB leprosy. This represents a change from the current standard treatment for PB leprosy, which is rifampicin and dapsone for 6 months, due to some evidence indicating better clinical outcomes with a 3-drug, 6-month regimen over a 2-drug, 6-month regimen. A potential advantage of using the same three drugs for PB and MB leprosy is simplification of treatment (i.e. the same blister pack could be used for treating both types of leprosy) and reduced impact of misclassification of MB leprosy as PB leprosy, since all patients will receive a 3-drug regimen. For MB leprosy, the current standard treatment is a 3-drug regimen for 12 months. Evidence on the potential benefits and harms of a shorter (6-month) 3-drug regimen was limited and inconclusive, with a potential increase in the risk of relapse. Therefore, the GDG determined that there was not enough evidence of equivalent outcomes to support a recommendation to shorten the treatment duration for MB leprosy.

For rifampicin-resistant leprosy, the guidelines recommend treatment with at least two second-line drugs (clarithromycin, minocycline or a quinolone) plus clofazimine daily for 6 months, followed by clofazimine plus one of these drugs for an additional 18 months. When ofloxacin resistance is also present, a fluoroquinolone should not be used as part of second-line treatment. The regimen of choice in such cases shall consist of 6 months of clarithromycin, minocycline and clofazimine followed by clarithromycin or minocycline plus clofazimine for an additional 18 months.

Resistance has been reported from several countries, although the number of patients is small. Evidence on the potential benefits and harms of alternative regimens for drug-resistant leprosy was not available. Therefore, recommendations for second-line regimens are based on expert opinion and the known activity of alternative drugs, including the likelihood of cross-resistance.

Prevention of leprosy through chemoprophylaxis

The guidelines recommend the use of single-dose rifampicin (SDR) as preventive treatment for adult and child (2 years of age and above) contacts of leprosy patients, after excluding leprosy and tuberculosis (TB) disease and in the absence of other contraindications. The COLEP[2] randomized controlled trial (RCT) found SDR in leprosy contacts associated with a 57% reduction in the risk of leprosy after 2 years and 30% after 5–6 years; SDR also appears highly cost–effective, with an incremental cost–effectiveness ratio of US$ 158 per additional prevented leprosy case.

2 COLEP: prospective sero-epidemiological study on contact transmission and chemoprophylaxis in leprosy

The ability of programmes to adequately identify and manage contacts of persons with leprosy is a prerequisite for successful implementation of the recommendation. Because leprosy is highly stigmatized, caution must be exercised when implementing SDR, particularly for contacts outside the patient's family. Programmes must respect the wish of patients to disclose or not disclose their diagnosis. When patients do not authorize disclosure, the GDG does not recommend identification or screening of contacts, which is a prerequisite for prescribing preventive treatment. In hyperendemic settings, a blanket approach (i.e. treatment of all community members without identifying contacts) might be more feasible and reduce potential harms related to disclosure of a leprosy diagnosis.

Table 1. Recommendations on diagnosis, treatment and chemoprophylaxis of leprosy (summary)

Area of the recommendation	Recommendation	Strength	Quality of evidence
Diagnosis			
Diagnosis of leprosy	The diagnosis of leprosy may be based on clinical examination, with or without slit-skin smears or pathological examination of biopsies.	Conditional	Low
Diagnosis of leprosy infection	There is currently no test recommended to diagnose leprosy infection (latent leprosy) among asymptomatic contacts.	Conditional	Low
Treatment			
Treatment of leprosy	The same 3-drug regimen of rifampicin, dapsone and clofazimine may be used for all leprosy patients, with a duration of treatment of 6 months for PB leprosy and of 12 months for MB leprosy.	Conditional	Low

Area of the recommendation	Recommendation	Strength	Quality of evidence
Treatment of drug-resistant leprosy	Leprosy patients with rifampicin resistance may be treated using at least two of the following second-line drugs: clarithromycin, minocycline or a quinolone (ofloxacin, levofloxacin or moxifloxacin), plus clofazimine daily for 6 months, followed by clofazimine plus one of the second-line drugs daily for an additional 18 months. Leprosy patients with resistance to both rifampicin and ofloxacin may be treated with the following drugs: clarithromycin, minocycline and clofazimine for 6 months followed by clarithromycin or minocycline plus clofazimine for an additional 18 months.	Conditional	No evidence retrieved (based on expert opinion)
Prevent ion			
Chemoprophylaxis for contacts of patients with leprosy	Single-dose rifampicin (SDR) may be used as leprosy preventive treatment for contacts of leprosy patients (adults and children aged 2 years and above), after excluding leprosy and tuberculosis (TB) disease, and in the absence of other contraindications. This intervention shall be implemented only by programmes that can ensure: (i) adequate management of contacts, and (ii) consent of the index case to disclose his/her disease.	Conditional	Moderate

Part I: Guideline development process

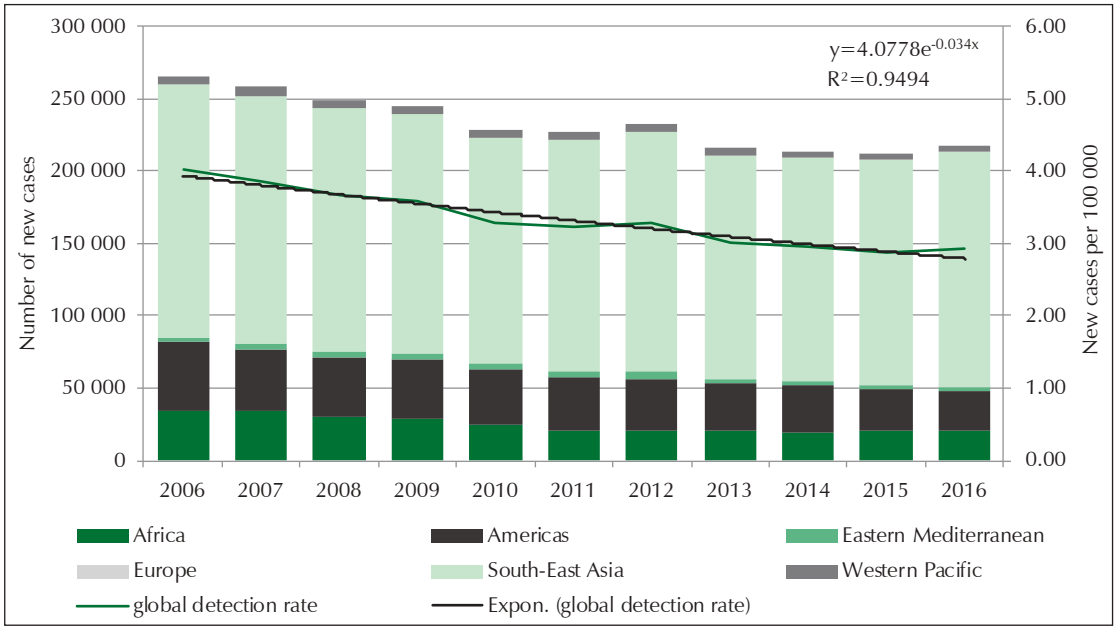
1. Introduction

Leprosy is a disease that predominantly affects the skin and peripheral nerves, resulting in neuropathy and associated long-term consequences, including deformities and disability. While in previous times it was common in temperate climates (e.g. Europe), today leprosy is mainly confined to tropical and subtropical regions. The disease is associated with stigma, especially when deformities are present. Transmission of leprosy is poorly understood, although it is thought to be through inhalation of droplets containing the causative agent, *Mycobacterium leprae* (*M. leprae*). However, transmission via skin contact or other means cannot be entirely excluded. Leprosy has a reservoir in armadillos and a few other animals.

Up to 95% of patients exposed to *M. leprae* will not develop the disease, suggesting that host immunity plays an important role in disease progression and control. The incubation time is variable, ranging from 2 to 20 years, or longer.

The fight against leprosy has achieved considerable success, as evidenced by the elimination of leprosy as a public health problem (defined as a point prevalence below 1 per 10 000 population) in 2000 globally and at the national level in most countries by 2005. However, the number of new patients diagnosed with leprosy is still significant, at more than 200 000 in 2016 *(1)*. The new case detection rate of the disease (a proxy for incidence rate) is only slowly declining (Fig. 1).

Fig. 1 . Trend in case detection and case detection rate, by WHO Region, 2006–2016



Leprosy is diagnosed by finding at least one of the following cardinal signs:

(1) definite loss of sensation in a pale (hypopigmented) or reddish skin patch;

(2) thickened or enlarged peripheral nerve, with loss of sensation and/or weakness of the muscles supplied by that nerve;

(3) presence of acid-fast bacilli in a slit-skin smear.

Leprosy is a highly variable disease, affecting different people in different ways, according to their immune response. Those at one end of the spectrum, with a high level of immunity, harbour a low number of bacilli and are referred to as patients with PB leprosy. Those with many bacilli in the body are referred to as patients with MB leprosy. In 2016, WHO launched the Global Leprosy Strategy 2016–2020 "Accelerating towards a leprosy-free world" *(2)* and in 2017, WHO revised the case definitions of PB and MB leprosy, through the release of a Monitoring and Evaluation Guide to the Global Strategy *(3)*, as follows:

Paucibacillary (PB) case: a case of leprosy with 1 to 5 skin lesions, without demonstrated presence of bacilli in a skin smear;

Multibacillary (MB) case: a case of leprosy with more than five skin lesions; or with nerve involvement (pure neuritis, or any number of skin lesions and neuritis); or with the demonstrated presence of bacilli in a slit-skin smear, irrespective of the number of skin lesions.

Early diagnosis and complete treatment with multidrug therapy (MDT) remain the key strategies for reducing the disease burden of leprosy. In addition, BCG vaccine is an effective tool for prevention of leprosy. Standard MDT regimens for PB (two drugs) and MB (three drugs) leprosy were introduced in 1982, with a duration of treatment of 6 months for PB leprosy and from initially minimum 24 months and in 1998 reduced to 12 months for MB leprosy upon a recommendation by the WHO Expert Committee *(4)*. MDT is provided in blister packs, each containing 4 weeks' treatment. Specific blister packs are available for MB and PB leprosy, with different doses for adults and children, as shown below:

The standard adult treatment regimen for MB leprosy is:

Rifampicin: 600 mg once a month

Clofazimine: 300 mg once a month, and 50 mg daily

Dapsone: 100 mg daily

Duration: 12 months (12 blister packs of 28 days each)

The standard adult treatment regimen for PB leprosy is:

Rifampicin: 600 mg once a month

Dapsone: 100 mg daily

Duration: 6 months (6 blister packs of 28 days each)

Standard child (ages 10–14 years) treatment regimen for MB leprosy is:

Rifampicin: 450 mg once a month

Clofazimine: 150 mg once a month, and 50 mg every other day

Dapsone: 50 mg daily

Duration: 12 months (12 blister packs of 28 days each)

The standard child (ages 10–14 years) treatment regimen for PB leprosy is:

Rifampicin: 450 mg once a month

Dapsone: 50 mg daily

Duration: 6 months (6 blister packs of 28 days each)

MDT is provided free-of-charge globally through an agreement between a pharmaceutical company and WHO. WHO manages distribution of MDT to countries in coordination with national leprosy programmes.

To date, no WHO recommendations on preventive strategies have been issued, though research on different antibiotics and combinations of antibiotics have been carried out since the 1990s.

2. Rationale

A WHO leprosy guideline using current WHO methods for guideline development is needed following demands from Member States for proper guidance in specific programme areas. Previous leprosy WHO guidance documents on clinical and public health aspects of leprosy were developed through expert committees and disseminated as committee meeting reports and/or other technical documents, without using a formal guideline development process (i.e. systematic evidence review or application of GRADE methods). The last WHO guidance on leprosy was issued in 2010 *(5)* and the one previous to that was issued in 1998 *(4)*.

A leprosy guideline is also needed to incorporate new evidence and address areas of clinical uncertainty in the diagnosis, treatment and prevention of leprosy. Diagnosis of early leprosy, particularly PB leprosy, remains a challenge, and a diagnostic test to detect early leprosy could be a key tool for preventing transmission, initiating early treatment, and preventing disabilities due to leprosy *(6)*. Furthermore, although prevention of leprosy is preferable to treating clinical disease, prior WHO guidance does not address prevention. In the absence of WHO evidence-based guidelines, some countries have issued their own policies on prevention *(7)*. Drug-resistant leprosy has been identified in several countries *(10,11)*, but there is no recent WHO guidance on treatment of drug-resistant leprosy. Surveillance guidelines for monitoring drug resistance in leprosy were issued by WHO in 2009 *(8)* with an updated guide published in October 2017 *(9)*. Therefore, the guidelines need to address treatment for leprosy, including use of standard MDT, with different regimens

for PB and MB leprosy, versus alternatives such as uniform MDT (UMDT), in which the same 3-drug 6-month regimen is used for both PB and MB leprosy.

3. Target audience

The objective of these guidelines is to provide policy-makers in ministries of health and medical staff working in low- and middle-income countries with recommendations on current tools to diagnose leprosy, on drug combinations for leprosy treatment and on preventive chemotherapy. These guidelines are also intended to assist officials as they develop national leprosy plans and guidelines. In addition, the guidelines will assist persons working in nongovernmental organizations (NGOs) that provide leprosy services to define relevant elements of the services they offer. The guidelines are intended to be helpful to clinicians who treat leprosy patients, and to researchers by highlighting gaps in research. The guidelines may be useful for donors to identify priorities for future funding.

4. Goals and objectives

The overall goal of these guidelines is to provide guidance and evidence-based recommendations for the diagnosis, treatment and prevention of leprosy. For prevention of leprosy, these guidelines focus on use of antibiotics (chemoprophylaxis). The primary audience for these WHO guidelines consists of persons involved in the formulation of policy for leprosy and clinicians who manage leprosy, particularly in low- and middle-income countries.

5. Methods

5.1 Contributors to guideline development

A number of groups contributed to the development of these guidelines. The roles and responsibilities of each of these groups are described below:

WHO Steering Group

The WHO Steering Group included staff members with expertise in the areas of leprosy, disease control, intellectual property, evaluation of essential medicines, management of NTD, and gender, equity, and human rights. The Steering Group contributed to the key questions, provided input to the planning process of the guidelines, and reviewed draft documents including the planning proposal, the literature reviews, and the draft guidelines.

Guidelines Development Group

The task of the GDG was to review the evidence as summarized in the systematic reviews and to develop recommendations. The GDG members consisted of persons with expertise

in diagnosis and management of leprosy (clinicians), persons affected by leprosy, civil society and non-state implementers (NGOs), and experts in the programmatic management of leprosy and in implementation. Diversity was sought with regard to gender, geographical representation, and intellectual perspectives. Given the disproportionate burden of the disease in the WHO South-East Asia Region, the Secretariat ensured representation from this Region in the GDG and ERG. The GDG met twice to develop these guidelines, once in New Delhi, India on 30–31 May 2017 and once via teleconference on 27 October 2017. The purpose of the second meeting was to review additional evidence published in August 2017 on treatment of leprosy. Recommendations were developed following discussion and consensus was sought on all recommendations. All recommendations were unanimous.

Other external contributors

Systematic review team

The WHO Secretariat commissioned systematic reviews on the diagnosis, treatment and prevention of leprosy. The reviews team was led by Dr Amudha Poobalan from the Institute of Applied Health Sciences, Aberdeen University, United Kingdom.

External Review Group

The ERG was composed of individuals with relevant expertise in leprosy, including disease/health programme implementation. The role of ERG was to identify any errors or missing data, to comment on clarity, to highlight specific issues and implications for implementation but not to modify the recommendations agreed by the GDG. Members of the ERG were identified after the GDG meeting in May 2017. The Secretariat ensured regional and gender balance and representation of different areas of expertise (clinical, public health, social sciences). A Declaration of Interest form was collected from all ERG members. The ERG included persons from the ILEP Panel of Women and Men Affected by Leprosy. This panel is composed of five affected persons from different countries (Brazil, Ghana, India, Nepal and Paraguay). Reviewers were required to disclose conflicts of interest. Because reviewers were not involved in the formulation of recommendations, presence of conflicts did not disqualify them.

Guidelines methodologist

The methodologist oversaw the entire process of collection and grading of evidence and facilitated the discussions during the GDG meetings, acting as vice-chair. The methodologist for these guidelines was Professor Roger Chou, Department of Medical Informatics and Clinical Epidemiology and Department of Medicine, Oregon Health and Science University, United States of America.

External partners

The key partner organizations involved in the review and dissemination of the guidelines document were:

- ILEP and its members (14 international NGOs working in the field of leprosy);
- The Nippon Foundation;
- Sasakawa Memorial Health Foundation (also an ILEP member).

The Nippon Foundation and the Sasakawa Memorial Health Foundation have been major donors to GLP for many years. Three of their staff attended the GDG meetings as observers. As observers they were not involved in the formulation of the recommendations.

5.2 Management of conflicts of interest

Management of conflicts of interest was a key task throughout the guideline development process. Before their appointment to the GDG or ERG, all potential members submitted a Declaration of Interest form. The GLP Team Leader, along with the Office of Compliance, Risk Management and Ethics (CRE) in WHO headquarters, reviewed the declarations and sought clarifications when necessary. The declarations were also submitted by the contractor for the literature review and the methodologist. All potential conflicts were assessed to determine whether any of several conflicts were warranted: exclusion from the panel; exclusion from one or more topic areas; inclusion in all of the evidence review sessions, but exclusion from final voting on recommendations; or no action required. Conflicts of interest were also reviewed at the beginning of the two GDG meetings and new disclosures assessed using the same process. In accordance with WHO policies, the Secretariat posted the names and biographies of all GDG members one month before the GDG meeting on WHO websites. No individual was determined to have a financial or non-financial conflict of interest that required exclusion from participation in any of the topics discussed. To ensure transparency, the details of each member's association with commercial organizations (with or without financial interests) within the last year, as well as potential intellectual conflicts, were shared with other members of the group, and the GDG members confirmed their disclosures. A summary of conflicts of interests declared by the ERG and GDG members and how conflicts were addressed is given in Annex 1.

In accordance with the WHO policies, the Secretariat posted on WHO websites the names and biographies of all GDG members 1 month before the first GDG meeting. Neither comments nor observations were received.

6. Key questions

The Steering Group developed the key questions used to guide the systematic review. The key questions were formulated using the PICO (Population, Intervention, Comparator and Outcomes) format. The questions addressed by the systematic review were as follows:

6.1. Questions on leprosy diagnosis

Question 1a: Is there a diagnostic test for leprosy disease (PB and/or MB) that has sufficient sensitivity and specificity and whose use is feasible under programmatic conditions?

Population	Intervention	Comparator	Outcomes
Adults and children with suspected leprosy and leprosy patients (PB and MB) diagnosed clinically	• Tests that detect *M. leprae* nucleic acids (PCR), antigens or other components • Tests that detect host biomarkers such as antibodies (i.e. PGL-1 or NDO-LID) or chemokines and cytokines (i.e. IP-10, IL-10) or that detect antibodies together with chemokines and cytokines • Tests that detect "effects of the disease" such as nerve enlargement by ultrasound	Diagnosis of leprosy on the basis of having one or more of the following: • definite loss of sensation in a hypopigmented or reddish skin patch; • thickened or enlarged peripheral nerve, with loss of sensation and/or weakness of the muscles supplied by that nerve; • presence of acid-fast bacilli in a slit-skin smear or in a skin biopsy • histopathological diagnosis (skin/nerve-biopsy)	• sensitivity • specificity • predictive values

Question 1b: Is there a diagnostic test that has sufficient sensitivity and specificity to diagnose M. leprae infection (latent leprosy) among contacts and whose use is feasible under programmatic conditions?

Population	Intervention	Comparator	Outcomes
Contacts of patients with leprosy: • contacts of patients with PB leprosy • contacts of patients with MB leprosy • household contacts (of PB and MB) • social contacts (of PB and MB) • neighbours of patients with leprosy (PB and MB)	• Tests that detect host biomarkers such as antibodies (i.e. PGL-1 or NDO-LID) or chemokines and cytokines (i.e. IP-10, IL-10) or that detect antibodies together with chemokines and cytokines	Diagnosis of leprosy based on the basis of having one or more of the following: • definite loss of sensation in a hypopigmented or reddish skin patch; • thickened or enlarged peripheral nerve, with loss of sensation and/or weakness of the muscles supplied by that nerve; • presence of acid-fast bacilli in a slit-skin smear or in tissue/biopsy • histopathological diagnosis over a biopsy	• sensitivity • specificity • predictive values • adverse effects

6.2. Questions on leprosy treatment

Question 2a: Is a single (uniform) treatment regimen for all patients with leprosy as effective and safe as the two currently recommended treatment regimens: the one for MB leprosy with a combination of three drugs for 12 months and the one for PB leprosy with a combination of two drugs for 6 months?

Population	Intervention	Comparator	Outcomes
Leprosy patients: • PB • MB	Single regimen for both PB and MB (MDT with three drugs: rifampicin, dapsone and clofazimine) for 6 months	• 6 months MDT regimen with rifampicin + dapsone for PB leprosy • 12 months MDT regimen with rifampicin + dapsone + clofazimine for MB leprosy	• Cure (treatment completion, clinical improvement) • Disease relapse • Drug adverse events • Cost–effectiveness

Question 2b: Which treatment regimen has better effectiveness and safety for leprosy patients detected with resistance to rifampicin, with or without associated resistance to dapsone or ofloxacin?

Population	Intervention	Comparator	Outcomes
Leprosy patients infected with strains showing DNA mutations associated with drug resistance to rifampicin alone or in combination with resistance to dapsone and/or fluoro-quinolones	• 400 mg ofloxacin + 100 mg minocycline + 50 mg clofazimine, daily for 6 months; followed by 400 mg ofloxacin daily • 100 mg minocycline + 50 mg clofazimine for at least 18 months	12 months MDT regimen (rifampicin+ dapsone + clofazimine)	• Cure (treatment completion), clinical improvement • Disease relapse • Drug adverse events • Cost–effectiveness

6.3. Questions on leprosy prevention

Question 3a: Is there an effective and safe chemoprophylaxis regimen for the prevention of leprosy among contacts of leprosy patients and for other high-risk populations that could be used under programmatic conditions?

Population	Intervention	Comparator	Outcomes
• Contacts of leprosy patients • High-risk populations (living in highly endemic areas where a case has been detected)	SDR 600 mg	No preventive treatment	• Leprosy disease • Cost–effectiveness • Drug adverse events

Question 3b: Is there an effective vaccine for the prevention of leprosy that could be used under programmatic conditions, with or without chemoprophylaxis, for contacts of leprosy patients and also among the general population?

Population	Intervention	Comparator	Outcomes
• General population • Contacts of leprosy patients	• BCG at birth ± SDR 600 mg for adults (10/15 mg kg for children) • BCG revaccination ± SDR 600 mg for adults (10/15 mg kg for children) • BCG + *M. leprae* vaccine • ICRC vaccine • *M. indicum pranii* vaccine • LepVax (IDRI)	• No vaccination • BCG at birth only	• Leprosy disease • Vaccine adverse events: – Serious adverse events – Mild adverse events

7. Systematic review methods

The systematic reviews were conducted by an independent reviewer commissioned by WHO. The WHO Steering Group and the methodologist provided oversight, including assessing and providing feedback on the protocol for each systematic review against the corresponding PICO question and the accompanying evidence tables, and checking data extraction.

Literature search strategy

Literature searches were conducted using terms for leprosy, diagnostic tests, antibiotic treatment and vaccinations, on the following databases: Embase, MEDLINE, and the Cochrane Central Register of Controlled Trials. For laboratory tests inclusion was limited to studies published after 1996, as laboratory techniques and processes have changed over the past 20 years and older studies were considered less relevant to current practice.

Data extraction methods

After relevant studies were identified, eligibility was confirmed by the reviewer and the GLP team. Data extraction was conducted by the reviewer and members of the Steering Group; the methodologist also checked a random sample of extracted studies. Risk of bias for each study was assessed using the Cochrane Risk of Bias tool for intervention studies or a tool designed for assessment of diagnostic accuracy studies, the QUADAS-2 tool *(16)*.

Meta-analysis

Meta-analysis was not conducted due to the small number of studies, methodological limitations in the studies, and heterogeneity across studies in populations, interventions and outcomes addressed.

Cost–effectiveness analysis

Cost–effectiveness is an important consideration for the development of leprosy guidelines. However, for most PICO questions no studies on cost–effectiveness were identified. The exception was preventive treatment, for which one published cost–effectiveness study was found and reviewed (13). Its results were taken into consideration when formulating the recommendation.

8. Assessment of the quality of the evidence

The quality/certainty of the body of evidence for each question was assessed using the GRADE method, modified for evaluation of diagnostic tests as appropriate *(14,15)*. The quality of evidence was categorized as high, moderate, low or very low (Table 2). In GRADE,

RCTs start as high quality. Although observational studies of interventions start as low quality in GRADE, for diagnostic accuracy, cross-sectional and cohort studies can provide reliable evidence *(15)*. Therefore, cross-sectional and cohort studies of diagnostic accuracy were initially categorized as high quality. The evidence was down-rated based on the presence of (i) risk of bias; (ii) inconsistency or heterogeneity; (iii) indirectness (addressing a different population than the one under consideration); or (iv) imprecision. Based on the rating of the available evidence, the quality of evidence was categorized as high, moderate, low, or very low.

Table 2. GRADE categories of the quality of evidence

Level of evidence	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the effect
Low	Further research is very likely to have an estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

9. Values, preferences and ethical considerations

Values and preferences can be an important consideration for informing clinical and public health recommendations. Therefore, searches of the published literature on values and preferences were conducted and an online survey was conducted. The survey was carried out in November 2017 with the support of the Panel of Women and Men Affected by Leprosy of ILEP. The face-to-face group discussions were conducted in persons affected by the disease, using standard questions regarding perceptions related to challenges for diagnosis, treatment and contact screening; suggestions were solicited for improvements in the provision of these services. The goal was to provide insight into the patient's perspective, identify hidden barriers or concerns with regard to diagnostic and treatment options for leprosy and receive suggestions to facilitate implementation of services in these core leprosy control areas. To ensure a diversity of viewpoints among persons affected by leprosy, surveys were conducted in four different countries (Colombia, Ghana, India and Nepal), targeted both men and women, patients with both PB and MB leprosy, and persons from different age groups. The tool used for the focus group discussion is provided in Annex 3.

A total of 70 persons affected by leprosy participated in focus group discussions. Participants included held 3 children, 36 women and 34 men. With regard to **diagnosis** of leprosy, all four groups reported stigma and lack of involvement of persons affected, and health systems issues (long distance to reach a health centre, unavailability of trained staff, non-inclusion of leprosy in doctors' and nurses' training curricula) as barriers.

With regard to **treatment,** all groups reported barriers related to the health system (availability of drugs and registers to start the treatment, short opening hours, distance of the treating centre from home). The groups from Colombia, Ghana and Nepal mentioned lack of proper counselling about the long-term nature of the treatment, as well as a lack of proper explanation of the side-effects of skin discoloration due to clofazimine as a possible cause of interruption of treatment. This was not reported by the group from India, which reported stigmatization and unfriendly care by the health-care workers as important barriers.

With regard to **preventive treatment (chemoprophylaxis)** and potential issues related to screening of contacts of leprosy patients, the groups from Ghana and Nepal reported no potential stigma-related problems; rather they suggested how to conduct it more easily through the involvement of persons with the disease and through camps, to facilitate access by the relatives of the patients. They also suggested providing health education to the general community and to community leaders, while providing chemoprophylaxis. The group from Colombia reported the problem of stigmatization and "a sense of guilt" for the patients, if the contact screening is not preceded by community education and proper counselling of patients. They also suggested a broader screening intervention to cover social contacts, not only family members, after proper counselling and provision of information about the activity. All groups suggested proper counselling of the target populations, along with ensuring the availability of treatment delivery "on the spot" right after the home screening. As an alternative, the group from Ghana suggested preventive treatment as part of mass drug administration (MDA) for lymphatic filariasis since MDA campaigns are done annually in their country through door-to-door campaigns.

In terms of safeguarding the guideline development process for a disease often associated with stigma, the Secretariat ensured that a representative from an association of persons affected by leprosy was member of the GDG, to provide insight into the potential impact of recommendations on patients. The GDG also considered possible human rights impacts. As per the UN Principles and Guidelines for the elimination of discrimination against persons affected by leprosy and their family members *(17)*, important human rights considerations such as effects on family life, employment, education and health care were considered. Two WHO staff (experts in human rights and gender) were included as part of the Steering Group; they reviewed the planning document and related PICO questions and the draft guidelines. In addition, four ERG members were persons affected by the disease (ILEP Panel) and two members were international experts in the field of stigma and discrimination related to communicable diseases (TB, HIV or NTDs, including leprosy).

10. Formulation of recommendations

The GDG, with the support of the Steering Group, formulated recommendations based on the evidence summarized in the systematic reviews on diagnostic accuracy and potential benefits and harms, and other factors, such as effects on service delivery, feasibility,

acceptability, cost–effectiveness and values and preferences of end users. The strength of each recommendation was graded as "strong" or "conditional".

The strength of a recommendation reflects the extent to which GDG was confident that the desirable effects of following a recommendation outweigh the potential undesirable effects. The strength is influenced by the following factors: the quality of the evidence, the balance of benefits and harms, values and preferences, and resource implications. Other factors that impact the strength of recommendations include effects on equity and human rights, acceptability and feasibility. A **strong** recommendation is one for which GDG was confident that the desirable effects of adhering to the recommendation outweigh the undesirable effects, there is confidence in the estimates of effect, the recommended action is acceptable to patients and promotes equity, the benefits are worth the costs, and the recommended action is feasible for implementation. A **conditional** recommendation is one for which GDG concluded that the desirable effects of adhering to the recommendation probably outweigh the undesirable effects, but the balance of benefits to harms was relatively small or there was less certainty about the conclusions. The implications of a conditional recommendation are that, although most programmes or settings would adopt the recommendation, some would not or would do so only under certain conditions. Reasons for making a conditional recommendation include the absence of high-quality evidence, imprecision in outcome estimates, uncertainty regarding patient preferences and how individuals value the outcomes, small benefits relative to harms, and benefits that may not be worth the costs (including the costs of implementing the recommendation).

The GDG discussed and agreed upon the proposed wording of the recommendations, with attention to using non-stigmatizing language. The recommendations incorporate human rights considerations as specified in the UN Principles and Guidelines for the elimination of discrimination against persons affected by leprosy and their family members, including special considerations for women, children or other vulnerable populations *(17)*.

All decisions were reached after thorough discussion of the proposed recommendations, including their strengths and, as needed, the conditions to be attached to the recommendations. Disagreements were discussed and resolved through review of the evidence and an informal consensus process facilitated by the Chair and Co-chair (methodologist) at the face-to-face meeting. Evidence-to-recommendation tables were formulated during the GDG meeting, with only minor editorial changes made subsequently (Annex 2). They were circulated to all GDG members for their endorsement and finalization. A draft of the guidelines was provided to GDG members during the consultation with the ERG and all GDG members approved the final version before submission to the GRC.

Although vaccinations could prevent leprosy, WHO regulations require that SAGE formulate all recommendations on vaccination (immunoprophylaxis). Therefore, the GDG reviewed evidence on vaccinations but did not formulate recommendations; rather, findings on vaccinations were shared with the SAGE BCG working group to help inform its recommendations.

Part II: Recommendations

1. Diagnosis

1.1 Diagnosis of leprosy disease

Recommendation

It is recommended to base the diagnosis of leprosy on the following: clinical examination, with or without slit-skin smears or pathological examination of biopsies (conditional recommendation, very low quality evidence).

Rationale

The diagnosis of leprosy in current practice is based on the presence of at least one of the three cardinal signs *(5)*: (i) definite loss of sensation in a pale (hypopigmented) or reddish skin patch; (ii) thickened or enlarged peripheral nerve with loss of sensation and/or weakness of the muscles supplied by that nerve; or (iii) presence of acid-fast bacilli in a slit-skin smear. The slit-skin smear requires technical expertise in taking the smear, fixation and staining, and reading the results *(18)*. Slit-skin smears are positive only in MB leprosy (i.e. any positive slit-skin smear is classified as MB irrespective of the number of patches and/or nerve involvement). The early clinical stages of leprosy and milder forms of leprosy (PB leprosy) are diagnostically the most challenging. The ELISA and lateral flow assays show low accuracy for PB leprosy. Although PCR-based assays using tissue specimens show higher sensitivity and specificity than ELISA and lateral flow assays, they would be difficult to perform in most field settings. PCR assays lack standardization, currently no PCR tests are commercially available, and they require technical and laboratory expertise. Although PCR-based assays using urine and blood samples are a less invasive potential alternative to skin smears and pathological examination of biopsy, studies indicate low sensitivity.

Summary of the evidence

Studies of the most commonly used ELISA and lateral flow tests show low sensitivity for PB leprosy, which is often harder to diagnose clinically than MB leprosy *(19–41)*. Based on estimated median sensitivities and specificities, negative tests are not that useful for ruling out PB leprosy and some patients with PB leprosy would be missed. Effects of missed or delayed diagnosis of PB leprosy are not known. Although some tertiary-level centres and highly specialized research centres can perform PCR to detect DNA of *M. leprae* on slit-skin smear or biopsy specimens, the tests that showed highest sensitivity and specificity *(43–49)* lack standardization and are not commercially available. In addition, studies showing higher accuracy of PCR used slit-skin smear or biopsy specimens rather than less invasive sampling techniques, e.g. blood or urine, for which sensitivity of PCR is low *(46,47)*.

Therefore, based on currently available evidence, newer ELISA, lateral flow and PCR tests do not represent a clear advantage over current standard diagnostic methods (clinical diagnosis with or without confirmatory tests such as slit-skin smear or biopsy).

No study of alternative tools for diagnosis of leprosy, such as ultrasound of the peripheral nerves, met inclusion criteria. Several publications support the use of ultrasound to diagnose leprosy-associated neuritis in persons known to have leprosy *(50–59)*.

1.2 Diagnosis of leprosy infection among asymptomatic contacts

Recommendation

There is no test that the GDG recommends to diagnose leprosy infection (latent leprosy) among asymptomatic contacts (conditional recommendation, low quality evidence).

Rationale

Evaluation of potential tests for *M. leprae* infection requires longitudinal follow-up to determine the incidence of clinical leprosy, to determine the predictive utility of the tests. Leprosy has a long incubation period (measured in years) between infection with *M. leprae* to the manifestation of signs and symptoms. It is assumed that there is a subclinical/latent infection stage after infection with *M. leprae,* which may subsequently lead to overt signs and symptoms of leprosy. A test to identify such latent infection would be useful for identifying persons who could benefit from preventive interventions. However, a systematic review on the predictive utility of tests for diagnosing latent leprosy found that many did not report long-term follow up, and among studies with some years of follow up, accuracy was poor for identifying persons who will develop leprosy *(42)*. Therefore, the GDG determined that presently available tests to identify contacts who have been infected by *M. leprae* are insufficiently accurate to recommend their use.

Summary of the evidence

In a review of seven studies on tests to detect leprosy infection among asymptomatic contacts with at least 1 year of follow up, relatively few people with positive tests go on to develop clinical leprosy, with an overall PPV of only 4% *(42)*.

2. Treatment for leprosy

2.1 Treatment regimens and duration of treatment for PB and MB leprosy

Recommendation

The GDG **recommends** the same 3-drug regimen with rifampicin, dapsone and clofazimine for all leprosy patients, with a duration of treatment of 6 months for PB leprosy and of 12 months for MB leprosy (conditional recommendation, very low-quality evidence).

Rationale

The currently recommended MDT for PB leprosy is rifampicin and dapsone for 6 months and the currently recommended MDT for MB leprosy is rifampicin, clofazimine and dapsone for 12 months. MDT is distributed in blister packs at the point of use (provided free-of-cost as a donation by a pharmaceutical company and distributed to national leprosy programmes by WHO) with specific packs for adults and children. The regimens require all patients with leprosy to be classified as either PB or MB, with further distinction between adults and children. Four different blister packs are available: PB adult, PB child, MB adult and MB child. The PICO question focused on benefits and harms of using the same 3-drug regimen with the same duration of treatment (6 months) for all leprosy patients (UMDT) compared with the currently recommended MDT regimens for PB and MB leprosy. Potential advantages of such an approach are simplification of the treatment regimen, reduced duration of treatment for patients with MB leprosy, reduced impact of misclassification of leprosy cases (persons with MB leprosy incorrectly classified as PB leprosy would receive three drugs with UMDT rather than two drugs with standard PB-MDT) and simplified logistics since only two types of blister packs of drugs (adult and child) would be required.

The GDG determined that a recommendation to use a 3-drug regimen for PB leprosy is justified, based on evidence showing potential benefits of a 3-drug over a 2-drug regimen for PB leprosy (10–14 more patients for 100 patients treated with a 3-drug regimen estimated to have a good clinical outcome after 12 months, and 26 more patients for 100 patients after 24 months); some evidence suggests a potential increase in risk of relapse in PB patients with the currently recommended 2-drug regimen. The 3-drug regimen has the potential to reduce the consequences of misclassification of MB patients as PB patients (based on lesion counts), and implementation advantages of using the same 3-drug combination for both MB and PB leprosy (Table 3). This is a conditional recommendation based on very low quality evidence, indicating that in persons with PB leprosy who are very concerned about the potential skin discoloration due to clofazimine, an alternative regimen (i.e. 2-drug therapy) could be considered. For MB leprosy, the GDG determined that there is not enough evidence of equivalent outcomes to support a recommendation to shorten the duration of treatment. Furthermore, the only available RCT found a potential increase in relapse rate with a shorter duration of treatment; the potential negative effects of a shorter duration of treatment on clinical outcomes and lack of evidence of benefits outweighed patient preferences for a shorter duration of treatment and considerations related to lower costs.

Table 3. Recommended treatment regimens

Age group	Drug	Dosage and frequency	Duration	
			MB	PB
Adult	Rifampicin	600 mg once a month	12 months	6 months
	Clofazimine	300 mg once a month and 50 mg daily		
	Dapsone	100 mg daily		
Children (10–14 years)	Rifampicin	450 mg once a month	12 months	6 months
	Clofazimine	150 mg once a month, 50 mg on alternate days		
	Dapsone	50 mg daily		
Children <10 years old or <40 kg	Rifampicin	10 mg/kg once month	12 months	6 months
	Clofazimine	100 mg once a month, 50 mg twice weekly		
	Dapsone	2 mg/kg daily		

Note: The treatment for children with body weight below 40 kg requires single formulation medications since no MDT combination blister packs are available. For children between 20 and 40 kg, it would be possible to follow the instructions of the Operational Manual, Global Leprosy Strategy 2016–2020 on how to partly use (MB-Child) blister packs for treatment (60).

Summary of the evidence

The evidence review identified a number of studies *(61–65)* of UMDT (rifampicin, clofazimine and dapsone for 6 months for both PB and MB leprosy). This regimen includes two changes from the current recommended MDT regimens; PB patients receive three drugs as opposed to two with the addition of clofazimine and MB patients receive the same regimen but the duration is reduced from 12 to 6 months. A number of controlled and several uncontrolled studies were included in the evidence review *(63,64,66–68)*.

For PB leprosy patients, there is evidence of better clinical outcomes with a 3-drug 6-month regimen compared with a 2-drug 6-month regimen *(63–68)*. The difference in likelihood of a good clinical outcome or marked improvement was 10% and 14% at 12 months and 26% at 24 months *(66–68)*. Evidence on risk of relapse of different regimens for PB leprosy was limited to an indirect analysis that found a higher relapse rate after treatment in PB patients using a shorter 2-drug regimen compared to the relapse rate in persons with MB leprosy using a longer 3-drug regimen *(69)*. Although this comparison involves persons with different types of leprosy, the relapse rate should be lower with PB than MB leprosy. Another consideration is some misclassification of persons with MB leprosy as PB leprosy is defined by lesion counts, which could lead to under-treatment with a 2-drug PB regimen. This under-treatment could be partly mitigated by the current recommendation to use a 3-drug regimen for PB leprosy. No study reported adverse events with clofazimine and compliance was similar among PB patients taking three drugs and those taking two drugs, despite concerns regarding skin discoloration with clofazimine.

For MB leprosy patients, evidence on potential benefits and harms of a shorter 3-drug 6-month regimen compared with a 3-drug 12-month regimen were limited and inconclusive *(63–65)*. Recently published results of an RCT found a 3-drug 6-month regimen associated with an increased risk of relapse (2.2% vs 0.3%, relative risk (RR) 6.3, 95% confidence interval (CI): 0.78–61), though the difference was not statistically significant and the estimate was imprecise *(65)*. The trial found no difference in the risk of leprosy reactions, rate of decrease in bacillary index or likelihood of disability progression beyond already affected limbs. A large non-randomized study reported zero relapses *(64)*. Another study found a 6-month regimen associated with a trend towards worse clinical outcomes compared with a 12-month regimen (good clinical response at 24 months 25% vs 77%, RR 0.33, 95% CI: 0.06–1.8) *(63)*. Several uncontrolled studies were included in the evidence review, but provided very limited data on relapses and clinical outcomes *(61,70,71)*. Results regarding side-effects of and compliance with a shorter MB leprosy regimen seem to be encouraging, though data were scarce.

The GDG concluded that changing to a 3-drug regimen with a duration of 6 months for PB leprosy might be associated with improved clinical outcomes and potential advantages with regard to implementation in the field. For MB leprosy, there was insufficient evidence to recommend a decrease in the duration of the current 3-drug regimen for MB leprosy from 12 to 6 months. In addition, the only available RCT found a potential association between shorter duration of treatment for MB leprosy and increased risk of relapse.

Remarks

Pharmacovigilance after the introduction of the new 3-drug regimen for PB leprosy is needed to ensure monitoring of adverse events. Treatment completion rates will have to be carefully monitored since studies supported by Netherlands Leprosy Relief (www.leprosy-information.org) indicate stigma associated with skin discoloration as a side-effect of the medications, despite the similar compliance seen with 3-drug versus 2-drug regimens *(61,65)*. In focus groups, persons affected by leprosy pointed out the need for (i) adequate health education of patients including information about side-effects such as skin discoloration and (ii) monitoring of treatment adherence.

2.2. Treatment for drug-resistant leprosy

Recommendation

The GDG **recommends** for leprosy patients with rifampicin resistance to be treated using at least two of the following second-line drugs: clarithromycin, minocycline, or a quinolone (ofloxacin, levofloxacin or moxifloxacin), plus clofazimine daily for 6 months, followed by clofazimine plus one of the second-line drugs daily for an additional 18 months.

In case of rifampicin plus ofloxacin resistance, a quinolone should not be chosen; therefore, the recommended regimen is clarithromycin, minocycline and clofazimine for

6 months followed by clarithromycin or minocycline plus clofazimine for an additional 18 months (conditional recommendation, based on expert opinion; no evidence retrieved).

Rationale

The number of leprosy patients tested for resistance globally is too small to allow for accurate estimates of drug resistance. However, several high-burden countries have reported cases of drug resistance among new and previously treated patients *(10,11)*. Five studies reported prevalence of rifampicin resistance, estimated at 1.4% in new cases and 8% in relapsed patients *(72–76)*. Cases with resistance to quinolones have also been detected. In India, the number of cases of quinolone resistance appears to equal the number of cases of dapsone resistance, highlighting the need to limit the use of quinolones to persons with clear indications. Recommendations on second-line treatments are needed to guide management of resistant leprosy. Because evidence on effectiveness of regimens to treat drug-resistant leprosy is lacking, recommendations are based on expert opinions, resistance patterns, and known activity of antibacterial alternatives.

Patients who start MDT and are found to have resistance to rifampicin alone or in association with resistance to dapsone, shall re-start a full course of second-line treatment, regardless of clinical outcomes with MDT. Recommended regimens for drug-resistant leprosy are given in Table 4:

Table 4. Recommended regimens for drug-resistant leprosy

Resistance type	Treatment	
	First 6 months (daily)	Next 18 months (daily)
Rifampicin resistance	Ofloxacin 400 mg* + minocycline 100 mg + clofazimine 50 mg	Ofloxacin 400 mg* OR minocycline 100 mg + clofazimine 50 mg
	Ofloxacin 400 mg* + clarithromycin 500 mg + clofazimine 50 mg	Ofloxacin 400 mg* + clofazimine 50 mg
Rifampicin and ofloxacin resistance	Clarithromycin 500 mg + minocycline 100 mg + clofazimine 50 mg	Clarithromycin 500 mg OR minocycline 100 mg + clofazimine 50 mg

**Ofloxacin 400 mg can be replaced by levofloxacin 500 mg OR moxifloxacin 400 mg*

Summary of the evidence

The evidence review found no studies meeting inclusion criteria on the effectiveness of regimens for rifampicin-resistant leprosy. Rifampicin is considered the most important drug in standard MDT. Several widely available drugs that are not part of standard MDT are known to have effects against *M. leprae (77)* and can be incorporated into an alternative second-line regimen for rifampicin-resistant leprosy. Treatment should consist of at least two

second-line drugs (clarithromycin, minocycline or a quinolone) plus clofazimine daily for 6 months, then clofazimine plus one of these drugs daily for an additional 18 months. In case of associated ofloxacin resistance, a fluoroquinolone should not be used as part of the second-line treatment regimen.

Because fluoroquinolones are active against TB, leprosy patients starting a second-line regimen should be investigated for signs and symptoms of TB, to ensure that persons with TB are treated with an appropriate regimen effective against both diseases, to avoid emergence of drug-resistant TB. Pharmacovigilance of recommended regimens for resistant leprosy is needed to determine adverse events. This includes electrocardiographic monitoring, due to the risk of QT interval prolongation and associated cardiac arrhythmia, which is associated with exposure to clarithromycin as well as minocycline and quinolones.

Patients treated for resistant leprosy should be registered and their treatment outcomes closely monitored and reported to national authorities and to WHO, to better inform future recommendations on optimal treatment strategies and outcomes for drug-resistant leprosy.

3. Prophylaxis

3.1. Prevention of leprosy through chemoprophylaxis

Recommendation

The GDG **recommends** the use of SDR as preventive treatment for contacts of leprosy patients (adults and children 2 years of age and above), after excluding leprosy and TB disease, and in the absence of other contraindications. This intervention shall be implemented by programmes that can ensure: (i) adequate management of contacts and (ii) consent of the index case to disclose his/her disease (conditional recommendation, moderate quality evidence).

Rationale

Leprosy is associated with important clinical and social consequences. Prevention of leprosy would be preferable to treating patients after clinical presentation and would provide additional public health benefits in terms of reducing the spread of the disease. An RCT found SDR effective at reducing risk of leprosy over 5–6 years in leprosy contacts. For every 1000 contacts treated with SDR, there were four leprosy cases prevented after 1–2 years and three cases prevented after 5–6 years. Recommended dosage schedules for SDR are given in Table 5.

Table 5. Rifampicin dose for single-dose rifampicin (SDR)

Age/weight	Rifampicin single dose
15 years and above	600 mg
10–14 years	450 mg
Children 6–9 years (weight ≥20 kg)	300 mg
Children <20 kg (≥2 years)	10–15 mg/kg

Summary of the evidence

The possibility of using one of the medications of MDT to prevent leprosy among contacts has been studied extensively, with a systematic review finding that dapsone for prolonged periods could prevent the occurrence of leprosy in contacts *(78)*. The latest studies focused on the effect of SDR. A double-blind RCT (COLEP study) found SDR in leprosy contacts associated with a reduction in risk of leprosy of 57% over 2 years and of 30% over 5–6 years *(79)*. For every 1000 contacts treated with SDR, there were four leprosy cases prevented after 1–2 years and three cases prevented after 5–6 years. The protective effect of SDR occurred in the first 2 years, with no additional effect after 4 and 6 years *(80)*. However, the total impact of the intervention remained statistically significant after 6 years. One analysis based on COLEP found that SDR was cost effective, with an incremental cost–effectiveness ratio of US$ 158 per additional prevented leprosy case *(13)*. A sub-study of the COLEP RCT showed that BCG at birth appears to potentiate the protective effect of SDR in contacts from 57% to 80% *(84)*. A recent systematic review did not identify any additional controlled data on effectiveness of SDR *(82)*, though a trial of combined post-exposure chemoprophylaxis and immunoprophylaxis is currently in progress *(83)*. A published expert meeting report found that SDR does not increase the risk of rifampicin-resistant *M. tuberculosis (85)*. Nonetheless, the GDG determined that it would be prudent to exclude TB before administering SDR to consenting contacts. More studies are needed to assess the efficacy of repeated SDR on long-term outcomes, since COLEP found that efficacy of SDR was higher at 2 years than after 5–6 years.

The impact of chemoprophylaxis is likely to be higher as the definition of contacts is expanded (e.g. from household contacts only to all contacts in a community). However, a broader definition would perhaps increase the costs/effort associated with screening, become less efficient according to the extent that it includes persons at lower risk of developing leprosy, and require even greater caution to prevent stigma. The GDG suggests that in areas of high endemicity and concomitant high population density a "blanket" approach of SDR for the whole community could be considered, although there is only one study showing efficacy of such an approach *(86)*.

The GDG concluded that the evidence supports a recommendation to use SDR in contacts of leprosy patients to prevent leprosy. Although the COLEP trial was conducted in one country, preliminary reports from the multicountry Leprosy Post-Exposure Prophylaxis (LPEP) study *(81)* are encouraging with regard to feasibility and acceptability in other settings

(unpublished data). Because leprosy is a highly stigmatized disease, caution must be exercised when implementing SDR in contacts, particularly for contacts outside the family of the patient. Programmes must respect the wish of patients to disclose or not disclose their diagnosis to contacts. When patients do not authorize disclosure, the GDG does not recommend identification or screening of contacts or prescribing preventive treatment to contacts. The blanket approach might be more feasible in a context of high stigma and discrimination; under this approach disclosure of index cases may not be required.

Remarks

The GDG concluded that the availability of an effective and simple (single dose) preventive treatment is likely to improve the quality and completeness of contact screening and treatment. However, implementation of the recommendation is conditional on two key factors: (i) adequate management of contact screening and (ii) assurance of obtaining patient consent before contact screening. The effectiveness of SDR for preventing leprosy is likely to require programmes to ensure high coverage of contact screening and use a broad definition for contacts, including social contacts. In addition, programmes need to employ mechanisms to ensure that patient consent is obtained appropriately and that contact tracing is not performed without patient consent, given the potential trade-offs between prevention of leprosy and harmful effects related to stigma, which could worsen inequities. Therefore, programmes and clinicians must adhere to patient preferences regarding disclosure of leprosy diagnosis. National guidelines on SDR should include clear guidance on how to obtain consent from the index case for identification and examination of contacts. Of critical importance is the need for efforts to minimize leprosy-related stigma in the community, so that the burden of actual and anticipated stigma does not promote withholding consent for SDR prophylaxis where it is otherwise recommended, and minimize situations in which patients and health-care workers face an "ethical dilemma" of either exposing and potentially stigmatizing the patient by treating contacts, or denying effective prophylaxis for an at-risk contact.

3.2. Prevention of leprosy through immunoprophylaxis (vaccines)

WHO regulations require that SAGE formulate all vaccination (immunoprophylaxis) recommendations. Therefore, the GDG reviewed evidence on vaccinations but did not formulate recommendations; rather, findings on vaccinations were shared with the SAGE BCG working group to help inform its recommendations.

Rationale

Vaccines are a core intervention to prevent and reduce the burden and impact of communicable diseases on population health. Evidence on the efficacy of BCG to prevent leprosy is well established *(87,88)*, but there have been no WHO recommendations for its use as a leprosy preventive tool before the start of this guideline development process. BCG is widely available and already part of the vaccination policy in most leprosy-endemic countries.

Summary of the evidence

A systematic review found BCG vaccination at birth effective at reducing risk of leprosy (pooled reduction in risk 55%), though the magnitude of the effect varied *(87)*. Most studies were conducted in high-burden countries. Evidence indicates that several vaccination interventions apart from BCG show similar or slightly lower efficacy compared to BCG for reducing the risk of leprosy *(87–90)*. These vaccines are killed myobacteria, as opposed to BCG, which is a live vaccine; however, only one, the *M. indicum pranii* vaccine (formerly known as *M. w*), is currently produced.

Two large RCTs *(91,92)* of BCG revaccination compared with BCG only given at birth were not included in the latest review on BCG and leprosy *(87)*. The first trial showed almost identical leprosy rates in both groups while in the other trial BCG revaccination was associated with a 49% reduction in risk of leprosy versus placebo. Therefore, the effectiveness of BCG revaccination is unclear. An analysis of data from the COLEP SDR trial also found that BCG at birth seems to potentiate the effect of SDR given as chemoprophylaxis in contacts of persons with leprosy *(86)*. An ongoing RCT is studying the effect of BCG revaccination among a large cohort of contacts of persons with leprosy *(83)*.

Conclusions shared with SAGE

- BCG at birth is effective at reducing the risk of leprosy; therefore, its use should be maintained at least in all leprosy high-burden countries or settings (good quality of evidence).
- BCG at birth appears to potentiate the protective effect of SDR in contacts from 57% to 80% (low quality of evidence).
- The effectiveness of BCG revaccination (second dose of BCG following a birth dose) is unclear, since two large trials on BCG revaccination showed conflicting results.
- Evidence indicates the efficacy (based on two RCTs) of *M. indicum pranii* in preventing leprosy (moderate quality of evidence).

The revised policy for BCG in the prevention of both TB and leprosy was released through a WHO position paper in February 2018 *(93),* which summarizes the BCG-related conclusions of the GDG of these guidelines.

4. Implementation and evaluation

With regard to implementation and evaluation of the guidelines, the GLP will work closely with WHO regional and country offices and implementing partners to ensure wide dissemination through regional and subregional events. WHO staff will provide telephone, email and direct assistance to country programme officers adapting the guidelines. Opportunities to discuss the implementation of the guidelines with country staff will be sought during planned country

visits. Regional dissemination workshops for the adaptation of the guidelines will be organized if resources permit. The GLP will also disseminate the guidelines through its collaboration with the ILEP Technical Commission and the ILEP network of country coordinators.

There will be an evaluation by the WHO Steering Group during the first year of implementation of the guidelines, focusing on their accessibility and acceptability. As an assessment of document uptake, the number of downloads of the document from the WHO websites will be monitored, as well as the number of hard copies of the guidance requested and distributed. After implementation, an evaluation of the impact of the guidelines will be undertaken through review of epidemiological data, following an assessment of the uptake of the recommendations and barriers to effective implementation.

WHO plans to monitor the impact of the guidelines on health outcomes. Following the recommended change in the PB leprosy regimen, WHO will monitor the proportion of treatment completers to evaluate effects on treatment compliance. The impact of the recommendation on preventive treatment with SDR will be monitored through assessment of disease trends and through analysis of disease incidence in leprosy contacts. This information is already requested by WHO through the annual leprosy data collection online tool (in use since 2016).

5. Updating

These guidelines are assumed to be valid until at least 2022, unless there is the emergence of significant new evidence that would require a review before that date.

Part III: Research priorities

1. Leprosy diagnosis

Tests with promising results for higher diagnostic accuracy (e.g. PCR tests using tissue samples) should be assessed in larger, well-designed studies using assays that are standardized and feasible for use in field settings. Such studies should also evaluate their accuracy for predicting the development of leprosy in contacts. In addition, research is needed on the diagnostic utility of other tools, including ultrasound and other imaging tests, as possible aids to diagnosis.

New biomarkers are needed to identify persons with leprosy. Tests for these should be more accurate than previously evaluated ELISA and lateral flow tests. A test protocol study reported the utility of mixed assays that detect cell-mediated responses (cytokines and chemokines) as well as *M. leprae*-specific antibodies to detect both PB and MB leprosy *(94)*. More studies are needed to determine the use of identified biomarkers for diagnosis. Longitudinal studies are needed to assess how well these tests predict the development of overt leprosy in contacts of persons with leprosy.

2. Leprosy treatment

Adequately powered, appropriately designed studies are needed on the benefits and harms of shorter MDT regimens for MB leprosy, including effects on bacteriological outcomes (e.g. tests of *M. leprae* viability in skin and nerves). For both PB and MB leprosy, more well-conducted studies are needed to better understand optimal treatment strategies.

Treatment for drug-resistant leprosy

The GDG emphasizes the need to enhance current antimicrobial resistance surveillance for leprosy. Given the small numbers of detected leprosy resistance, an RCT on the efficacy of different second-line regimens is unlikely to be feasible. However, observational studies that employ systematic methods to collect clinical and bacteriological outcomes of treatment for resistant *M. leprae* would be useful for understanding potential benefits and harms of alternative strategies.

3. Prevention of leprosy

3.1 Prevention of leprosy through chemoprophylaxis

Studies that evaluate the effectiveness of alternatives to SDR for chemoprophylaxis (e.g. regimens that use drugs other than rifampicin or multiple doses) are needed. In addition, research is needed to understand the effectiveness of chemoprophylaxis provided through a "blanket/high-risk population" approach rather than through identification of contacts, since the former might increase feasibility and reduce the risk of stigma compared to contact tracing-based approaches.

3.2 Prevention of leprosy through vaccines

Trials are needed on new and existing vaccines, including studies on LepVax, a new subunit vaccine currently in stage 1a studies. Trials are also needed on the effects of combined post-exposure immunoprophylaxis and chemoprophylaxis. The GDG recommends that any new TB vaccine be evaluated for the prevention of other mycobacterial diseases such as leprosy and Buruli ulcer and vice versa.

References

(1) World Health Organization, Department of Control of Neglected Tropical Diseases. Global leprosy update, 2015: time for action, accountability and inclusion. Wkly Epidemiol Rec. 2016; 91(35):405–20.

(2) World Health Organization, Regional Office for South-East Asia, Global Leprosy Programme. Global Leprosy Strategy 2016–2020: accelerating towards a leprosy-free world. New Delhi: WHO Regional Office for South-East Asia; 2016 (http://apps.who.int/iris/bitstream/handle/10665/208824/9789290225096_en.pdf, accessed 14 May 2018).

(3) World Health Organization, Regional Office for South-East Asia, Global Leprosy Programme. Global Leprosy Strategy 2016–2020: Monitoring and Evaluation Guide. Accelerating towards a leprosy-free world. New Delhi: WHO Regional Office for South-East Asia; 2017 (http://apps.who.int/iris/bitstream/handle/10665/254907/9789290225492-eng.pdf, accessed 14 May 2018).

(4) WHO Expert Committee on Leprosy.ý WHO Expert Committee on Leprosy: seventh report. WHO Technical Report Series No. 874. Geneva: WHO; 1998 (http://www.who.int/iris/handle/10665/42060, accessed 14 May 2018).

(5) WHO Expert Committee on Leprosy. WHO expert committee on Leprosy: eighth report. WHO Technical Report Series No. 968. Geneva: WHO; 2010.

(6) Meima A, Smith WC, van Oortmarssen GJ, Richardus JH, Habbema JD. The future incidence of leprosy: a scenario analysis. Bull World Health Organ. 2004;82(5):373–80.

(7) Gillini L, Cooreman E, Wood T, Pemmaraju VR, Saunderson P. Global practices in regard to implementation of preventive measures for leprosy. PLoS Negl Trop Dis. 2017;11(5):e0005399. doi: 10.1371/journal.pntd.0005399. eCollection 2017 May.

(8) WHO Regional Office for South-East Asia. Guidelines for global surveillance of drug resistance in leprosy. New Delhi: WHO; 2009.

(9) WHO Regional Office for South-East Asia, Department of Control of Neglected Tropical Diseases. A guide for surveillance of antimicrobial resistance in leprosy: 2017 Update. New Delhi: WHO; 2017.

(10) Surveillance of drug resistance in leprosy: 2009. Wkly Epidemiol Rec. 2010;85(29):281.

(11) Cambau E, Saunderson P, Matsuoka M, Cole S, Kai M, Suffys P et al.; WHO surveillance network of antimicrobial resistance in leprosy. Antimicrobial resistance in leprosy: results of the first prospective open survey conducted by a WHO surveillance network for the period 2009–2015. Clin Microbiol Infect. 2018 Mar 1. pii: S1198-743X(18)30197-6. doi: 10.1016/j.cmi.2018.02.022. [Epub ahead of print]

(12) World Health Organization. WHO Handbook for Guideline Development. 2nd ed. Geneva: WHO; 2014 (http://www.who.int/publications/guidelines/handbook_2nd_ed.pdf, accessed 12 February 2018).

(13) Idema WJ, Majer IM, Pahan D, Oskam L, Polinder S, Richardus JH. Cost–effectiveness of a chemoprophylactic intervention with single dose rifampicin in contacts of new leprosy patients. PLoS Negl Trop Dis. 2010;4(11):e874. doi: 10.1371/journal.pntd.0000874.

(14) Schunemann HJ, Oxman AD, Brozek J, Glasziou P, Jaeschke R, Vist GE et al.; GRADE Working Group. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. BMJ. 2008;336(7653):1106–10. doi: 10.1136/bmj.39500.677199.AE.

(15) Gopalakrishna G, Mustafa RA, Davenport C, Scholten RJ, Hyde C, Brozek J et al. Applying Grading of Recommendations Assessment, Development and Evaluation (GRADE) to diagnostic tests was challenging but doable. J Clin Epidemiol. 2014;67(7):760–8. doi: 10.1016/j.jclinepi.2014.01.006.

(16) Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529–36. doi: 10.7326/0003-4819-155-8-201110180-00009.

(17) United Nations Human Rights Council. Resolution adopted by the Human Rights Council on 2 July 2015. Doc. No. 29/5. Elimination of discrimination against persons affected by leprosy and their family members. New York, July 2015.

(18) Desikan KV, Rao KV, Bharambe MS, Rao PV. Appraisal of skin smear reports of field laboratories. Lepr Rev. 2006;77(4):311–16.

(19) Triccas JA , Roche PW, Britton WJ. Specific serological diagnosis of leprosy with a recombinant mycobacterium leprae protein purified from a rapidly growing mycobacterial host. J Clin Microbiol. 1998;36(8):2363–5.

(20) Roche PW, Failbus SS, Britton WJ, Cole R. Rapid method for diagnosis of leprosy by measurements of antibodies to the *M. Leprae* 35-kDa protein: comparison with PGL-I antibodies detected by ELISA and "dipstick" methods. Int J Lepr Other Mycobact Dis. 1999;67(3):279–86.

(21) Torres P, Camarena JJ, Gomez JR, Nogueira JM, Gimeno V, Navarro JC et al. Comparison of PCR mediated amplification of DNA and the classical methods for detection of *Mycobacterium leprae* in different types of clinical samples in leprosy patients and contacts. Lepr Rev. 2003;74(1):18–30.

(22) Sinha S, Kannan S, Nagaraju B, Sengupta U, Gupte MD. Utility of sero-diagnostic tests for leprosy: a study in an endemic population in South-India. Lepr Rev. 2004;75(3):266–73.

(23) Prakash O, Kumar A, Nigam A, Franken KL, Ottenhoff TH. Evaluation of recombinant serine-rich 45-kDa antigen (ML0411) for detection of antibodies in leprosy patients. Scand J Immunol. 2006;64(4):450–5.

(24) Duthie MS, Goto W, Ireton GC, Reece ST, Cardoso LP, Martelli CM et al. Use of protein antigens for early serological diagnosis of leprosy. Clin Vaccine Immunol. 2007;14(11):1400–8.

(25) Maeda Y, Mukai T, Kai M, Fukutomi Y, Nomaguchi H, Abe C et al. Evaluation of major membrane protein-II as a tool for serodiagnosis of leprosy. FEMS Microbiol Lett. 2007;272(2):202–5.

(26) Da Silva RC, Lyon S, Lyon AC, Grossi MA, Lyon SH, Bührer-Sékula S et al. Correlation between ELISA and ML Flow assays applied to 60 Brazilian patients affected by leprosy. Trans R Soc Trop Med Hyg. 2010;104(8):546–50. doi: 10.1016/j.trstmh.2010.05.001. Epub 2010 Jun 17.

(27) Kai M, Nguyen Phuc NH, Hoang Thi TH, Nguyen AH, Fukutomi Y, Maeda Y et al. Serological diagnosis of leprosy in patients in Vietnam by enzyme-linked immunosorbent assay with *Mycobacterium leprae*-derived major membrane protein II. Clin Vaccine Immunol. 2008;15(12):1755–9. doi: 10.1128/CVI.00148-08. Epub 2008 Oct 22.

(28) Hatta M, Makino M, Ratnawati, Mashudi, Yadi, Sabir M et al. Detection of serum antibodies to *M. leprae* major membrane protein-II in leprosy patients from Indonesia. Lepr Rev. 2009;80(4):402–9.

(29) Oo KN, Htwe MM, Win KZ, Wai KT, Myint K, Kyaw K. Application of new serological (Major Membrane Protein II) enzyme linked immunosorbent assay for leprosy patients in Myanmar. The Myanmar Health Sciences Research Journal. 2009;21(3):121–5.

(30) Lobato J, Costa MP, Reis Ede M, Gonçalves MA, Spencer JS, Brennan PJ et al. Comparison of three immunological tests for leprosy diagnosis and detection of subclinical infection. Lepr Rev. 2011;82(4):389–401.

(31) Barreto JG, Guimarães Lde S, Leão MR, Ferreira DV, Lima RA, Salgado CG. Anti-PGL-I seroepidemiology in leprosy cases: household contacts and school children from a hyperendemic municipality of the Brazilian Amazon. Lepr Rev. 2011;82(4):358–70.

(32) Vaz Cardoso LP, Dias FR, Freitas AA, Hungria AM, Oliveira MR, Collovati M et al. Development of a quantitative rapid diagnostic test for multibacillary leprosy using smart phone technology. BMC Infectious Diseases. 2013;13:497. doi: 10.1186/1471-2334-13-497.

(33) Wen Y, Xing Y, Yuan L, Liu J, Zhang Y, Li HY. Whole-blood nested-PCR amplification of *M. leprae*-specific DNA for early diagnosis of leprosy. Am J Trop Med Hyg. 2013;88(5):918–22. doi: 10.4269/ajtmh.11-0253.

(34) Moura RS, Penna GO, Fujiwara T, Pontes MA, Cruz R, Gonçalves Hde S et al. Evaluation of a rapid serological test for leprosy classification using human serum albumin as the antigen carrier. J Immunol Methods. 2014;412:35–41. doi: 10.1016/j.jim.2014.06.014.

(35) da Conceição Oliveira Coelho Fabri A, Carvalho AP, Araujo S, Goulart LR, de Mattos AM, Teixeira HC et al. Antigen-specific assessment of the immunological status of various groups in a leprosy endemic región. BMC Infect Dis. 2015;15:218. doi: 10.1186/s12879-015-0962-4.

(36) Wang H, Liu W, Jin Y, Yu M, Jiang H, Tamura T et al. Detection of antibodies to both *M. leprae* PGL-I and MMP-II to cognize leprosy patients at an early stage of disease progression. Diagn Microbiol Infect Dis. 2015;83(3):274–7. doi: 10.1016/j.diagmicrobio.2015.07.012.

(37) Da Silva CR, Lyon S, Araos R, Lyon AC, de Faria Grossi MA, Lyon SE et al. The result patterns of ML Flow and ELISA (PGL-I) serological tests in leprosy-endemic and non-endemic areas. Rev Soc Bras Med Trop. 2008;41 Suppl 2:19–22.

(38) Tsukamoto Y, Maeda Y, Makino M. Evaluation of major membrane protein-I as a serodiagnostic tool of paucibacillary leprosy. Diagn Microbiol Infect Dis. 2014;80(1):62–5. doi: 10.1016/j.diagmicrobio.2014.06.004.

(39) Duthie MS, Raychaudhuri R, Tutterrow YL, Misquith A, Bowman J, Casey A et al. A rapid ELISA for the diagnosis of MB leprosy based on complementary detection of antibodies against a novel protein-glycolipid conjugate. Diagn Microbiol Infect Dis. 2014;79(2):233–9. doi: 10.1016/j.diagmicrobio.2014.02.006.

(40) Duthie MS, Orcullo FM, Abbelana J, Maghanoy A, Balagon MF. Comparative evaluation of antibody detection tests to facilitate the diagnosis of multibacillary leprosy. Appl Microbiol Biotechnol. 2016;100(7):3267–75. doi: 10.1007/s00253-016-7328-8.

(41) Stefani MM, Grassi AB, Sampaio LH, Sousa AL, Costa MB, Scheelbeek P et al. Comparison of two rapid tests for anti-phenolic glycolipid-I serology in Brazil and Nepal. Mem Inst Oswaldo Cruz. 2012;107 Suppl 1:124–31.

(42) Penna ML, Penna GO, Iglesias PC, Natal S, Rodrigues LC. Anti-PGL-1 positivity as a risk marker for the development of leprosy among contacts of leprosy cases: systematic review and meta-analysis. PLoS Negl Trop Dis. 2016;10(5):e0004703. doi: 10.1371/journal.pntd.0004703. eCollection 2016 May.

(43) Rudeeaneksin J, Srisungngam S, Sawanpanyalert P, Sittiwakin T, Likanonsakul S, Pasadorn S et al. LightCycler real-time PCR for rapid detection and quantitation of *Mycobacterium leprae* in skin specimens. FEMS Immunol Med Microbiol. 2008;54(2):263–70. doi: 10.1111/j.1574-695X.2008.00472.x.

(44) Bang PD, Suzuki K, Phuong le T, Chu TM, Ishii N, Khang TH. Evaluation of polymerase chain reaction-based detection of *Mycobacterium leprae* for the diagnosis of leprosy. J Dermatol. 2009;36(5):269–76. doi: 10.1111/j.1346-8138.2009.00637.x.

(45) Martinez AN, Ribeiro-Alves M, Sarno EN, Moraes MO. Evaluation of qPCR-based assays for leprosy diagnosis directly in clinical specimens. PLoS Negl Trop Dis. 2011;5(10):e1354. doi: 10.1371/journal.pntd.0001354.

(46) Caleffi KR, Hirata RD, Hirata MH, Caleffi ER, Siqueira VL, Cardoso RF. Use of the polymerase chain reaction to detect *Mycobacterium leprae* in urine. Braz J Med Biol Res. 2012;45(2):153–7.

(47) Wen Y, Xing Y, Yuan LC, Liu J, Zhang Y, Li HY. Whole-blood nested-PCR amplification of *M. leprae*-specific DNA for early diagnosis of leprosy. Am J Trop Med Hyg. 2013;88(5):918–22. doi: 10.4269/ajtmh.11-0253.

(48) Banerjee S, Biswas N, Kanti Das N, Sil A, Ghosh P, Hasanoor Raja AH et al. Diagnosing leprosy: revisiting the role of the slit-skin smear with critical analysis of the applicability of polymerase chain reaction in diagnosis. Int J Dermatol. 2011;50(12):1522–7. doi: 10.1111/j.1365-4632.2011.04994.x.

(49) Silva AR, Queiroz MFA, Ishikawa AYE, Silvestre MPSA, Xavier MB. Evaluation of agreement between tests for the diagnosis of leprosy. J Bras Pat Med Lab. 2017;53(2):100–7.

(50) Jain S, Visser LH, Praveen TL, Rao PN, Surekha T, Ellanti R et al. High Resolution Sonography: a new technique to detect nerve damage in leprosy. PLoS Negl Trop Dis. 2009;3(8):e498. doi: 10.1371/journal.pntd.0000498.

(51) Elias J Jr, Nogueira-Barbosa MH, Feltrin LT, Furini RB, Foss NT, Marques W Jr et al. Role of ulnar nerve sonography in leprosy neuropathy with electrophysiologic correlation. J Ultrasound Med. 2009;28(9):1201–9.

(52) Bathala L, Kumar K, Pathapati R, Jain S, Visser LH. Ulnar neuropathy in Hansen disease: clinical, high-resolution ultrasound and electrophysiological correlations. J Clin Neurophysiol. 2012;29(2):190–3. doi: 10.1097/WNP.0b013e31824d969c.

(53) Bathala L, Kumar P, Kumar K, Visser LH. Ultrasonographic cross-sectional area normal values of the ulnar nerve along its course in the arm with electrophysiological correlations in 100 Asian subjects. Muscle Nerve. 2013;47(5):673–6. doi: 10.1002/mus.23639.

(54) Frade MA, Nogueira-Barbosa MH, Lugão HB, Furini RB, Marques Júnior W, Foss NT. New sonograhic measures of peripheral nerves: a tool for the diagnosis of peripheral nerve involvement in leprosy. Mem Inst Oswaldo Cruz. 2013 May;108(3). pii: S0074-02762013000300257. doi: 10.1590/S0074-02762013000300001.

(55) Lugão HB, Nogueira-Barbosa MH, Marques Jr W, Foss NT, Frade MAC. Asymmetric nerve enlargement: a characteristic of leprosy neuropathy demonstrated by ultrasonography. PLoS Negl Trop Dis. 2015;9(12): e0004276 (https://doi.org/10.1371/journal.pntd.0004276, accessed 15 May 2018).

(56) Gupta S, Bhatt S, Bhargava SK, Singal A, Bhargava S. High resolution sonographic examination: a new technique to study ulnar nerve neuropathy in leprosy. Lepr Rev. 2016;87:464–75.

(57) Lugão HB, Frade MA, Marques W Jr, Foss NT, Nogueira-Barbosa MH. Ultrasonography of leprosy neuropahty: a longitudinal prospective study. PLoS Negl Trop Dis. 2016;10(11):e0005111. doi: 10.1371/journal.pntd.0005111.

(58) Bathala L, Kumar P, Kumar K, Shaik A, Visser LH. Normal values of median nerve cross-sectional area obtained by ultrasound along its course in the arm with electrophysiological correlations, in 100 Asian subjects. Muscle Nerve. 2014;49(2):284–6.

(59) Boehm J, Scheidl E, Bereczki D, Schelle T, Aranyi Z. High-resolution ultrasonography of peripheral nerves: measurements on 14 nerve segments in 56 healthy subjects and reliability assessments. Ultraschall Med. 2014;35(5):459–67. doi: 10.1055/s-0033-1356385.

(60) World Health Organization, Regional Office for South-East Asia, Global Leprosy Programme. Global Leprosy Strategy 2016–2020: Operational Manual 2016. Accelerating towards a leprosy-free world. New Delhi: WHO Regional Office for South-East Asia; 2016 (http://apps.searo.who.int/PDS_DOCS/B5233.pdf, accessed 15 May 2018).

(61) Manickam P, Mehendale SM, Nagaraju B, Katoch K, Jamesh A, Kutaiyan R et al. International open trial of uniform multidrug therapy regimen for leprosy patients: findings implications for national leprosy programmes. Indian J Med Res. 2016;144(4):525–35. doi: 10.4103/0971-5916.200888.

(62) Ferreiral P, Buhrer-Sékula S, De Oliveira MR, Gonçalves Hde S, Pontes MA, Penna ML et al. Patient profile and treatment satisfaction of Brazilian leprosy patients in a clinical trial of uniform six-month multidrug therapy (U-MDT/CT-BR). Lepr Rev. 2014;85(4):267–74.

(63) Rao PN, Suneetha S, Pratap DV. Comparative study of uniform-MDT and WHO MDT in Pauci and Multi bacillary leprosy patients over 24 months of observation. Lepr Rev. 2009;80(2):143–55.

(64) Butlin RC, Pahan D, Kya A, Maug J, Withington S, Nicholls P et al. Outcome of 6 months MBMDT in MB patients in Bangladesh-preliminary results. Lepr Rev. 2016;87(2):171–82.

(65) Penna GO, Bührer-Sékula S, Kerr LRS, Stefani MMA, Rodrigues LC, de Araújo MG et al. Uniform multidrug therapy for leprosy patients in Brazil (U-MDT/CT-BR): results of an open label, randomized and controlled clinical trial, among multibacillary patients. PLoS Negl Trop Dis. 2017;11(7):e0005725. doi: 10.1371/journal.pntd.0005725.

(66) Gonçalves Hde S, Pontes MA, Bührer-Sékula S, Cruz R, Almeida PC, Moraes ME, Penna GO. Brazilian clinical trial of uniform multidrug therapy for leprosy patients: the correlation between clinical disease types and adverse effects. Mem Inst Oswaldo Cruz. 2012;107 Suppl 1:74–8.

(67) Hungria EM, Morillas Oliveira R, Penna GO, Cartaxo Aderaldo L, de Andrade Pontes MA, Cruz R et al. Can baseline ML Flow test results predict leprosy reactions? An investigation in a cohort of patients enrolled in the uniform multidrug therapy clinical trial for leprosy patients in Brazil. Infect Dis Poverty. 2016;5(1):110.

(68) Prasad PVS, Babu A, Kaviarasan PK, Viswanathan P, Tippoo R. MDT-MB therapy in paucibacillary leprosy: a clinicopathological assessment. Indian J Dermatol Venereol Leprol. 2005;71(4):242–5.

(69) World Health Organization, The Leprosy Unit, Division of Control of Tropical Diseases. Risk of relapse in leprosy. Doc No. WHO/CTD/LEP/94.1. Geneva, 1994 (http://apps.who.int/iris/bitstream/handle/10665/61868/WHO_CTD_LEP_94.1.pdf, accessed 15 May 2017).

(70) Kroger A, Pannikar V, Htoon MT, Jamesh A, Katoch K, Krishnamurthy P et al. International open trial of uniform multi-drug therapy regimen for 6 months for all types of leprosy patients: rationale, design and preliminary results. Trop Med Int Health. 2008;13(5):594–602. doi: 10.1111/j.1365-3156.2008.02045.x.

(71) Shen J, Bathyalan N, Kroeger A, Arana B, Pannikar V, Mou H et al. Bacteriological results and leprosy reactions among MB leprosy patients treated with uniform multidrug therapy in China. Lepr Rev. 2012;83(2):164–71.

(72) Beltran-Alzate C, Lopez Diaz F, Romero-Montoya M, Sakamuri R, Li W, Kimura M et al. Leprosy drug resistance surveillance in Colombia: the experience of a sentinel country. PLoS Negl Trop Dis. 2016;10(10):e0005041. doi: 10.1371/journal.pntd.0005041.

(73) Liu D, Zhang Q, Sun Y, Wang C, Zhang Y, Fu X et al. Drug resistance in Mycobacterium leprae from patients with leprosy in China. Clin Exp Dermatol. 2015;40(8):908–11. doi: 10.1111/ced.12665.

(74) Matsuoka M, Budiawan T, Aye KS, Kyaw K, Tan EV, Cruz ED et al. The frequency of drug resistance mutations in Mycobacterium leprae isolates in untreated and relapsed leprosy patients from Myanmar, Indonesia and the Philippines. Lepr Rev. 2007;78(4):343–52.

(75) Rocha Ada S, Cunha M, Diniz LM, Salgado C, Aires MA, Nery JA et al. Drug and multidrug resistance among Mycobacterium leprae isolates from Brazilian relapsed leprosy patients. J Clin Microbiol. 2012;50(6):1912–17. doi: 10.1128/JCM.06561-11.

(76) You EY, Kang TJ, Kim SK, Lee SB, Chae GT. Mutations in genes related to drug resistance in Mycobacterium leprae isolates from leprosy patients in Korea. J Infect. 2005;50(1):6–11.

(77) World Health Organization. Chemotherapy of Leprosy for Control Programmes. Report of a WHO Study Group. Technical Report Series 675. Geneva: WHO; 1982 (http://apps.who.int/iris/bitstream/handle/10665/38984/WHO_TRS_675.pdf, accessed 15 May 2018).

(78) Reveiz L, Buendia JA, Tellez D. Chemoprophylaxis in contacts of patients with leprosy: systematic review and meta-analysis. Rev Panam Salud Publica. 2009;26(4):341–9.

(79) Moet FJ, Pahan D, Oskam L, Richardus JH; COLEP Study Group. Effectiveness of single dose rifampicin in preventing leprosy in close contacts of patients with newly diagnosed leprosy: cluster randomized controlled trial. BMJ. 2008;336(7647):761–4. doi: 10.1136/bmj.39500.885752.BE.

(80) Feenstra SG, Pahan D, Moet FJ, Oskam L, Richardus JH. Patient-related factors predicting the effectiveness of rifampicin chemoprophylaxis in contacts: 6 year follow up of the COLEP cohort in Bangladesh. Lepr Rev. 2012;83(3):292–304.

(81) Barth-Jaeggi T, Steinmann P, Mieras L, van Brakel W, Richardus JH, Tiwari A et al. Leprosy post-exposure prophylaxis (LPEP) programme: study protocol for evaluating the feasibility and impact on case detection rates of contact tracing and single dose rifampicin. BMJ Open. 2016;6(11):e013633. doi: 10.1136/bmjopen-2016-013633.

(82) Ferreira SMB, Yonekura T, Ignotti E, Oliveira LB, Takahashi J, Soares CB. Effectiveness of rifampicin chemoprophylaxis in preventing leprosy in patient contacts: a systematic review of quantitative and qualitative evidence. JBI Database System Rev Implement Rep. 2017;15(10):2555–84. doi: 10.11124/JBISRIR-2016-003301.

(83) Richardus RA, Alam K, Pahan D, Feenstra SG, Geluk A, Richardis JH. The combined effect of chemoprophylaxis with single dose rifampicin and immunoprophylaxis with BCG to prevent leprosy in contacts of newly diagnosed leprosy cases: a cluster randomized controlled trial (MALTALEP study). BMC Infect Dis. 2013;13:456. doi: 10.1186/1471-2334-13-456.

(84) Schuring RP, Richardus JH, Pahan D, Oskam L. Protective effect of the combination BCG vaccination and rifampicin prophylaxis in leprosy prevention. Vaccine. 2009;27(50):7125–8. doi: 10.1016/j.vaccine.2009.09.054.

(85) Mieras L, Anthony R, van Brakel W, Bratschi MW, van den Broek J, Cambau E et al. Negligible risk of inducing resistance in Mycobacterium tuberculosis with single-dose rifampicin as post-exposure prophylaxis for leprosy. Infect Dis Poverty. 2016 Jun 8;5(1):46. doi: 10.1186/s40249-016-0140-y.

(86) Bakker MI, Hatta M, Kwenang A, Van Benthem BH, Van Beers SM, Klatser PR et al. Prevention of leprosy using rifampicin as chemoprophylaxis. Am J Trop Med Hyg. 2005;72(4):443–8.

(87) Merle CS, Cunha SS, Rodrigues LC. BCG vaccination and leprosy protection: review of current evidence and status of BCG in leprosy control. Expert Rev Vaccines. 2010;9(2):209–22. doi: 10.1586/erv.09.161.

(88) Smith WC, Saunderson P. Leprosy. BMJ Clin Evid. 2010;2010. pii: 0915.

(89) Sharma P, Mukherjee R, Talwar GP, Sarathchandra KG, Walia R, Parida SK et al. Immunoprophylactic effects of the anti-leprosy Mw vaccine in household contacts of leprosy patients: clinical field trials with a follow up of 8–10 years. Lepr Rev. 2005;76(2):127–43.

(90) Gupte MD, Vallishayee RS, Anantharaman DS, Nagaraju B, Sreevatsa, Balasubramanyam S et al. Comparative leprosy vaccine trial in south India. Indian J Lepr. 1998;70(4):369–88.

(91) Cunha SS, Alexander N, Barreto ML, Pereira ES, Dourado I, Maroja Mde F et al. BCG revaccination does not protect against leprosy in the Brazilian Amazon: a cluster randomised trial. PLoS Negl Trop Dis. 2008;2(2):e167. doi: 10.1371/journal.pntd.0000167.

(92) Randomised controlled trial of single BCG, repeated BCG, or combined BCG and killed Mycobacterium leprae vaccine for prevention of leprosy and tuberculosis in Malawi. Karonga prevention Trial Group. Lancet. 1996;348(9019):17–24.

(93) World Health Organization. BCG vaccines: WHO position paper – February 2018. Wkly Epidemiol Rec. 2018;93(8):73–96.

(94) van Hooji A, Tjon Kon Fat EM, Richardus R, van den Eeden SJF, Wilson L, de Dood CJ et al. Quantitative lateral flow strip assays as user-friendly tools to detect biomarker profile for leprosy. Sci Rep. 2016;6:34260. doi: 10.1038/srep34260.

Annexes

Annex 1: Summary on review of conflicts of interest

Guidelines Development Group

The following members declared no conflicts: Professor Marcos Boulos, Professor Sang Nae Cho, Professor Roger Chou, Professor Nilanthi R. da Silva, Dr Sara Irène Eyangoh, Professor Jacques Grosset, Dr Deanna Hagge, Dr Marie Jocelyn Te, Dr Anil Kumar, Professor Bhushan Kumar, Professor Mourad Mokni, Dr Indranil Mukhopadhyay, Dr Paul Saunderson, Dr Vineeta Shanker, Dr Cita Rosita Sigit Prakoeswa, Mr Narsappa Vagavathali and Dr Rie Yotsu.

The following members declared only minor interests that were judged not to be in conflict with the policy of WHO, or the objectives of the meeting: Professor Emmanuelle Cambau, Professor Travis Porco, Professor W. Cairns Smith, Dr Willem Kuipers and Dr Marcos Virmond. For these GDG members, conflicts were reviewed in detail by a team composed of the WHO Steering Group and the CRE unit in WHO headquarters. Details regarding declared conflicts, clarifications from the GDG member, and the WHO assessment regarding participation in the GDG are summarized below.

Professor Emmanuelle Cambau

Professor Cambau received funding by Haine Lifescience to carry out research focused solely on genotypic mutation conferring resistance to rare mycobacteria, including *M. leprae*. It was determined that this would not influence the discussion over diagnostics. Therefore, it was determined that this interest did not present a conflict in respect of the meeting and Professor Cambau could participate as an expert of the GDG.

Professor Travis Porco

Professor Travis Porco reported that a portion of his salary in 2016 was supported by the Novartis Foundation. After being sought for clarifications, it was noted that, even though Dr Porco's institute received funding from the Novartis Foundation for the NTD Modelling Consortium (which looks at the real burden of leprosy and potential impact of different public health interventions), US$ 10 000 of which went towards his salary, this interest was not immediately related to the subject matter of these guidelines. In addition, the funding stopped in 2016 and no further proposal for funding had been submitted to the Novartis Foundation by himself nor his employer (the University of California). Therefore, it was determined that this interest did not present a conflict in respect of the meeting and Professor Travis Porco could participate as an expert of the GDG.

Professor W. Cairns Smith

Professor Smith was asked to provide more information regarding reported funding by Novartis to support his participation at the International Leprosy Congress in Beijing, China in September 2016. He communicated that he received the funding from the Novartis Foundation and not from Novartis Pharmaceuticals. The funding he has received for travel from the Novartis Foundation was for a total amount of £ 8000 over 4 years (2013–2017), which is an annual amount below the ceiling of US$ 5000 defined by the WHO DOI policy as a significant financial interest. Therefore, it was determined that this interest did not present a conflict in respect of the meeting and Professor Smith could participate as an expert of the GDG.

Dr Willem (Pim) Kuipers

Dr Willem (Pim) Kuipers received funding from the LRI through his role as researcher at the Griffith University, Queensland, Australia. The LRI is funded solely by NGOs so the funding is not provided by and/or for a pharmaceutical/for-profit company. Therefore, it was determined that this interest did not present a conflict in respect of the meeting and Dr Kuipers could participate as an expert of the GDG.

Dr Marcos da Cunha Lopes Virmond

Dr Marcos da Cunha Lopes Virmond received US$ 300 from the Novartis Foundation in August 2015 to attend an international conference on leprosy, which is below the ceiling of US$ 5000 defined in the WHO DOI policy as a significant financial interest. On the basis of these considerations it was determined that this interest did not present a conflict in respect of the meeting and Dr Marcos Virmond could participate as an expert of the GDG.

External Review Group

The following ERG members declared no interest related to the objectives of the guidelines: Mr Mathias Duck, Professor N.K. Ganguly, Professor Mohan Gupte, Dr Ibtissam Khoudri, Mrs R. Khumari, Dr Jean-Norbert Mputu, Professor Takahiro Nanri, Mr Kofi Nyarko, Dr Vijaykumar Pannikar, Mrs P. Soares Brandao, Mr A. Timalsina, Dr Nestor Vera, Professor Mitchell Weiss.

The following ERG members declared the following:

- Mrs Marivic F. Balagon had received a grant of US$ 164 349 from the Novartis Foundation to field-test a diagnostic test for leprosy; and another grant of € 292 276 from the LRI through the National Infectious Disease Center of the Philippines to co-fund the same study on diagnostic test; and an additional € 109 223 to test a nerve function monitoring tool.

- Dr Davis Hughes has been employed by Novartis Pharmaceuticals since 2011.
- Dr Shengelia Bakhuti has been employed by the Novartis Foundation since 2015.
- Professor Eliane Ignotti has received a grant of 82 000 Swiss francs from the Novartis Foundation to carry out the LPEP study in Brazil and to attend the annual meeting of the research multicountry project on post-exposure prophylaxis for leprosy with SDR in 2016.
- Dr Herman-Joseph Kawuma has been employed by the German Tuberculosis and Leprosy Relief Association, an NGO that provides leprosy care services. He was a member of WHO's Technical Advisory Group on Leprosy till June 2016 and is currently a member of the Regional Programme Review Group on case management NTDs of the WHO African Region.
- Professor Jan Hendrik Richardus received funding from the Novartis Foundation during the period 2014–2017 to carry out research in the following area: post-exposure prophylaxis through the supervision role on the LPEP multicountry study and as part of the NTD modelling consortium (€ 860 000). The latter grant for an amount of € 330 000 was provided by the Bill & Melinda Gates Foundation channelled through the Novartis Foundation.
- Dr Wim van Brakel declared that the organization he worked for (Netherlands Leprosy Relief) received a grant of € 300 000 for the period 2014–2017 to carry out a pilot project on post-exposure prophylaxis for leprosy with SDR in India and Indonesia as part of the multicountry LPEP study.

Literature reviewer

The systematic reviews of evidence were undertaken by Dr Amudha Poobalan, Institute of Applied Health Sciences, University of Aberdeen, United Kingdom. She declared no conflict of interest and she did not participate in the formulation of the policy recommendations.

Annex 2: Evidence-to-recommendation tables

Question 1a: Is there a diagnostic test for the diagnosis of leprosy disease (PB and/or MB) that has sufficient sensitivity and specificity and whose use is feasible under programmatic conditions?

Population:	Adults and children with suspected leprosy and leprosy patients and controls	Background: Since 1996, WHO recommended diagnosis of leprosy based on at least one of three cardinal signs: (i) hypopigmented skin patch with loss or reduced sensation; (ii) enlarged nerve; (iii) slit-skin smear positive for leprosy bacilli. However, several studies on leprosy diagnostics, including on blood/serum samples have been carried out. Presently, confirmatory tests for leprosy (microscopy on slit-skin smears and biopsy) are usually carried out only in referral centres.
Intervention:	ELISA tests Antibodies to PGL-1, MMP-I and -II, NDO-LID Immunochromatographic/lateral flow tests PCR Combined antibody/cytokine and/or chemokine tests	
Comparison:	Clinical diagnosis based on the three cardinal signs and/or slit-skin smear or biopsy	
Main outcomes:	Sensitivity/specificity	
Setting:	All settings (low- and high-burden); developing countries	
Perspective:	Clinic/field	

Assessment

	Judgement	Research evidence	Additional consideration
Problem	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ✓ **Yes** ○ Varies ○ Don't know	A diagnostic test for leprosy, especially one able to detect the disease in its early stages, could be key for an early diagnosis and for reducing transmission. This would be important with the burden of the disease reducing and prospective decline in experience among physicians in dealing with the disease.	
Desirable effects	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ✓ **Don't know**	**Desirable anticipated effects:** Some studies show good sensitivity for both MB and PB leprosy; however, they are very small studies with high imprecision and methodological limitations. Most assays showing higher sensitivity for PB leprosy are complicated to perform at the primary health-care level where the majority of patients are diagnosed. We don't know the effect on patient outcomes of using a diagnostic test compared to standard methods to detect early leprosy.	The GDG determined that the evidence shows that no test is available that shows sufficient sensitivity and specificity, especially for diagnosing PB leprosy. A desirable feature of a new diagnostic test would be one that uses a less invasive sample than skin smear or biopsy. It is noted that PCR on skin biopsy specimens shows relatively higher sensitivity and very high specificity, but based on the low level of the quality of evidence along with technical complexity with current tools, and the lack of a commercial/ clinically available test, it is not feasible for use outside referral or research centres.

<table>
<tr><th></th><th>Judgement</th><th>Research evidence</th><th>Additional consideration</th></tr>
<tr>
<td>Undesirable effects</td>
<td>
How substantial are the undesirable anticipated effects?
○ Large
○ Moderate
○ Small
○ Trivial
○ Varies
✓ Don't know
</td>
<td>
Undesirable anticipated effects:

Direct harms are likely to be very low given the nature of the tests (simple blood tests) but there are no direct data. Further, undesirable anticipated effects relate to false-positive and false-negative results leading to incorrect and missed diagnoses.

Studies of the most commonly investigated ELISA and lateral flow tests show low sensitivity for PB leprosy. Negative tests are not that useful for ruling out PB leprosy. Effects of missed or delayed diagnosis of PB leprosy are not known.

Summary of findings:
<table>
<tr><th>Condition (accuracy measure)</th><th>Estimate</th><th>Quality</th></tr>
<tr><td colspan="3">ELISA for anti-PGL</td></tr>
<tr><td>Sens: MB</td><td>Median 76% (17–98)</td><td>Very low</td></tr>
<tr><td>Sens: PB</td><td>Median 24% (0–70)</td><td>Very low</td></tr>
<tr><td>Spec:</td><td>83–96%</td><td>Very low to low</td></tr>
<tr><td colspan="3">ELISA for anti-MMP-I</td></tr>
<tr><td>Sens: MB</td><td>74% (46–86%)</td><td>Very low</td></tr>
<tr><td>Sens: PB</td><td>22% (7.3–55%)</td><td>Low</td></tr>
<tr><td>Spec:</td><td>87–100%</td><td>Very low</td></tr>
<tr><td colspan="3">ELISA for anti-MMP-II</td></tr>
<tr><td>Sens: MB</td><td>Median 82% (70–98)</td><td>Very low</td></tr>
<tr><td>Sens: PB</td><td>Median 48% (39–62%)</td><td>Low</td></tr>
<tr><td>Spec:</td><td>14–100%</td><td>Very low to low</td></tr>
<tr><td colspan="3">NDO LID lateral flow</td></tr>
<tr><td>Sens: MB</td><td>87–96%</td><td>Low</td></tr>
<tr><td>Sens: PB</td><td>20% and 32%</td><td>Very low</td></tr>
<tr><td>Spec:</td><td>75–98%</td><td>Very low to low</td></tr>
<tr><td colspan="3">ML flow</td></tr>
<tr><td>Sens: MB</td><td>84% (87–90%)</td><td>Low</td></tr>
<tr><td>Sens: PB</td><td>30% (0–38%)</td><td>Low</td></tr>
<tr><td>Spec:</td><td>86–100%</td><td>Very low to low</td></tr>
<tr><td colspan="3">PCR : biopsy</td></tr>
<tr><td>Sens: MB</td><td>42–100%</td><td>Very low</td></tr>
<tr><td>Sens: PB</td><td>50–75%</td><td>Very low</td></tr>
<tr><td>Spec:</td><td>73–100%</td><td>Very low</td></tr>
</table>
</td>
<td>
Single or few studies of ELISA for 45-kDa antigen, LID-1, PGL-1/LID-1 (rapid ELISA); lateral flow tests (MMP-1, SD Leprosy and On Site Leprosy AB Rapid Test); PCR tests using whole blood or nasal secretions; sum of errors (SOE) for all very low.

Predictive values for ELISA for MMP-II similar to ELISA for anti-PGL-I and not shown here.
</td>
</tr>
</table>

<table>
<tr><th></th><th>Judgement</th><th>Research evidence</th><th>Additional consideration</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><th></th><th>Pre-test disease probability</th><th>PPV</th><th>Probability of leprosy with a negative test (1-NPV)</th></tr>
<tr><td colspan="4">ELISA for anti-PGL-I</td></tr>
<tr><td>MB</td><td>1%</td><td>10%</td><td>0.25%</td></tr>
<tr><td>MB</td><td>10%</td><td>55%</td><td>3%</td></tr>
<tr><td>MB</td><td>20%</td><td>73%</td><td>6%</td></tr>
<tr><td>PB</td><td>1%</td><td>4%</td><td>0.80%</td></tr>
<tr><td>PB</td><td>10%</td><td>29%</td><td>8%</td></tr>
<tr><td>PB</td><td>20%</td><td>48%</td><td>16%</td></tr>
</table>
</td><td></td></tr>
<tr><td>Certainty of evidence</td><td>What is the overall certainty of the evidence of effects?
✓ Very low
○ Low
○ Moderate
○ High
○ No included studies</td><td>The quality of the evidence for diagnostic accuracy ranks as very low and low. There is even less certainty about how diagnostic accuracy translates into effects on clinical outcomes.</td><td>No evidence on direct harms of procedures though probably low (most based on simple blood testing). Other harms related to diagnostic accuracy (see above); with low sensitivity/ high false-negative results for PB</td></tr>
<tr><td>Values</td><td>Is there important uncertainty about, or variability in, the extent to which people value the main outcomes?
○ Important uncertainty or variability
✓ Possibly important uncertainty or variability
○ Probably no important uncertainty or variability
○ No important uncertainty or variability
○ No known undesirable outcomes</td><td>The main outcome is diagnosis by a laboratory test (no smear, no biopsy). People are likely to value diagnostic accuracy as an outcome but there is uncertainty about how diagnostic accuracy translates to clinical outcomes.</td><td>Providers would need to interpret a test that might be of a suboptimal accuracy (most likely for PB).</td></tr>
</table>

	Judgement	Research evidence	Additional consideration
Balance of effects	**Does the balance between desirable and undesirable effects favour the intervention or the comparison?** ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ✓ **Don't know**	Low quality evidence on diagnostic accuracy, suboptimal sensitivity (particularly for PB leprosy), and unclear how diagnostic accuracy impacts clinical outcomes.	
Resources required	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ✓ **Don't know**	No research evidence was identified.	The cost of the test likely to vary according to country and might require laboratory investments (equipment, training, biosafety tools). Cost–effectiveness difficult to calculate given the lack of data on impact on clinical outcomes.

	Judgement	Research evidence	Additional consideration
Certainty of evidence of required resources	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High ✓ **No included studies**	No research evidence was identified.	See above regarding variability in costs and resources.
Cost-effectiveness	**Does the cost–effectiveness of the intervention favour the intervention or the comparison?** ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ✓ **No included studies**	No research evidence was identified.	It is difficult to estimate cost–effectiveness due to uncertainty regarding costs as well as effects on clinical outcomes.

	Judgement	Research evidence	Additional consideration
Equity	**What would be the impact on health equity?** ○ Reduced ✓ **Probably reduced** ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Utilizing blood tests to diagnose leprosy might increase identification and reduce health inequity, if the test is sufficiently accurate and available in clinical settings.	A test not very sensitive for early forms of leprosy might lead to under-detection and under-treatment. Concerns are expressed for increased cost for detection compared to clinical examination.
Acceptability	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ✓ **Varies** ○ Don't know	No research evidence was identified, but stakeholders likely to vary with regard to acceptable diagnostic accuracy thresholds.	Stakeholders may be reluctant to implement a laboratory test that is more expensive than clinical examination or other tests such as smear. Patients might prefer to undergo a blood test than a more invasive confirmatory test such as smear or biopsy.
Feasibility	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ○ Yes ✓ **Varies** ○ Don't know	No research evidence was identified. Likely to vary depending on availability of testing resources.	The feasibility might be high only for referral centres. Drawing blood might be simpler than performing a slit-skin smear or a biopsy.

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
Desirable effects	Trivial	Small	Moderate	Large		Varies	**Don't know**	
Undesirable effects	Large	Moderate	Small	Trivial		Varies	**Don't know**	
Certainty of evidence	**Very low**	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes	
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either intervention or comparison	Probably favours the intervention	Favours the intervention	Varies	**Don't know**	
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**	
Certainty of evidence of required resources	Very low	Low	Moderate	High			**No included studies**	
Cost–effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either intervention or comparison	Probably favours the intervention	Favours the intervention	Varies	**No included studies**	
Equity	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		**Varies**	Don't know	

Conclusion: Is there a diagnostic test for leprosy disease (PB and/or MB) that has sufficient sensitivity and specificity and whose use is feasible under programmatic conditions?

Type of recommendation	Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
Recommendation	The GDG **does not recommend** the addition of any biological test to current methods for the diagnosis of leprosy under programmatic conditions				
Justification	Although many studies have been published on additional biological tests for leprosy, almost all of them show insufficient accuracy for diagnosis, or they are not commercially/clinically available or feasible for use at the field level. Based on currently available evidence, they do not represent a clear advantage in comparison to clinical diagnosis or to current confirmatory tests such as slit-skin smear or skin biopsy. The difficulty of interpreting a positive test among household contacts should be noted; specifically, it is difficult to determine whether a positive test is a false-positive or indication of preclinical infection. The GDG acknowledges that the costs of such tests have not been reviewed.				
Subgroup considerations	None.				
Implementation considerations	There are no new implementation considerations as the current approach is based on current practice.				
Monitoring and evaluation	There are no new monitoring or evaluation concerns.				
Research priorities	Assays that show promise of greater diagnostic accuracy and are feasible for use at the field level, should be tested in larger, well-designed studies that would allow assessment of their accuracy for detection among contacts.				

Question 1b: Is there a diagnostic test for the detection of *M. leprae* infection (latent leprosy) among contacts that has sufficient sensitivity and specificity and whose use is feasible under programmatic conditions?

Population:	Contacts of leprosy patients	Background: Under the operational plan of the Global Leprosy Strategy contacts (household contacts or social contacts depending on the epidemiological setting) are supposed to be screened for leprosy shortly after the detection and commencement of treatment of the "index" case and then screened annually for 5 years. Preventive treatment with SDR shows some efficacy. No major adverse events have been reported till date.
Intervention:	ELISA tests Antibodies to PGL-1, MMP-I and -II, NDO-LID Immunochromatographic/lateral flow tests PCR Others	
Comparison:	No possibility to detect leprosy infection	
Main outcomes:	Sensitivity/specificity	
Setting:	All settings (low- and high-burden)	
Perspective:	Clinic/field	

Assessment

<table>
<tr><th></th><th>Judgement</th><th>Research evidence</th><th>Additional consideration</th></tr>
<tr><td>Problem</td><td>Is the problem a priority?
○ No
○ Probably no
○ Probably yes
○ Yes
✓ Varies
○ Don't know</td><td>The treatment of all contacts with an effective, inexpensive and safe preventive tool might be an effective public health intervention limiting the usefulness of having a test to detect who among the exposed is infected. However, availability of a test for infection would help target a more specific and effective preventive intervention. The utility of a diagnostic test will be higher in settings in which high priority is placed on not treating uninfected exposed persons.</td><td>Considering the strong interest in using preventive tools for leprosy, the identification of persons with latent infection might be important to target preventive actions. It might also facilitate early detection among persons with known latent infection. It might be key to bring the burden to zero in very low endemic contexts.

On the other hand, feasibility of post-exposure prophylaxis might limit the usefulness of a test for detection of infection (see research evidence).</td></tr>
<tr><td>Desirable effects</td><td>How substantial are the desirable anticipated effects?
○ Trivial
○ Small
○ Moderate
○ Large
○ Varies
✓ Don't know</td><td>Desirable anticipated effects:

Diagnosis might facilitate better targeting of preventive interventions, but low sensitivity and PPV together with unknown effects on outcomes associated with earlier detection result in unclear benefits.</td><td>The GDG considered that the tests are insufficiently accurate to allow detection of leprosy infection.</td></tr>
<tr><td>Undesirable effects</td><td>How substantial are the undesirable anticipated effects?
○ Large
○ Moderate
○ Small
○ Trivial
○ Varies
✓ Don't know</td><td>Undesirable anticipated effects:

Relatively few people with positive tests will go on to develop clinical leprosy (PPV 4%), thus many people would still be treated unnecessarily.

Stigmatization of infected persons perceived as having a disease.

Summary of findings:

Based on a systematic review of seven studies with at least 1-year follow-up on predictive utility of ELISA for anti-PGL-I for subsequent leprosy in contacts. Findings were similar when restricted to studies with longer (at least 4 years) follow-up. The quality of evidence was graded as low; it was downgraded two levels due to moderate risk of bias and serious inconsistency.

<table><tr><th>Condition (accuracy measure)</th><th>Estimate</th></tr><tr><td>Sens:</td><td>Median 26% (2–39)</td></tr><tr><td>Spec:</td><td>Median 89% (83–98)</td></tr><tr><td>PPV:</td><td>Median 4% (1–18)</td></tr></table></td><td>No evidence on direct harms of procedures though probably low (most based on simple blood testing). Other harms related to diagnostic accuracy (see above); with low sensitivity/high false-negative results/low predictive values</td></tr>
</table>

	Judgement	Research evidence	Additional consideration
Certainty of evidence	**What is the overall certainty of the evidence of effects?** ○ Very low ✓ **Low** ○ Moderate ○ High ○ No included studies	The quality of the evidence for tests to detect infection ranks as moderate; however, the number of studies is limited. No evidence of impact on clinical outcome.	
Values	**Is there important uncertainty about, or variability in, the extent to which people value the main outcomes?** ○ Important uncertainty or variability ✓ **Possibly important uncertainty or variability** ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	People are likely to value the main outcome (diagnostic accuracy for predicting subsequent clinical leprosy); however, there is uncertainty regarding how diagnostic accuracy translates to clinical outcomes.	

	Judgement	Research evidence	Additional consideration
Balance of effects	**Does the balance between desirable and undesirable effects favour the intervention or the comparison?** ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ✓ **Don't know**	Low quality evidence on predictive utility; don't know how predictive utility translates to clinical outcomes.	
Resources required	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ✓ **Don't know**	No research evidence was identified. Resource requirements will depend on the costs of the assays (plus associated facility/personnel costs).	No evidence on costs of post-exposure prophylaxis versus testing and periodical screening.
Certainty of evidence of required resources	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High ✓ **No included studies**	No research evidence was identified. Costs of the assays are likely to vary across settings.	Need to compare costs of post-exposure prophylaxis against costs of testing paired with post-exposure prophylaxis and/or close clinical follow up/screening.

	Judgement	Research evidence	Additional consideration
Cost-effectiveness	**Does the cost–effectiveness of the intervention favour the intervention or the comparison?** ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ✓ **No included studies**	No research evidence was identified.	No cost–effectiveness analysis is possible since there are no data on impact on outcomes. Must consider cost of testing household contacts versus prophylactic treatment without testing.
Equity	**What would be the impact on health equity?** ○ Reduced ✓ **Probably reduced** ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Concern about stigma in persons who test positive but do not develop clinical leprosy.	A test that is not very sensitive might lead to under-use of potentially effective preventive tools.
Acceptability	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ✓ **Don't know**	No research evidence was identified. Acceptability likely to depend on how stakeholders view use of prophylactic treatments in contacts and low sensitivity of the assay.	Stakeholders may be reluctant to implement a laboratory test that lacks sensitivity/PPV.

	Judgement	Research evidence	Additional consideration
Feasibility	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ○ Yes ✓ **Varies** ○ Don't know	No research evidence was identified. Feasibility will vary depending on the cost/availability of the assays.	The feasibility might be there only for referral centres.

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
Desirable effects	Trivial	Small	Moderate	Large		Varies	**Don't know**	
Undesirable effects	Large	Moderate	Small	Trivial		Varies	**Don't know**	
Certainty of evidence	Very low	**Low**	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			No known undesirable outcomes	
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	**Don't know**	
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**	
Certainty of evidence of required resources	Very low	Low	Moderate	High			**No included studies**	
Cost–effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	**No included studies**	
Equity	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	**Don't know**	
Feasibility	No	Probably no	Probably yes	Yes		**Varies**	Don't know	

Conclusion: Is there a diagnostic test for the detection of M. leprae infection (latent leprosy) among contacts that has sufficient sensitivity and specificity and whose use is feasible under programmatic conditions?

Type of recommendation	Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
Recommendation	The GDG does not recommend a test to identify contacts at higher risk for developing subsequent leprosy disease.				
Justification	Low accuracy shown by the tests studied. The GDG recognizes that the costs of such tests have not been reviewed.				
Subgroup considerations	None.				
Implementation considerations	There are no implementation considerations as the current approach does not include testing household contacts for infection.				
Monitoring and evaluation	There are no new monitoring or evaluation concerns.				
Research priorities	Further studies are needed to identify new accurate biomarkers of leprosy infection to be used to develop a test for detecting infection under field conditions.				

Question 2a: Is a single (uniform) treatment regimen for all patients with leprosy as effective and safe as the two currently recommended treatment regimens: the one for MB leprosy with a combination of three drugs for 12 months and the one for PB leprosy with a combination of two drugs for 6 months?

Population:	Adults and children with PB and MB leprosy	Background: Presently, there are two regimens for treating leprosy based on disease classification into PB and MB leprosy. However, some patients might be wrongly classified (usually MB leprosy misclassified as PB leprosy). Shorter treatment regimens are likely to be more acceptable and less costly. Epidemiological evidence exists of a higher relapse rate after treatment in PB patients using a shorter 2-drug regimen compared to treatment in MB patients using a longer 3-drug regimen. Moreover, there is evidence of some degree of misclassification of PB based on lesion counts when compared to skin smear findings.
Intervention:	Uniform regimen with three drugs	
Comparison:	PB regimen: two drugs for 6 months MB regimen: three drugs for 12 months	
Main outcomes:	Clinical improvement Reactions Relapse Adverse events	
Setting:	Clinical and field setting	
Perspective:	Clinician	

Assessment

	Judgement	Research evidence	Additional consideration
Problem	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ✓ **Yes** ○ Varies ○ Don't know	Leprosy is a condition with important clinical, social and public health consequences. Effective treatments are an important priority. At a public health level having a single regimen effective for all types of leprosy would be desirable given limited availability of expertise in classification of leprosy. A single regimen may also facilitate the logistics of drug distribution.	With the management of leprosy at the primary health-care level, having a single regimen might be beneficial. The risk of receiving a suboptimal treatment regimen for wrongly classified PB cases might be reduced.
Desirable effects	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ○ Large ✓ **Varies** ○ Don't know	**Desirable anticipated effects:** A 3-drug 6-month regimen may be beneficial in PB patients by improving clinical and histological outcomes compared with a 2-drug 6-month regimen In MB patients, one RCTfound a 3-drug 6-month regimen associated with non-statistically significant trend towards increased risk of relapse versus a 3-drug 12-month regimen, but the estimate was very imprecise. One non-randomized study found a 3-drug 6-month regimen associated with a trend towards worse clinical outcomes at 6 months than a 12-month regimen.	The GDG considered that the risk of misclassification of patients in the field might be an issue and that, together with the evidence of the benefits of a 3-drug regimen for PB leprosy could justify the recommendation of using a 3-drug regimen for both forms of the disease. For PB leprosy, some evidence of superior outcomes with a 3-drug 6-month regimen versus a 2-drug 6-month regimen. For MB leprosy, the available evidence does not provide enough certainty on potential risks associated with a shorter regimen, i.e. worse clinical outcomes and risk for relapse. The results on side-effects and compliance seem to be encouraging, though again very limited. The GDG concluded that using a 3-drug PB regimen for 6 months might be associated with improved clinical outcomes while there was insufficient evidence to shorten the duration of 3-drug therapy for MB patients from 12 to 6 months.

<table>
<tr><th></th><th>Judgement</th><th>Research evidence</th><th>Additional consideration</th></tr>
<tr>
<td>Undesirable effects</td>
<td>
How substantial are the undesirable anticipated effects?
○ Large
○ Moderate
✓ Small
○ Trivial
○ Varies
○ Don't know
</td>
<td>
Undesirable anticipated effects:
UMDT (3-drug 6-month regimen) may be associated with adverse events and/or lower compliance in PB patients
Summary of findings:
UMDT (3-drug 6-month regimen) vs MB-MDT and PB-MDT
<table>
<tr><th>Outcome</th><th>Effect estimate</th><th>Quality</th></tr>
<tr><td colspan="3">PB</td></tr>
<tr><td>Good clinical outcome at 6 months</td><td>RR 1.9 (0.4–8.6) and 3.3 (1.7–6.7)</td><td>Very low</td></tr>
<tr><td>12 months</td><td>RR 2.0 (0.4–8.6) and 1.1 (1.0–1.3)</td><td>Very low</td></tr>
<tr><td>24 months</td><td>RR 1.4 (0.8–2.7)</td><td>Very low</td></tr>
<tr><td>Good histological outcome at 6 months</td><td>RR 1.1 (0.7–1.8) and 1.6 (1.2–2.2)</td><td>Very low</td></tr>
<tr><td>12 months</td><td>RR 1.2 (0.9–1.6) and 1</td><td>Very low</td></tr>
<tr><td colspan="3">MB</td></tr>
<tr><td>Good clinical outcome at 12 months</td><td>RR 0.12 (0.01–1.9)</td><td>Very low</td></tr>
<tr><td>24 months</td><td>0.33 (0.06–1.8)</td><td>Very low</td></tr>
<tr><td>Good histological outcome at 12 months</td><td>0.5 (0.12–1.8)</td><td>Very low</td></tr>
<tr><td>Relapses</td><td>RCT: RR 6.2 (0.78–61)
Non-RCT: no relapses in >1600 patients</td><td>Very low</td></tr>
<tr><td>Death</td><td>7.6% vs 8.6%
P = 0.48</td><td>Low</td></tr>
<tr><th>Adverse event</th><th>Effect estimate</th><th>SOE</th></tr>
<tr><td>Leprosy reactions in PB</td><td>○ RR 1.5 (0.7z7–3.0 and 2.4 (0.11–56)</td><td>Low</td></tr>
<tr><td>Leprosy reactions in MB</td><td>RR 1.0 (0.86–1.30)</td><td>Low</td></tr>
<tr><td>Anaemia in PB</td><td>RR 13.0 (0.78–216)</td><td>Very low</td></tr>
</table>
</td>
<td>
Several uncontrolled studies included in the evidence review, not included in the table.
For the PB group, there is at least some trend towards better clinical and histological outcomes. But in the MB group data were somewhat mixed: no difference in risk of death, no difference in risk of disability; possibly higher risk of relapse in the UMDT arm of the only RCT.
For PB leprosy, 10 to 14 more patients for 100 treated with a 3-drug regimen estimated to have a good clinical outcome after 12 months, 26 more patients for 100 treated with a 3-drug regimen estimated to have a good outcome after 24 months, compared with treatment with a 2-drug regimen.
</td>
</tr>
</table>

	Judgement	Research evidence	Additional consideration
Certainty of evidence	**What is the overall certainty of the evidence of effects?** ○ Very low ✓ **Low** ○ Moderate ○ High ○ No included studies	Data on effects of UMDT vs MB-MDT in patients with MB leprosy are from one RCT, otherwise quasi-randomized or non-randomized studies. Data on risk of relapse in patients with MB leprosy are scarce (an imprecise estimate from one RCT and no cases in a large non-randomized study).	
Values	**Is there important uncertainty about, or variability in, the extent to which people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ✓ **Probably no important uncertainty or variability** ○ No important uncertainty or variability ○ No known undesirable outcomes	Main outcome is clinical improvement/cure, which is likely to be highly valued by most persons.	

	Judgement	Research evidence	Additional consideration
Balance of effects	**Does the balance between desirable and undesirable effects favour the intervention or the comparison?** ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ✓ **Varies** ○ Don't know	In PB patients, the benefit of a 3-drug treatment in clinical outcomes appears to outweigh harms. In MB patients, it is less clear if benefits of a 3-drug 6-month regimen on clinical outcomes outweigh harms due to the potential for worse short-term clinical outcomes and relapse, based on limited evidence.	Different comparisons and findings for treatment of PB and MB leprosy.
Resources required	**How large are the resource requirements (costs)?** ○ Large costs ✓ **Moderate costs** ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was identified. The cost of a 3-drug regimen is higher in PB patients and the cost of a 6-month regimen is lower in MB patients than current regimens; costs may be lowered by the simplified logistics of the same 3-drug combination for all leprosy patients on the part of pharmaceutical company providing the drugs. If a 6-month regimen was to be used for MB patients, there would be additional costs related to the need for follow-up in MB patients to monitor for relapse.	MDT is provided free of charge to patients based on an agreement with a pharmaceutical company. Probably the costs of producing a 3-drug combination only will not be substantially higher than producing two different combinations of medications.

	Judgement	Research evidence	Additional consideration
Certainty of evidence of required resources	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High ✓ **No included studies**	No research evidence was identified. See above.	If the pharmaceutical company increases the availability of MB-MDT (3-drug combination), there might be no costs for programmes
Cost–effectiveness	**Does the cost–effectiveness of the intervention favour the intervention or the comparison?** ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ✓ **No included studies**	No research evidence was identified. Difficult to estimate cost–effectiveness due to uncertainty regarding clinical outcomes.	Hard to estimate cost–effectiveness given the limited clinical outcome data and differential effects in various groups; also costs of follow-up examinations have to be accounted for.

	Judgement	Research evidence	Additional consideration
Equity	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ✓ **Probably increased** ○ Increased ○ Varies ○ Don't know	UMDT may increase health equity by providing a uniform regimen that is not dependent on expertise in classification of leprosy, in settings where leprosy expertise is limited or not available.	The reduced length of MB treatment is likely to facilitate compliance and reduce the need of visits to the health facility. The protective factor in PB leprosy might reduce costs associated with relapses and reactions. Patients referred to primary health-care centres where fewer skills are available compared to referral centres for disease classification, they will all receive a single regimen.
Acceptability	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ✓ **Varies** ○ Don't know	No research evidence was identified. Acceptability may be influenced by preferences regarding the use of traditional regimens for PB and MB leprosy.	Stakeholders may be reluctant to implement a shorter regimen since leprosy has been treated for years in the past and since it is difficult to assess clinical improvement because lesions do not disappear quickly. Patients might prefer to take a shorter-duration treatment.
Feasibility	**Is the intervention feasible to implement?** ○ No ○ Probably no ✓ **Probably yes** ○ Yes ○ Varies ○ Don't know	No research evidence was identified. Implementation may be easier because UMDT does not require that leprosy be accurately classified. Patients with MB leprosy may require additional follow-up to ensure adequate treatment response.	Easier care at the primary health-care level with reduced costs for both the health system and patients. Limited capacity to differentiate between PB and MB leprosy at the primary health-care level might be overcome by a single regimen.

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
Desirable effects	Trivial	Small	Moderate	Large		**Varies**	Don't know	
Undesirable effects	Large	Moderate	**Small**	Trivial		Varies	Don't know	
Certainty of evidence	**Very low**	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			No known undesirable outcomes	
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either intervention or comparison	Probably favours the intervention	Favours the intervention	**Varies**	Don't know	
Resources required	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
Certainty of evidence of required resources	Very low	Low	Moderate	High			**No included studies**	
Cost–effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either intervention or comparison	Probably favours the intervention	Favours the intervention	Varies	**No included studies**	
Equity	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
Feasibility	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusion: Is a single (uniform) treatment regimen for all patients with leprosy as effective and safe as the two currently recommended treatment regimens: the one for MB leprosy with a combination of three drugs for 12 months and the one for PB leprosy with a combination of two drugs for 6 months?

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
Recommendation	The GDG recommends the use of a 3-drug regimen with rifampicin, dapsone and clofazimine for all patients with leprosy with a duration of treatment of 6 months for PB leprosy and of 12 months for MB leprosy.				
Justification	For PB there is some evidence of better outcomes with three drugs; for every 100 patients treated with three drugs instead of two, there would be an estimated 10 to 14 more patients with good clinical outcomes at 1 year and 26 more patients with good clinical outcomes at 2 years. There is not enough evidence of equivalent outcomes to shorten the duration of treatment of MB from 12 to 6 months. The uniform regimen in terms of number of drugs may partially mitigate the adverse consequences of misclassification of MB leprosy as PB leprosy.				
Subgroup considerations	Duration of treatment is different for PB and MB leprosy.				
Implementation considerations	The cost of treatment for PB leprosy is increased with three drugs but the reduced drug management cost might help offset the costs. Having a uniform combination of drugs may make it easier to implement in the field and reduce the effect of potential misclassification. However, training of health-care workers would still be needed. It would be advisable to develop standard health education material to further support adherence to the new treatment recommendations by both health-care workers and patients.				
Monitoring and evaluation	Monitoring of compliance among PB patients after change of regimen from two to three drugs. Monitoring of adverse events through pharmacovigilance would be needed.				
Research priorities	Studies on tools for bacteriological tests (including on *M. leprae* bacilli viability) to effectively monitor the outcomes among patients are needed along with studies on tools to differentiate relapse from persistence of lesion activity, reactions and reinfections. Studies on neuritis, its immunological aspects and on clinical management of reactions are needed to reduce the disability progression and/or occurrence during and after antibiotic treatment.				

Question 2b: Which treatment regimen has better efficacy and safety for leprosy patients detected with resistance to rifampicin, with or without associated resistance to dapsone or ofloxacin?

Population:	Adults and children with detected resistance to rifampicin	Background: There is increasing evidence of the existence of resistance to drugs in leprosy and WHO is launching a new surveillance guide that aims to expand the availability of data and widen access to detection of resistance for individual patients. In 2010, the Expert Committee formulated recommendations for treatment using second-line drugs on the basis of expert opinion, but no leprosy guidelines were ever formulated; the suggestions for treatment of such patients have never been stated as part of a guideline document.
Intervention:	Second-line treatment regimens	
Comparison:	MB-MDT	
Main outcomes:	Clinical and histological outcomes	
Setting:	Clinical and field setting	
Perspective:	Clinician/health system	

Assessment

	Judgement	Research evidence	Additional consideration
Problem	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ✓ **Don't know**	The magnitude of patient testing for resistance globally (small) does not allow for accurate assessment of the extent of the problem of drug resistance. However, all the high-burden countries have reported resistance among new and previously treated cases. No evidence on how detected resistance impacts clinical outcomes.	Five studies reported prevalence of rifampicin resistance: 1.36% in new cases, 8% in relapsed cases. Formal reports were received concerning a total of 1086 relapsed cases and of 776 new cases tested globally before the end of 2015, among which resistance to rifampicin was identified in 57 cases (5.2%) and 16 cases (2.1%), respectively (unpublished data from the latest coordination meeting of the surveillance network 2016).

	Judgement	Research evidence	Additional consideration
Desirable effects	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ✓ **Don't know**	**Desirable anticipated effects:** Unable to estimate due to lack of evidence.	The GDG considered that in view of the lack of evidence there was still a need to provide recommendations on second-line treatment for cases found with resistance. For patients who started MDT and obtained the drug resistance testing results during the course of treatment, the GDG experts' opinion is to ignore the duration of treatment already taken in case of resistance to rifampicin and to start a full course of second-line treatment, independently of the clinical outcomes under MDT.
Undesirable effects	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ✓ **Don't know**	Unable to estimate due to lack of evidence **Summary of findings:** No studies on second-line treatment for patients with drug resistance.	The GDG considered that in view of the lack of evidence there was still a need to provide recommendations on second-line treatment for cases found with drug resistance. For patients who start MDT and obtain drug resistance testing results during the course of treatment, the GDG experts' opinion is to ignore the duration of treatment already taken in case of resistance to rifampicin and to start a full course of second-line treatment, independent of clinical outcomes with MDT.
Certainty of evidence	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ○ Moderate ○ High ✓ **No included studies**	No data.	

	Judgement	Research evidence	Additional consideration
Values	**Is there important uncertainty about, or variability in, the extent to which people value the main outcomes?** ○ Important uncertainty or variability ✓ **Possibly important uncertainty or variability** ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	The main outcome is successful treatment of patients with detected resistance; likely to be highly valued by people.	
Balance of effects	**Does the balance between desirable and undesirable effects favour the intervention or the comparison?** ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ✓ **Don't know**	No research evidence was identified.	

	Judgement	Research evidence	Additional consideration
Resources required	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ✓ **Don't know**	No research evidence was identified.	
Certainty of evidence of required resources	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High ✓ **No included studies**	No research evidence was identified.	
Cost–effectiveness	**Does the cost–effectiveness of the intervention favour the intervention or the comparison?** ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ✓ **No included studies**	No research evidence was identified.	

	Judgement	Research evidence	Additional consideration
Equity	**What would be the impact on health equity?** ○ Reduced ✓ **Probably reduced** ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified. Some patients may not be able to afford/access second-line treatments.	MDT is free of charge but this may not necessarily apply to second-line drugs; therefore, some patients might not be able to access medications especially for 24 months
Acceptability	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ✓ **Don't know**	No research evidence was identified. Costs may vary in different settings and impact acceptability.	Programmes might be reluctant to implement due to potential costs (limited in any case by the probable small number of cases).
Feasibility	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ○ Yes ✓ **Varies** ○ Don't know	No research evidence was identified. Alternative regimens are available but may be more costly and require longer treatment.	May be feasible only for patients who can afford a longer-duration treatment.

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	**Don't know**	
Desirable effects	Trivial	Small	Moderate	Large		Varies	**Don't know**	
Undesirable effects	Large	Moderate	Small	Trivial		Varies	**Don't know**	
Certainty of evidence	Very low	Low	Moderate	High			**No included studies**	
Values	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes	
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either intervention or comparison	Probably favours the intervention	Favours the intervention	Varies	**Don't know**	
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**	
Certainty of evidence of required resources	Very low	Low	Moderate	High			**No included studies**	
Cost–effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either intervention or comparison	Probably favours the intervention	Favours the intervention	Varies	**No included studies**	
Equity	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	**Don't know**	
Feasibility	No	Probably no	Probably yes	Yes		**Varies**	Don't know	

Conclusion: Which treatment regimen has better efficacy and safety for leprosy patients detected with resistance to rifampicin alone and/or with associated resistance to dapsone and ofloxacin?

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
Recommendation	The GDG recommends that patients detected with resistance to rifampicin use at least two second-line drugs (clarithromycin, minocycline, ofloxacin/levofloxacin/moxifloxacin) plus clofazimine daily for 6 months, then clofazimine plus one of these drugs daily for an additional 18 months. In case of associated ofloxacin resistance, ofloxacin/levofloxacin/moxifloxacin should not be chosen.				
Justification	Patients with drug-resistant *M. leprae* would benefit from second-line treatment. Despite lack of evidence on effective regimens for drug-resistant *M. leprae*, several drugs are known to have an effect against *M. leprae* and can be incorporated into second-line treatments. Molecular testing of resistance may help guide selection of second-line regimens.				
Subgroup considerations	None.				
Implementation considerations	There are concerns regarding implementation as the current approach is not routinely implemented. Second-line regimens may be more costly and require longer duration of treatment.				
Monitoring and evaluation	Data on resistance must be expanded and trends have to be monitored. Additional data on second-line treatment outcomes should be collected as per guidance included in the "A guide for surveillance of antimicrobial resistance in leprosy-2017 Update" (WHO Regional Office for South-East Asia, October 2017). Pharmacovigilance to properly monitor adverse events shall be put in place.				
Research priorities	The GDG emphasizes the need to enhance the current antimicrobial resistance surveillance for leprosy. Given the low burden of leprosy disease, it is unlikely that an RCT of the efficacy of different second-line regimens can be carried out. However, systematic collection of clinical and bacteriological outcomes for different regimens used for drug-resistant *M. leprae* using observational methods would be useful for understanding potential benefits and harms.				

Question 3a: Is there an effective and safe chemoprophylaxis regimen for prevention of leprosy among contacts of leprosy patients and for high-risk populations that could be used under programmatic conditions?

Population:	Adults and children contacts of patients with PB and MB leprosy Population of endemic areas	Background: Contact screening has been recommended as a core programmatic intervention since 2010. However, despite the demonstrated higher risk of contacts for developing leprosy, to date no studies so far has clearly shown the efficacy of any post-exposure preventive regimen except with extended use of dapsone. Additionally, it is noted that contact screening, though recommended, has not been carried out effectively by most leprosy programmes.
Intervention:	SDR post-exposure prophylaxis for contacts Double-dose rifampicin post-exposure prophylaxis for contacts Double-dose rifampicin post-exposure prophylaxis for population in endemic areas	
Comparison:	No intervention (no chemoprophylaxis)	
Main outcomes:	Occurrence of leprosy disease Adverse events	
Setting:	All settings	
Perspective:	Clinic/field	

Assessment

	Judgement	Research evidence	Additional consideration
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ✓ **Yes** ○ Varies ○ Don't know	Leprosy is associated with important clinical and social consequences. Although effective antibiotic treatments are available, prevention of disease would be preferable and may have additional public health benefits for containing further spread of disease and reduction in disability.	With the possibility of prevention, the burden of leprosy is likely to be significantly reduced. Additionally, the availability of a preventive treatment, even if only partly effective, is likely to improve the screening of contacts, facilitating earlier detection of the disease.
Desirable effects	How substantial are the desirable anticipated effects? ○ Trivial ○ Small ✓ **Moderate** ○ Large ○ Varies ○ Don't know	Desirable anticipated effects: SDR is associated with a reduction in risk of leprosy of ~30% over 5–6 years versus placebo in contacts. The number needed to treat to prevent one case of leprosy infection is ~333.	Although the implementation of the study was only in one country, preliminary reports from the multicountry feasibility study are encouraging. However, because leprosy is a highly stigmatized disease, caution must be taken when implementing SDR for contacts outside the family of the patient and the programmes must respect the wishes of patients to disclose or not disclose their diagnosis of leprosy. With no authorization to disclose, no screening of contacts should be carried out, nor should preventive treatment to contacts without leprosy disease be prescribed. The group concluded that in areas of high endemicity and overcrowding a "blanket" approach using SDR for the whole community could be considered, although there is only one study showing the efficacy of such an approach. The availability of a preventive treatment is likely to improve the quality and completeness of contact screening.

<table>
<tr><th></th><th>Judgement</th><th>Research evidence</th><th>Additional consideration</th></tr>
<tr>
<td>Undesirable effects</td>
<td>How substantial are the undesirable anticipated effects?
○ Large
○ Moderate
○ Small
○ Trivial
○ Varies
✓ Don't know</td>
<td>Undesirable anticipated effects:
No data on adverse events (likely to be limited since treatment is a single dose of rifampicin). Protection and benefits appear to occur only in the first 1–2 years.
Summary of findings:
SDR vs placebo.
<table>
<tr><th>Outcome</th><th>Effect estimate</th><th>Quality*</th></tr>
<tr><td>Leprosy diagnosis 1–2 years</td><td>0.3% vs 0.7%
RR 0.43 (0.28–0.67)</td><td>Moderate</td></tr>
<tr><td>Leprosy diagnosis 3–4 years</td><td>0.6% vs 0.9%
RR 0.65 (0.47–0.90)</td><td>Moderate</td></tr>
<tr><td>Leprosy diagnosis 5–6 years</td><td>0.8% vs 1.1%
RR 0.72 (0.54–0.6</td><td>Moderate</td></tr>
</table>
*The quality of evidence was downgraded one level because inconsistency could not be assessed (estimates were based on one study).</td>
<td>No evidence on direct harms from procedures though probably low (most based on simple blood testing). Other harms related to diagnostic accuracy (see above); with low sensitivity/high false-negative results/low predictive values.
For every 1000 contacts treated with SDR, four cases of leprosy are prevented after 1–2 years and three cases are prevented after 5–6 years.</td>
</tr>
<tr>
<td>Certainty of evidence</td>
<td>What is the overall certainty of the evidence of effects?
○ Very low
○ Low
✓ Moderate
○ High
○ No included studies</td>
<td>Estimates of effects are based on a large, placebo-controlled, double-blind RCT with follow-up over 5–6 years</td>
<td></td>
</tr>
</table>

	Judgement	Research evidence	Additional consideration
Values	Is there important uncertainty about, or variability in, the extent to which people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ✓ **Probably no important uncertainty or variability** ○ No important uncertainty or variability ○ No known undesirable outcomes	The main outcome, prevention of leprosy, is likely to be important to people. There may be some variability in interpretation of the magnitude of benefit or duration of benefits.	The only partial and temporary protection might be interpreted differently by different stakeholders.
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ✓ **Probably favours the intervention** ○ Favours the intervention ○ Varies ○ Don't know	The results of the RCT suggest desirable effects on preventing leprosy infections. Although the absolute benefit is not large, it is significant from a public health perspective. There are no data on adverse events, but they are likely to be minor, given the nature of the intervention (single dose rifampicin). Therefore, the balance of effects probably favours the intervention.	There is efficacy, though limited in time, and the intervention is also likely to improve early case detection among contacts.

	Judgement	Research evidence	Additional consideration
Resources required	How large are the resource requirements (costs)? ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ✓ **Don't know**	No research evidence was identified. Although the costs of the intervention (SDR) are likely to be low where contact screening occurs, there are additional costs related to contact tracing and follow-up that are more difficult to estimate.	Costs probably not negligible especially in high-burden countries.
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)? ○ Very low ○ Low ○ Moderate ○ High ✓ **No included studies**	No research evidence was identified.	See above.
Cost–effectiveness	Does the cost–effectiveness of the intervention favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ✓ Probably favors **the intervention** ○ Favours the intervention ○ Varies ○ No included studies	A cost–effectiveness analysis of the RCT carried out in Bangladesh found an incremental cost–effectiveness ratio of < US$ 200 per case of leprosy averted. Costs may vary in other countries and indirect costs were not measured.	Hard to estimate with limited evidence. Probably not very high given the limited in time efficacy.

	Judgement	Research evidence	Additional consideration
Equity	What would be the impact on health equity? ○ Reduced ○ Probably reduced ✓ **Probably no impact** ○ Probably increased ○ Increased ○ Varies ○ Don't know	Preventive treatment might improve health equity by preventing future cases of leprosy but could worsen health equity due to stigma or other social effects.	If rifampicin were to be self-purchased by the patient, the costs would probably be affordable. Reduced occurrence of the disease would represent a benefit for contacts that constitute the high-risk group.
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ✓ **Probably yes** ○ Yes ○ Varies ○ Don't know	One qualitative study found that people found preventive treatment to be acceptable.	One qualitative study found that people found preventive treatment to be acceptable.
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ✓ **Probably yes** ○ Yes ○ Varies ○ Don't know	No research evidence was identified. Providing SDR is probably feasible but contact tracing may be more difficult to implement.	Preliminary reports for LPEP show feasibility under pilot-study conditions.

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
Desirable effects	Trivial	Small	**Moderate**	Large		Varies	Don't know	
Undesirable effects	Large	Moderate	Small	Trivial		Varies	**Don't know**	
Certainty of evidence	Very low	Low	**Moderate**	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			No known undesirable outcomes	
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either intervention or comparison	**Probably favours the intervention**	Favours the intervention	Varies	Don't know	
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**	
Certainty of evidence of required resources	Very low	Low	Moderate	High			**No included studies**	
Cost–effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either intervention or comparison	**Probably favours the intervention**	Favours the intervention	Varies	No included studies	
Equity	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know	
Feasibility	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusion: Is there an effective and safe chemoprophylaxis regimen for prevention of leprosy among contacts of leprosy patients and for high-risk populations that could be used under programmatic conditions?

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
Recommendation	The GDG recommends the use of SDR as preventive treatment for contacts of leprosy patients, in adults and children 2 years of age and above, after excluding leprosy and TB disease and other contraindications, by programmes that can ensure adequate management of contacts and upon agreement of the index case to disclose his/her disease.				
Justification	Moderate efficacy demonstrated by a single double-blind RCT. For every 1000 contacts treated with SDR, it is estimated that four cases of leprosy would be prevented at 1–2 years and three cases prevented at 5–6 years. The provision of chemoprophylaxis is likely to improve contact screening and preliminary reports suggest feasibility and acceptability under programmatic conditions. One study showed that the intervention was cost effective.				
Subgroup considerations	None.				
Implementation considerations	Good coverage of contact screening is essential. Detailed guidelines will be necessary to ensure confidentiality considering stigma, discrimination and contextual sensitivity and the delivery of appropriate health education to patients and contacts. The recommendation is conditional upon the ability of programmes to be able to adequately identify and manage contacts of leprosy patients.				
Monitoring and evaluation	There will be a need for additional adverse events monitoring, and monitoring of effects related to stigma.				
Research priorities	Studies that evaluate the effectiveness of alternative regimens (different drugs and different durations of treatment) are encouraged as well as studies that investigate the efficacy of chemoprophylaxis provided through a "blanket/high-risk population" approach, since such an approach might show more effectiveness, increase feasibility, and may result in less risk of stigma. Studies are also needed of the possible effect of repeating administration of SDR in contacts every 2 years.				

Question 3b: Is there an effective vaccine for the prevention of leprosy that could be used under programmatic conditions, with or without chemoprophylaxis, for contacts of leprosy patients and also among the general population?

Population:	Adults and children in general population Adults and children contacts of patients with leprosy	Background: Despite known evidence of the efficacy of BCG to prevent leprosy, no WHO recommendations have been released for its use as a preventive tool against leprosy. Several studies especially from high-burden countries assessed the efficacy of other vaccines and of the combination of post-exposure prophylaxis with BCG at birth and/or with BCG revaccination.
Intervention:	BCG BCG revaccination BCG + SDR BCG + *M. leprae* Other vaccines (ICRC, *M. indicum pranii*)	
Comparison:	No intervention (no vaccination)	
Main outcomes:	Occurrence of leprosy disease	
Setting:	All settings	
Perspective:	Clinic/field	

Assessment

	Judgement	Research evidence	Additional consideration
Problem	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ✓ **Yes** ○ Varies ○ Don't know	Leprosy is a preventable infectious disease with important clinical, social and public health consequences. Vaccines are a core intervention to prevent and effectively bring down the burden of communicable diseases and their impact on the health of the population.	With only partial efficacy of a chemoprophylaxis regimen, the availability of a vaccine becomes an important tool.
Desirable effects	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ○ Large ✓ **Varies** ○ Don't know	**Desirable anticipated effects:** Evidence indicates that several vaccination interventions are effective at reducing the risk of leprosy.	The GDG considered that immunoprophylaxis could be important in leprosy.

<table>
<tr><th></th><th>Judgement</th><th>Research evidence</th><th>Additional consideration</th></tr>
<tr>
<td>Undesirable effects</td>
<td>

How substantial are the undesirable anticipated effects?

○ Large

○ Moderate

○ Small

○ Trivial

○ Varies

✓ **Don't know**

</td>
<td>

Undesirable anticipated effects:

Data on adverse events of vaccinations are limited.

Summary of findings:

Effects of vaccination on risk of leprosy.

One RCT found effects of SDR greater in persons who also received childhood BCG (quality: low)

- Placebo: OR 1 (reference)
- SDR and childhood BCG: OR 0.20 (0.08–0.49)
- Childhood BCG alone: OR 0.43 (0.25–0.75)
- SDR alone: OR 0.42 (0.26–0.69)

<table>
<tr><th>Comparison</th><th>Findings</th><th>Quality</th></tr>
<tr><td>BCG at birth vs no BCG or placebo</td><td>Pooled OR 0.45 (0.34–0.56) from SR and 0.43 (0.25–0.75) from additional RCT</td><td>Moderate*</td></tr>
<tr><td>BCG at birth plus killed M. leprae vs placebo</td><td>RRR 64% (50–74%)</td><td>Low^</td></tr>
<tr><td>BCG plus killed M. leprae vs BCG alone</td><td>RR 1.06 (0.62 to 1.82), RR 0.89 (95% CI 0.53 to 1.47), and RR 0.55 (CI not available)</td><td>Low*</td></tr>
<tr><td>BCG revaccination in contacts vs no BCG</td><td>RR 0.51 (0.26–0.99), RR 0.99 (0.69–1.43),</td><td>Low+</td></tr>
<tr><td>ICRC vaccine vs placebo</td><td>RRR 66% (48–77%)</td><td>Low^</td></tr>
<tr><td>M.indicum pranii vs placebo</td><td>OR 0.61 (0.46–0.80) and RRR 26% (1.9–44%)</td><td>Moderate~</td></tr>
<tr><td colspan="3">*Downgraded one level due to inconsistency
^Downgraded two levels due to moderate risk of bias and inability to assess consistency (estimate based on 1 study)
+Downgraded two levels due to moderate risk of bias and inconsistency
~Downgraded one level due to moderate risk of bias</td></tr>
</table>

</td>
<td></td>
</tr>
</table>

	Judgement	Research evidence	Additional consideration
Certainty of evidence	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ✓ **Moderate** ○ High ○ No included studies	Evidence for some vaccine intervention is moderate. Data on adverse events is limited but they are likely to be few for BCG based on experience on its use in tuberculosis prevention.	
Balance of effects	**Does the balance between desirable and undesirable effects favour the intervention or the comparison?** ✓ **Favours the comparison** ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	Strongest evidence is for BCG at birth. Evidence is limited for other vaccination interventions but suggests benefit of BCG at birth plus killed *M. leprae*, ICRC vaccine, and *M. indicum pranii*. BCG + rifampicin more effective than either intervention alone in contacts in one sub-study from the RCT. Evidence on adverse events is limited.	For other vaccines and revaccination there is limited evidence. No appraisal of evidence on adverse events.

	Judgement	Research evidence	Additional consideration
Resources required	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ✓ **Don't know**	No research evidence was identified. Costs of BCG at birth are likely to be mainly related to the cost of the vaccine; costs of vaccination of contacts will include costs of contact tracing.	
Certainty of evidence of required resources	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High ✓ **No included studies**	No research evidence was identified.	

	Judgement	Research evidence	Additional consideration
Cost–effectiveness	**Does the cost–effectiveness of the intervention favour the intervention or the comparison?** ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ✓ **No included studies**	No research evidence was identified.	
Equity	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ✓ **Probably increased** ○ Increased ○ Varies ○ Don't know	Universal vaccination at birth likely to improve health equity by preventing leprosy and not focusing prevention on contacts, which may result in stigma.	

	Judgement	Research evidence	Additional consideration
Acceptability	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ✓ **Varies** ○ Don't know	No research evidence was identified. However, in some settings vaccination programmes are already performed and appear acceptable.	Programmes might be reluctant to implement due to potential costs.
Feasibility	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ○ Yes ✓ **Varies** ○ Don't know	No research evidence was identified. However, BCG at birth is already routine in most high leprosy endemic countries and vaccination of contacts is performed in some settings.	For other vaccines uncertain – not current practice in the field.

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
Desirable effects	Trivial	Small	Moderate	Large		**Varies**	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	**Don't know**	
Certainty of evidence	Very low	Low	**Moderate**	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			No known undesirable outcomes	
Balance of effects	**Favours the comparison**	Probably favours the comparison	Does not favour either intervention or comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**	

	Judgement							Implications
Certainty of evidence of required resources	Very low	Low	Moderate	High			**No included studies**	
Cost–effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either intervention or comparison	Probably favours the intervention	Favours the intervention	Varies	**No included studies**	
Equity	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		**Varies**	Don't know	

Conclusion: Is there an effective and safe tool for prevention of leprosy that could be used under programmatic conditions in the form of immunoprophylaxis, with or without chemoprophylaxis, for contacts of leprosy patients and also among the general population?

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
Recommendation	The GDG brings to the attention of SAGE the following considerations: • BCG at birth is effective in reducing the risk of leprosy disease and therefore its use should be maintained at least in all leprosy high-burden countries. • The GDG points out the efficacy of the following vaccine, still in production, in preventing leprosy, according to RCTs: – *M. indicum pranii* • Presently, there is insufficient evidence of the efficacy of BCG revaccination among contacts to recommend its use.				
Justification	Evidence suggests the efficacy of BCG and other vaccines to prevent leprosy. BCG is easily accessible and already part of the vaccination policy of most endemic countries. Other vaccines show similar or slightly lower efficacy compared to BCG.				
Subgroup considerations	None.				
Implementation considerations	Implementation considerations for BCG at birth are similar to other vaccinations given at birth (already routinely administered in most high-endemic countries). Vaccination assumes the availability of BCG.				
Monitoring and evaluation	There might be the need to implement a monitoring system for adverse events if other vaccines are used (BCG adverse events monitoring already part of the EPI).				
Research priorities	Trials of new and existing vaccines, including studies of LepVax, a new subunit vaccine Any novel TB vaccines should also be evaluated for leprosy and Buruli ulcer prevention and vice versa				

Annex 3: Guide for the focus group discussions to identify values and preferences of persons affected by leprosy

Focus group composition:

- between 7 and 10 people
- men and women
- younger and older people
- preferably persons affected with a relatively recent diagnosis (not more than 5–7 years)
- PB and MB past leprosy diagnosis
- former patients with and without disabilities
- rural and urban

Instructions for focus group discussion: reunite the group and discuss the questions one at the time. Let the discussion flow. At the end of the discussion of each topic ask the group to agree on a list of the most important problems and suggestions, rate their importance from 1 to 4 (with 1 being the most important). Please tick the name of your country and fill in the information on attendance.

Outcome of the focus group discussion

1. Diagnosis

In your experience, what are the major problems that prevent people from obtaining an accurate diagnosis of leprosy?

1	2	3	4

What are your suggestions for the most important changes to improve diagnosis of leprosy?

1	2	3	4

2. *Medical treatment/MDT*

In your experience, what are the major problems that prevent people from starting and completing appropriate medical treatment/MDT for leprosy?

1	2	3	4

Did you notice during the discussion if the problems mentioned were different for people diagnosed with PB compared to those with MB leprosy? If yes, indicate here which problems have been raised by one of the two groups only.

What are your suggestions for the most important changes to improve access and completion of medical treatment/MDT?

1	2	3	4

Did you notice during the discussion if the suggestions or ideas were different for people diagnosed with PB compared to those with MB leprosy? If yes, indicate here which suggestions have been raised by one of the two groups only.

3. *Contact tracing and follow up for prevention of leprosy*

After a person has been diagnosed with leprosy, services often seek to follow up with their family and friends for contact tracing and prevention. What are your concerns about this?

1	2	3	4

What could leprosy services do to reduce your concerns about contact tracing and follow up?

1	2	3	4

If there was a treatment that could probably help prevent leprosy, what should services do to offer that treatment more easily to family and friends?

1	2	3	4

Remarks

Add any comments that could not be easily captured/summarized in the grid above:

Country:

- Colombia
- Ghana
- India
- Nepal

How many people participated?

- Total number:
- Number of men:
- Number of women:
- Number of children:
- Number with previous PB disease:
- Number with disabilities:
- Number from urban areas:
- Number of people who were diagnosed with leprosy more than 5 years ago:

Date and venue where the focus group discussion took place:

Annex 4: GRADE tables and literature review report

The GRADE tables for each set of PICO questions and the report of the literature review can be accessed on the webpage of WHO's Global Leprosy Programme.

The Guidelines for the Diagnosis, Treatment and Prevention of Leprosy provide state-of-the-art knowledge and evidence on leprosy diagnosis, treatment and prevention based on a public health approach in endemic countries. The target audience of this document includes policy-makers in leprosy or infectious diseases in the ministries of health (especially but not limited to endemic countries), nongovernmental organizations, clinicians, pharmaceutical companies, donors and affected persons. These leprosy guidelines have been developed by strictly following WHO's GRADE approach wherein all available evidence published in English has been taken into consideration. Funding support was received from The Nippon Foundation.

ISBN 978-92-9022-638-3

World Health Organization
REGIONAL OFFICE FOR South-East Asia